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Strategies for using topical corticosteroids in children and adults with eczema (Review)

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[Intervention Review]

Strategies for using topical corticosteroids in children and adults with eczema

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ABSTRACT

Background

Eczema is a common skin condition. Although topical corticosteroids have been a first-line treatment for eczema for decades, there are uncertainties over their optimal use.

Objectives

To establish the effectiveness and safety of different ways of using topical corticosteroids for treating eczema.

Search methods

We searched databases to January 2021 (Cochrane Skin Specialised Register; CENTRAL; MEDLINE; Embase; GREAT) and five clinical trials registers. We checked bibliographies from included trials to identify further trials.

Selection criteria

Randomised controlled trials in adults and children with eczema that compared at least two strategies of topical corticosteroid use. We excluded placebo comparisons, other than for trials that evaluated proactive versus reactive treatment.

Data collection and analysis

We used standard Cochrane methods, with GRADE certainty of evidence for key findings. Primary outcomes were changes in clinician-reported signs and relevant local adverse events. Secondary outcomes were patient-reported symptoms and relevant systemic adverse events. For local adverse events, we prioritised abnormal skin thinning as a key area of concern for healthcare professionals and patients.

Main results

We included 104 trials (8443 participants). Most trials were conducted in high-income countries (81/104), most likely in outpatient or other hospital settings. We judged only one trial to be low risk of bias across all domains. Fifty-five trials had high risk of bias in at least one domain, mostly due to lack of blinding or missing outcome data.

Stronger-potency versus weaker-potency topical corticosteroids

Sixty-three trials compared different potencies of topical corticosteroids: 12 moderate versus mild, 22 potent versus mild, 25 potent versus moderate, and 6 very potent versus potent. Trials were usually in children with moderate or severe eczema, where specified, lasting one to five weeks. The most reported outcome was Investigator Global Assessment (IGA) of clinician-reported signs of eczema.

We pooled four trials that compared moderate- versus mild-potency topical corticosteroids (420 participants). Moderate-potency topical corticosteroids probably result in more participants achieving treatment success, defined as cleared or marked improvement on IGA (52% versus 34%; odds ratio (OR) 2.07, 95% confidence interval (CI) 1.41 to 3.04; moderate-certainty evidence). We pooled nine trials that compared potent versus mild-potency topical corticosteroids (392 participants). Potent topical corticosteroids probably result in a large increase in number achieving treatment success (70% versus 39%; OR 3.71, 95% CI 2.04 to 6.72; moderate-certainty evidence). We pooled 15 trials that compared potent versus moderate-potency topical corticosteroids (1053 participants). There was insufficient evidence of a benefit of potent topical corticosteroids compared to moderate topical corticosteroids (OR 1.33, 95% CI 0.93 to 1.89; moderate-certainty evidence). We pooled three trials that compared very potent versus potent topical corticosteroids (216 participants). The evidence is uncertain with a wide confidence interval (OR 0.53, 95% CI 0.13 to 2.09; low-certainty evidence).

Twice daily or more versus once daily application

We pooled 15 of 25 trials in this comparison (1821 participants, all reported IGA). The trials usually assessed adults and children with moderate or severe eczema, where specified, using potent topical corticosteroids, lasting two to six weeks.

Applying potent topical corticosteroids only once a day probably does not decrease the number achieving treatment success compared to twice daily application (OR 0.97, 95% CI 0.68 to 1.38; 15 trials, 1821 participants; moderate-certainty evidence).

Local adverse events

Within the trials that tested 'treating eczema flare-up' strategies, we identified only 26 cases of abnormal skin thinning from 2266 participants (1% across 22 trials). Most cases were from the use of higher-potency topical corticosteroids (16 with very potent, 6 with potent, 2 with moderate and 2 with mild). We assessed this evidence as low certainty, except for very potent versus potent topical corticosteroids, which was very low-certainty evidence.

Longer versus shorter-term duration of application for induction of remission

No trials were identified.

Twice weekly application (weekend, or 'proactive therapy') to prevent relapse (flare-ups) versus no topical corticosteroids/reactive application

Nine trials assessed this comparison, generally lasting 16 to 20 weeks. We pooled seven trials that compared weekend (proactive) topical corticosteroids therapy versus no topical corticosteroids (1179 participants, children and adults with a range of eczema severities, though mainly moderate or severe).

Weekend (proactive) therapy probably results in a large decrease in likelihood of a relapse from 58% to 25% (risk ratio (RR) 0.43, 95% CI 0.32 to 0.57; 7 trials, 1149 participants; moderate-certainty evidence).

Local adverse events

We did not identify any cases of abnormal skin thinning in seven trials that assessed skin thinning (1050 participants) at the end of treatment. We assessed this evidence as low certainty.

Other comparisons

Other comparisons included newer versus older preparations of topical corticosteroids (15 trials), cream versus ointment (7 trials), topical corticosteroids with wet wrap versus no wet wrap (6 trials), number of days per week applied (4 trials), different concentrations of the same

topical corticosteroids (2 trials), time of day applied (2 trials), topical corticosteroids alternating with topical calcineurin inhibitors versus topical corticosteroids alone (1 trial), application to wet versus dry skin (1 trial) and application before versus after emollient (1 trial). No trials compared branded versus generic topical corticosteroids and time between application of emollient and topical corticosteroids.

Authors' conclusions

Potent and moderate topical corticosteroids are probably more effective than mild topical corticosteroids, primarily in moderate or severe eczema; however, there is uncertain evidence to support any advantage of very potent over potent topical corticosteroids. Effectiveness is similar between once daily and twice daily (or more) frequent use of potent topical corticosteroids to treat eczema flare-ups, and topical corticosteroids weekend (proactive) therapy is probably better than no topical corticosteroids/reactive use to prevent eczema relapse (flare-ups). Adverse events were not well reported and came largely from low- or very low-certainty, short-term trials. In trials that reported abnormal skin thinning, frequency was low overall and increased with increasing potency. We found no trials on the optimum duration of treatment of a flare, branded versus generic topical corticosteroids, and time to leave between application of topical corticosteroids and emollient. There is a need for longer-term trials, in people with mild eczema.

PLAIN LANGUAGE SUMMARY

What is the best way to use topical corticosteroids to treat people with eczema?

Key messages

- Generally, stronger topical corticosteroids (steroid cream applied to the skin) are probably more effective than weaker preparations. Strong steroid cream applied once daily is probably as good as twice daily, and using steroid cream for two consecutive days weekly probably prevents eczema flare-ups.

- About a third of studies looked for skin thinning, but cases were very low. This made it difficult to judge differences between strategies, although there were more cases with stronger steroid cream.

- We need better-quality research on unwanted effects, over longer timeframes, but intermittent use of steroid cream probably causes fewer unwanted effects.

What is eczema and how is it treated?

Eczema is a common, long-lasting condition that results in inflamed, dry, itchy patches of skin and its severity varies; it is incurable currently, so treatment aims to control symptoms (inflammation and itching). The first choice of treatment is emollients (moisturisers) combined with treatment to reduce inflammation, often steroid cream.

What did we want to find out?

Steroid creams can be used in different ways to treat eczema, and people often feel confused about which ones to use, and how often and how best to use them. We wanted to investigate the effectiveness of different ways (strategies) of using steroid cream and whether they cause unwanted effects.

What did we do?

We summarised evidence from studies that tested different ways of using steroid cream in adults and children. We assessed treatment strategies based on changes in eczema severity assessed by doctors/researchers or participants, and unwanted effects, such as skin thinning (the skin may bruise and tear more easily). We compared and summarised their results, and rated our confidence in the evidence, based on factors such as trial methods and sizes.

What did we find?

Most studies were conducted in high-income countries, likely in hospitals, and were short term (range 1 to 6 weeks); studies that assessed prevention of eczema flares lasted longer, but under 6 months. Participant age varied; 43 studies included children only. Eczema was moderate or severe in 51 studies, mild to moderate in 16 studies, mild to severe in 3 studies, and 34 studies did not report severity. Approximately half of the studies were funded by companies that produced the steroid cream or had links to industry; 44 did not report their funding source.

We included 104 studies with 8443 people.

- Stronger versus weaker steroid cream (63 studies). We combined data from 31 studies and 2018 people. The chances of achieving cleared or marked improvement, assessed by a healthcare practitioner, were probably increased with use of stronger-potency steroid cream. For 1000 people treated, it is likely that 340 to 390 would be clear or almost clear using mild-potency steroid cream; 460 to 520 would be clear or almost clear using moderate-potency steroid cream; and 530 to 710 would be clear or almost clear using potent steroid cream.

- Twice daily versus once daily steroid cream application (25 studies). We combined data from 15 studies with 1821 people. Applying strong steroid cream once daily is probably as effective as twice daily application. Studies did not report unwanted effects well, and we are uncertain about some results. Twenty-two studies (2266 people) reported skin thinning. They identified 26 possible cases, 16 with very strong steroid cream, 6 with strong, 2 with moderate, and 2 with mild steroid cream.

- Longer versus shorter steroid cream duration (0 studies)

- Twice-weekly application (using steroid cream for two consecutive days per week) to prevent flare-ups versus no application (9 studies). We combined data from 7 studies (1149 people). Twice weekly steroid cream probably decreases the chance of eczema flare-ups. For 1000 people using flare-control creams twice weekly, we would expect approximately 248 to have one or more new flare-up compared to 576 people not using this strategy. No cases of skin thinning were identified in 7 flare-up prevention studies (1050 people).

- Other comparisons. We also looked at newer versus older steroid cream preparations, cream versus ointment, steroid cream used with wet wrap, daily versus less frequent application, different strengths of the same steroid cream, time of day applied, steroid cream alternating with topical calcineurin inhibitors (e.g. Protopic and Elidel) versus steroid cream alone, application to wet versus dry skin, and before versus after emollients. No studies compared branded versus generic steroid cream or time between application of emollient and steroid cream.

What are the limitations of the evidence?

Overall, we are moderately confident about the results on the effectiveness of steroid creams to treat eczema, but we have little confidence in results on unwanted effects, because studies were small and did not always use the most reliable methods.

How up to date is this evidence?

The evidence is up to date to January 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Moderate-potency compared to mild-potency topical corticosteroid

Moderate compared to mild-potency **topical corticosteroid for people with eczema**

Patient or population: children and adults with mild to severe eczema
Setting: outpatient and inpatient settings in high- and lower-middle-income countries
Intervention: moderate-potency topical corticosteroid (TCS)
Comparison: mild-potency topical corticosteroid (TCS)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants/**sides treated** (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with mild-potency TCS	Risk with moderate-potency TCS				
Clinician-reported signs of eczema: IGA (number with cleared or marked improvement); short term (earliest time within 1-5 weeks)	Trial population 342 per 1000	519 per 1000 (423 to 613)	OR 2.07 (1.41 to 3.04) indicating higher odds of improvement with moderate TCS	449[a] (4 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	
Patient-reported symptoms of eczema: 1-5 weeks	Whilst no trials reported PGA, two within-participant trials in 64 participants (128 sides treated) incorporated parent or patient judgements into a clinician preference outcome and favoured moderate-potency TCS. In addition, 3 trials reporting pruritus favoured moderate-potency TCS (n = 292; 321 sides treated)			449[c] (5 RCTs)	⊕⊕⊖⊖ **Low**[d,e]	
Local adverse events: skin thinning; end of treatment (2-5 weeks)	No cases with moderate TCS (n = 239) or mild TCS (n = 233)			472[f] (4 RCTs)	⊕⊕⊖⊖ **Low**[b,g]	
Systemic adverse events: abnormal cortisol; end of treatment (6-28 days)	No cases with moderate TCS (n = 15) or mild TCS (n = 18)			33 (2 RCTs)	⊕⊖⊖⊖ **Very low**[d,h]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IGA:** Investigator Global Assessment; **OR**: odds ratio; **PGA:** Patient Global Assessment; **RCT:** randomised controlled trial; **TCS:** topical corticosteroids

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Actual number of participants = 420; 391 from parallel-group trials and 29 from within-participant trials where data from both sides of the same individual were included in the meta-analysis with variance correction (449 = 391 + 29 x 2).
[b]Downgraded once for risk of bias: unclear or high risk judgements for most domains; specific concerns with incomplete outcome data.
[c]Actual number of participants = 356; 263 from parallel-group trials and 93 from within-participant trials where data from both sides of the same individual were included (449 = 263 + 93 x 2).
[d]Downgraded once for risk of bias: unclear or high risk judgements for most domains; specific concerns with lack of blinding and incomplete outcome data.
[e]Downgraded once for imprecision: small number of participants.
[f]Actual number of participants = 417; 362 from parallel-group trials and 55 from within-participant trials where data from both sides of the same individual were included (472 = 362 + 55 x 2). In one RCT, a subgroup of 36 participants were treated for up to 25 weeks.
[g]Downgraded once for imprecision: no events.
[h]Downgraded two levels for imprecision: small number of participants and no events.

Summary of findings 2. Potent compared to mild-potency topical corticosteroid

Potent compared to mild-potency **topical corticosteroid for people with eczema**

Patient or population: children and adults with mild to severe eczema
Setting: community, outpatient and inpatient settings in high-, upper-middle- and lower-middle-income countries
Intervention: potent topical corticosteroid (TCS)
Comparison: mild-potency topical corticosteroid (TCS)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants/**sides treated** (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with mild-potency TCS	Risk with potent TCS				
Clinician-reported signs of eczema: IGA (number with cleared or marked improvement); short term (earliest time point within 1-4 weeks)	Trial population		OR 3.71 (2.04 to 6.72) indicating higher odds of improvement with potent TCS	458[a] (9 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	
	392 per 1000	705 per 1000 (568 to 813)				
Patient-reported symptoms of eczema: 1-18 weeks	Whilst no trials reported PGA, 4 trials in 403 participants/sides treated reported itch measures; 2 suggested modest improvement in itch with potent TCS, however there was little difference overall. 2 of these trials also reported no difference in sleep measures (n = 285)			483[c] (5 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	

	1 within-participant trial reported that almost half of participants judged potent TCS to be better than mild TCS (n = 40; 80 sides treated)			
Local adverse events: skin thinning; end of treatment (2-18 weeks)	4 cases with potent TCS (n = 221); 2 cases with mild TCS (n = 219)	440 (5 RCTs)	⊕⊕⊖⊖ **Low**[b,d]	All cases were reported in the same trial
Systemic adverse events: abnormal cortisol; end of treatment (6-30 days)	11 cases with potent TCS (n = 43); 4 cases with mild TCS (n = 39).	82 (3 RCTs)	⊕⊖⊖⊖ **Very low**[b,e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IGA:** Investigator Global Assessment; **OR**: odds ratio; **PGA:** Patient Global Assessment; **RCT:** randomised controlled trial; **TCS:** topical corticosteroids

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Actual number of participants = 392; 326 from parallel-group trials and 66 from within-participant trials where data from both sides of the same individual were included in the meta-analysis with variance correction (458 = 326 + 66 x 2).
[b]Downgraded once for risk of bias: unclear or high risk for most domains.
[c]Actual number of participants = 423; 363 from parallel-group trials and 66 from within-participant trials where data from both sides of the same individual were included (483 = 363 + 60 x 2).
[d]Downgraded once for imprecision: few events.
[e]Downgraded two levels for imprecision: small number of participants and few events.

Summary of findings 3. Potent compared to moderate-potency topical corticosteroid

Potent compared to moderate-potency **TCS for people with eczema**

Patient or population: children and adults, most with moderate to severe eczema
Setting: outpatient and inpatient settings in high- and middle-income countries
Intervention: potent topical corticosteroid (TCS)
Comparison: moderate-potency topical corticosteroid (TCS)

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)		Comments

	Risk with moderate-potency TCS	Risk with potent TCS		№ of participants/**sides treated** (trials)	**Certainty of the evidence (GRADE)**
Clinician-reported signs of eczema: IGA (number with cleared or marked improvement); short term (earliest time point within 1-4 weeks)	Trial population		OR 1.33 (0.93 to 1.89) indicating a lack of evidence of improvement with potent TCS.	1173[a] (15 RCTs)	⊕⊕⊕⊖ **Moderate**[b]
	456 per 1000	527 per 1000 (438 to 613)			
Patient-reported symptoms of eczema: PGA; short-term (week 1)	Whilst no trials reported usable PGA data, 1 trial (n = 60) reported that PGA was consistent with IGA (OR for IGA in that trial: 4.46; 95% CI 0.47 to 42.51) 1 further within-participant trial reported that 35 of 66 participants judged potent TCS to be superior.			192[c] (2 RCTs)	⊕⊕⊖⊖ **Low**[d,e]
Local adverse events: skin thinning; end of treatment (1 to 3 weeks)	2 cases with potent TCS (n = 268) and 2 cases with moderate TCS (n = 273)			541[f] (10 RCTs)	⊕⊕⊖⊖ **Low**[d,g]
Systemic adverse events: abnormal cortisol; end of treatment (6 days to 4 weeks)	9 cases with potent TCS (n = 55). 1 case with moderate TCS (n = 44)[h]			99 (3 RCTs)	⊕⊖⊖⊖ **Very low**[i,j,k]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IGA:** Investigator Global Assessment; **OR**: odds ratio; **PGA:** Patient Global Assessment; **RCT:** randomised controlled trial; **TCS:** topical corticosteroids

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Actual number of participants = 1053; 933 from parallel-group trials and 120 from within-participant trials where data from both sides of the same individual were included in the meta-analysis with variance correction (1173 = 933 + 120 x 2).
[b]Downgraded once for risk of bias: unclear or high risk judgements for most domains.
[c]Actual number of participants = 126; 60 from a parallel-group trial and 66 from a within-participant trial where data from both sides of the same individual were included (192 = 60 + 66 x 2).
[d]Downgraded once for risk of bias: unclear for most domains with some high-risk domains. Specific concerns about lack of blinding.
[e]Downgraded once for imprecision: small number of participants.

[f]Actual number of participants = 526; 511 from parallel-group trials and 15 from within-participant trials where data from both sides of the same individual were included in the meta-analysis with variance correction (541 = 511 + 15 x 2).
[g]Downgraded once for imprecision: few events.
[h]The nine cases occurring with potent topical corticosteroid are from a multi-arm trial comparing potent with mild, and moderate-potency topical corticosteroid (Queille 1984). Therefore, these cases are also included in the potent topical corticosteroid arm of Summary of findings 2.
[i]Downgraded once for risk of bias: unclear for most domains; high risk from lack of blinding.
[j]Downgraded once for inconsistency: one trial reported more events with potent topical corticosteroid; one trial reported an event with moderate topical corticosteroid; a third reported no events in either group.
[k]Downgraded once for imprecision: small number of participants; few events.

Summary of findings 4. Very potent compared to potent topical corticosteroid

Very potent compared to potent TCS for people with eczema

Patient or population: adults with mild to severe eczema
Setting: outpatient and inpatient settings in high-income countries
Intervention: very potent topical corticosteroid (TCS)
Comparison: potent topical corticosteroid (TCS)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants/sides treated (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with potent TCS	Risk with very potent TCS				
Clinician-reported signs of eczema: IGA (number with cleared or marked improvement); short term (earliest time point within 1-2 weeks)	Trial population 933 per 1000	881 per 1000 (645 to 967)	OR 0.53 (0.13 to 2.09) indicating a lack of evidence of improvement with very potent TCS.	243[a] (3 RCTs)	⊕⊕⊖⊖ **Low**[b,c]	
Patient-reported symptoms of eczema: PGA (number judging excellent); short term (day 8)	9 judged excellent with very potent TCS (n = 58); 3 judged excellent with potent TCS (n = 58)			116[d] (1 RCT)	⊕⊖⊖⊖ **Very low**[e,f]	These data were from a within-participant trial in which very potent TCS was applied twice daily and potent TCS was second-generation, applied once daily
Local adverse events: skin thinning; end of treatment (day 11-day 22)	No cases with very potent TCS (n = 116) or potent TCS (n = 117)			233[g] (2 RCTs)	⊕⊖⊖⊖ **Very low**[f,h]	58 participants were from a within-participant trial in which very potent TCS was applied twice daily and potent TCS was

				second-generation, applied once daily
Systemic adverse events: abnormal cortisol	Whilst no trials reported abnormal cortisol data, 1 trial reported no systemic adverse events (unspecified)	117 (1 RCTs)	⊕⊖⊖⊖ **Very low**[b,f]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IGA:** Investigator Global Assessment; **OR**: odds ratio; **PGA:** Patient Global Assessment; **RCT:** randomised controlled trial; **TCS:** topical corticosteroids

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Actual number of participants = 216; 189 from parallel-group trials and 27 from within-participant trials where data from both sides of the same individual were included in the meta-analysis with variance correction (243 = 189 + 27 x 2).
[b]Downgraded once for risk of bias: unclear or high judgements for most domains.
[c]Downgraded once for imprecision: small number of participants.
[d]Actual number of participants = 58 as data from both sides of the same individual were included (116 = 58 x 2).
[e]Downgraded once for risk of bias: lack of blinding.
[f]Downgraded two levels for imprecision: small number of participants and few events.
[g]Actual number of participants = 175; 117 from a parallel-group trial and 58 from a within-participant trial where data from both sides of the same individual were included (233 = 117+58*2).
[h]Downgraded once for risk of bias: unclear or high judgements for most domains with particular concerns over lack of blinding within one trial.

Summary of findings 5. Twice daily or more compared to once daily topical corticosteroid

Twice daily or more compared to once daily topical corticosteroid **for people with eczema**

Patient or population: children and adults, most with moderate to severe eczema
Setting: hospital settings in high-income countries
Intervention: twice daily or more topical corticosteroid (TCS)
Comparison: once daily topical corticosteroid (TCS)

Outcomes	**Anticipated absolute effects*** **(95% CI)**	**Relative effect (95% CI)**	№ of participants/**sides treated** (trials)	**Certainty of the evidence (GRADE)**	**Comments**

	Risk with once daily TCS	Risk with twice or more daily TCS			
Clinician-reported signs of eczema: IGA (number with cleared or marked improvement); short term (earliest time point within 1-4 weeks)	Trial population 635 per 1000	628 per 1000 (542 to 706)	OR 0.97 (0.68 to 1.38) indicating similar odds of improvement with twice daily TCS	1970[a] (15 RCTs)	⊕⊕⊕⊖ **Moderate**[b]
Patient-reported symptoms of eczema: PGA (number with cleared or marked improvement); short term (earliest time point within 1-4 weeks)	Trial population 765 per 1000	862 per 1000 (669 to 950)	OR 1.91 (0.62 to 5.83) indicating similar odds of improvement with twice daily TCS	300 (2 RCTs)	⊕⊕⊖⊖ **Low**[c,d]
Local adverse events: skin thinning; end of treatment (2-6 weeks)	10 cases with twice daily use (n = 706) and 10 cases with once daily use (n = 717)[e]			1423[f] (11 RCTs)	⊕⊕⊖⊖ **Low**[g,h]
Systemic adverse events: abnormal cortisol; end of treatment (1-6 weeks)	5 cases with twice daily use (n = 124) and no cases with once daily use (n = 125)			249 (4 RCTs)	⊕⊖⊖⊖ **Very low**[i,j]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IGA:** Investigator Global Assessment; **OR**: odds ratio; **PGA:** Patient Global Assessment; **RCT:** randomised controlled trial; **TCS:** topical corticosteroids

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Actual number of participants = 1821; 1672 from parallel-group trials and 149 from within-participant trials where data from both sides of the same individual were included in the meta-analysis with variance correction (1970 = 1672 + 149 x 2).
[b]Downgraded once for risk of bias: unclear judgements for most domains; high risk from lack of blinding.
[c]Downgraded once for risk of bias: unclear judgements for most domains; high risk from incomplete outcome data.
[d]Downgraded once for inconsistency: unexplained statistical heterogeneity.
[e]Of the 10 cases occurring with twice daily use, eight participants had been treated with a very potent TCS and two had been treated with a moderate-potency TCS. Of the 10 cases occurring with once daily use, eight participants had been treated with a very potent TCS and two had been treated with a second-generation potent TCS. As one trial reporting cases of skin thinning compared twice daily use of a moderate TCS versus once daily use of a potent TCS (Nolting 1991), these cases are also included in Summary of findings 3.
[f]Actual number of participants = 1183; 943 from parallel-group trials and 240 from within-participant trials where data from both sides of the same individual were included (1423 = 943 + 240 x 2).
[g]Downgraded once for risk of bias: unclear judgements for most domains; high risk from lack of blinding and incomplete outcome data.

[h]Downgraded once for imprecision: few events.
[i]Downgraded once for risk of bias: unclear judgements for most domains; high risk from lack of blinding and one trial where allocation was clearly influenced.
[j]Downgraded two levels for imprecision: small number of participants and few events.

Summary of findings 6. Longer-term compared to shorter-term duration of use of topical corticosteroid

Longer- compared to shorter-term duration of use of topical corticosteroid **to induce remission for people with eczema**

Patient or population: adults or children with eczema
Setting: community or hospital settings

Intervention: longer duration of topical corticosteroid use

Comparison: shorter duration of topical corticosteroid use

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with shorter duration	Risk with longer duration				
Clinician-reported signs of eczema	-		-	(0 RCTs)	-	
Patient-reported symptoms of eczema	-		-	(0 RCTs)	-	
Local adverse events	-		-	(0 RCTs)	-	
Systemic adverse events	-		-	(0 RCTs)	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 7. Weekend therapy compared to no topical corticosteroid

Weekend therapy compared to no topical corticosteroid**/reactive application for people with eczema** (for flare prevention following a two- to four-week stabilisation phase)

Patient or population: children and adults with mild to severe eczema
Setting: community and outpatient settings in high- and middle-income countries
Intervention: weekend therapy with topical corticosteroid (TCS)
Comparison: no topical corticosteroid (TCS)/reactive application

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants/sides treated (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with no TCS/reactive application	Risk with weekend therapy				
Clinician-reported signs of eczema: number of participants with one or more relapses (16-20 weeks)	Trial population		RR 0.43 (0.32 to 0.57) indicating lower risk of relapse with weekend therapy	1149 (7 RCTs)	⊕⊕⊕⊖ **Moderate**[a,b]	
	576 per 1000	248 per 1000 (184 to 328)				
Patient-reported symptoms of eczema: PGA (number judging excellent/good); end of treatment (20 weeks + 4 weeks acute phase)	322 per 1000	725 per 1000 (551 to 953)	RR 2.25 (1.71, 2.96) indicating higher chance of excellent or good responses with weekend therapy	343 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	
Local adverse events: skin thinning; end of treatment (16-20 weeks + 2-4 weeks acute phase)	No new cases with weekend therapy (n = 572) or no TCS (n = 478)			1050 (7 RCTs)	⊕⊕⊖⊖ **Low**[a,c]	1 RCT (n = 30) treated participants for up to 12 months
Systemic adverse events: abnormal cortisol; end of treatment (16 weeks + 4 weeks acute phase)	Although 5 trials measured cortisol levels, we could not calculate a combined total number of events, as either the number of cases or the number of participants tested was unclear			(5 RCTs)	⊕⊖⊖⊖ **Very low**[a,d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IGA:** Investigator Global Assessment; **OR**: odds ratio; **PGA:** Patient Global Assessment; **RCT:** randomised controlled trial; **TCS:** topical corticosteroids

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded once for risk of bias: unclear judgements for most domains.
[b]I^2 statistic = 67% for number of relapses and 0% for time to relapse; visual inspection shows consistency, so we have not downgraded this.
[c]Downgraded once for imprecision: no events.
[d]Downgraded two levels for imprecision: unclear numbers of participants and events.

BACKGROUND

Description of the condition

Eczema (also called 'atopic dermatitis' or 'atopic eczema') is a chronic inflammatory skin condition, characterised by dry skin with itchy patches, which typically fluctuates between periods of remission and flares. Eczema often occurs concurrently with atopic diseases including asthma, allergic rhinitis/hay fever and food allergy. These diseases share a common pathogenesis, and frequently present together in the same individual and family. 'Atopy' refers to the genetic tendency to produce immunoglobulin E (IgE; see: Table 1 for abbreviations) antibodies in response to small amounts of common environmental proteins such as pollen, house dust mite, and food allergens (Stone 2002; Thomsen 2015). Around 30% of people with eczema develop asthma and 35% develop allergic rhinitis (Luoma 1983). However, it is known that atopy does not concurrently occur in all people with atopic eczema. In view of this, there have been recent proposals to use the term 'eczema' to define people both with and without atopy. In agreement with the 'Revised nomenclature for allergy for global use' (Johansson 2004), and for consistency with other Cochrane Reviews that evaluate eczema therapies (Van Zuuren 2017), we will use the term 'eczema' throughout the review.

Eczema is a common condition throughout the world affecting approximately one in five children, and up to 5% of adults (Barbarot 2018; Odhiambo 2009). The incidence of eczema is highest in the first year of life and can often resolve during childhood (Ban 2018; Kim 2016). However, a recent review has shown that persistence into adolescence and early adulthood may be more common than previously thought, particularly for those with persistent and severe disease or late onset disease (Abuabara 2018).

Eczema can have a significant impact on quality of life (Eckert 2017); and there is a high burden associated with eczema when compared to other skin diseases (Hay 2014). Both the individual and their family can be affected by the disease through factors including disturbed sleep due to itching and scratching, time off work or school for frequent visits to healthcare professionals, restrictions to daily activities, and the need to apply daily, time-consuming treatments (Drucker 2016; Eckert 2018).

Clinical features

Eczema may be acute (short and severe) with weeping vesicles on red, swollen skin, or it may be chronic (long-term) with inflammation, lichenification (thickening of the skin caused by repeated rubbing or scratching), excoriation (abrasion because of rubbing or scratching), hyperpigmentation, and exaggerated surface markings (Weidinger 2016). The typical distribution and type of lesions vary during different stages of life and between different ethnicities. In infants, the extremities and face are usually affected. By around two years of age, lesions mainly appear on the limbs, particularly in the creases of the elbows and knees, as well as the neck, wrists, and ankles. In adulthood, the lesions can become more widespread than those seen in childhood (Bieber 2008a).

The severity of eczema can vary enormously, ranging from dry skin with the occasional itchy inflamed patch, to involvement of the whole body with secondary infections. The course of eczema may also vary from a relapsing-remitting one affecting a few areas recurrently to a continuous one with prolonged periods of inflamed skin covering most of the body (Berke 2012). Itching can induce a vicious cycle of scratching, leading to skin damage, which in turn causes itchiness—often referred to as the 'itch-scratch cycle' (Pavlis 2017).

Treatment of eczema

There is currently no cure for eczema, so the treatment goal is control of the disease using the wide range of treatments available including emollients (NICE 2007; SIGN 2011). First-line therapy is the daily application of emollients combined with anti-inflammatory therapy. The most commonly used anti-inflammatory therapy is topical corticosteroids, but topical calcineurin inhibitors are also used. These can be combined with bandages and phototherapy for those who do not respond sufficiently to topical treatment alone. Severe eczema may require systemic treatments such as oral ciclosporin, methotrexate or azathioprine. New biologic agents such as dupilumab are now available for cases of eczema that do not respond to other systemic treatments (Snast 2018). Although topical corticosteroids have been the mainstay of eczema treatment for over 60 years, there are still many unanswered questions about how best to use them (Batchelor 2013).

Description of the intervention

Topical corticosteroids were first introduced in the 1950s when topical hydrocortisone was found to improve various dermatoses (Sulzberger 1952). Since then, a huge number of topical corticosteroids of increased potency have been developed, and are available in various formulations such as creams and ointments. Mometasone furoate is one of the newer generation of products developed with the intention of producing a safer, potent topical corticosteroid (Prakash 1998). Topical corticosteroids are all classified by their potency from mild through to very potent, although the classification of potency varies around the world (British National Formulary 2018; WHO 1997). The choice of potency to be used is based on age, body site to be treated and severity of eczema. Low- to moderate-potency topical corticosteroids are usually sufficient for mild eczema and are also used on sensitive skin such as the face and flexural areas. Potent or very potent topical corticosteroids are usually used in severe, thick eczematous plaques over thicker skin sites, such as limbs and palmoplantar surfaces. The advice is to use topical corticosteroids, of appropriate potency, once a day until the eczema is controlled, then 'as required' (NICE 2007).

Local side effects of topical corticosteroids include the possibility of skin atrophy (skin thinning), striae (stretch marks) and purpura (discolouration). To a degree, thinning can be a desirable effect of topical corticosteroid use in restoring abnormally thickened eczematous skin. Abnormal skin thinning, however, can lead to bruising, tearing, and small blood vessels becoming more visible. It has been reported that the skin can recover once topical corticosteroids are stopped (Eichenfield 2014b). Systemic side effects include hypothalamic pituitary axis suppression and growth suppression (Callen 2007). Skin thinning and effects on growth and development have been reported to be the main concerns amongst people using topical corticosteroids (Li 2017). Side effects of topical corticosteroids are thought to be rare in usual practice and are more likely to occur if topical corticosteroids have been used inappropriately, such as continuous use or if potent corticosteroids are applied to areas with high permeability,

such as eyelids (Callen 2007; Nankervis 2016). This inappropriate use could lead to systemic side effects such as hypothalamic pituitary axis suppression or hyperglycaemia (Gilbertson 1998). But, despite their relative safety, concerns and confusion about the use of topical corticosteroids amongst people with eczema and the healthcare professionals who treat them are widespread. Negative beliefs about the use of topical corticosteroids are thought to contribute to poor treatment adherence (Aubert-Wastiaux 2011; Li 2017; Teasdale 2017).

How the intervention might work

Topical corticosteroids have traditionally been used reactively (in response to a worsening of the eczema) to control inflammation under the skin. They work by reducing skin inflammation by acting on a number of inflammatory pathways. They bind to glucocorticoid intracellular receptors, which then results in a number of anti-inflammatory actions. These include inhibition of phospholipase A2 activity, resulting in reduced production of lipid mediators; inhibition of cyclo-oxygenase induction, causing decreased prostaglandin production; inhibition of nitric oxide synthase production; inhibition of cytokine, causing suppression of cell-mediated inflammation; inhibition of mast cell activity, resulting in decreased levels of mast cell inflammatory mediators; and vasoconstriction (local blood flow reduction; Ahluwalia 1998).

A number of different ways (or 'strategies') of using topical corticosteroids for treating eczema have been proposed. Proactive use of topical corticosteroids for two days per week between flares is thought to help to prevent eczema flares and therefore reduce the need for more intense periods of topical corticosteroid use to treat flares, which may be associated with an increase in adverse events (Schmitt 2011). Applying topical corticosteroids to wet skin after bathing or use of wet wraps may increase penetration through the skin and increase delivery of the cream or ointment into the upper layers, thus increasing efficacy of the topical corticosteroid (González-López 2017; Kohn 2016). Topical calcineurin inhibitors (pimecrolimus or tacrolimus) can be used instead of topical corticosteroids and a strategy of alternating between these two treatments may be as effective as using topical corticosteroids alone, but may reduce the adverse events associated with topical corticosteroids, such as skin thinning (Broeders 2016).

Some strategies aim to reduce adverse events whilst increasing or maintaining effectiveness of the topical corticosteroid. Applying topical corticosteroids once daily may be as effective as two or more times a day but may reduce the likelihood of adverse events occurring (Green 2004). Another strategy Is to use different potency topical corticosteroids, possibly combined with different duration of use, such as a more potent topical corticosteroid for a shorter period compared to milder potency topical corticosteroids for a longer duration. This reduces the length of time the topical corticosteroid would be used although more potent topical corticosteroids may be associated with increased adverse events (Thomas 2002).

Since topical corticosteroids are used with emollients, other proposed strategies concern the combined use of these two treatments, such as the order in which the treatments are applied and the optimum time lapse between application of each treatment. Current guidance in the UK from the National Health Service (NHS) is to apply emollients first then wait for 30 minutes before applying the topical corticosteroid for maximal benefit (NHS 2019). Additionally, different preparations of topical corticosteroids (e.g. ointments, creams) have been developed to increase the efficacy; and different concentrations (e.g. hydrocortisone 0.5% versus 2.5%). More recently, 'second-generation' once daily topical corticosteroids (mometasone furoate and fluticasone propionate) have been proposed as a safer and effective alternative to the older topical corticosteroid preparations (Bieber 2008b).

Why it is important to do this review

It is well established that some patients, parents and clinicians have considerable concerns about using topical corticosteroids for treating eczema (Charman 2000; Li 2017; Teasdale 2017). As a result, topical corticosteroids are often under-used in Western countries, resulting in poorly controlled disease (Lundin 2018). Conversely, in other areas of the world, such as India, potent topical corticosteroid use is often unregulated and patients are able to obtain these steroids over the counter. Subsequent inappropriate use of potent topical corticosteroids can lead to an increase in adverse events (Coondoo 2014).

This situation is exacerbated by the lack of clarity as to how the different ways of using topical corticosteroids — such as once-a-day or twice-a-day application, increasing topical corticosteroid potency in response to a flare, or twice-a-week use to proactively prevent flares — affect both effectiveness and safety profile. The British National Formulary (BNF) provides little reassurance, describing adrenal suppression as rare but providing no quantification of other side effects (British National Formulary 2018). Concerns and uncertainties around topical corticosteroids were highlighted in the James Lind Alliance Priority Setting Partnership for eczema, in which the following two topics relating to topical corticosteroid safety were identified by patients and healthcare professionals as priority areas for research (Batchelor 2013).

- “What is the best and safest way of using topical corticosteroids?”
- “What is the long-term safety of topical corticosteroids?”

This comprehensive systematic review is needed to summarise the available evidence on the effectiveness and safety of different ways of using topical corticosteroids to support patients and clinicians in making informed treatment choices. However, since most eczema trials have a relatively short follow-up, this review will primarily address the first of these two questions.

The strategies included in this review will refer to different methods of using topical corticosteroids to improve effectiveness or safety, or both, and hence achieve the best outcomes for patients. A strategy may aim to improve the long-term control of eczema, for example, in the case of proactive topical corticosteroid treatment. This strategy involves weekly application of topical corticosteroid, for two consecutive days, to previously affected or new sites of eczema, to reduce the risk of flares (Schmitt 2011). Alternatively, a strategy such as reducing the frequency of application may be designed to improve the safety of the drug whilst maintaining effectiveness (Green 2004; Williams 2007).

This review forms part of a body of work funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research (grant no: RP-PG-0216-20007) to develop an online behavioural intervention to support self-care of eczema in children,

adolescents and young adults (Eczema Care Online, ECO), and the findings will contribute to development of the intervention by providing data on the best and safest ways to use topical corticosteroids.

This review will be complemented by another ongoing Cochrane Review, which will incorporate a network meta-analysis: 'Topical treatments for eczema: a network meta-analysis' The ongoing Cochrane Review will compare topical corticosteroids to other topical treatments, such as topical calcineurin inhibitors.

OBJECTIVES

To establish the effectiveness and safety of different ways of using topical corticosteroids in people with eczema.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) where randomisation is at any level (including cluster and within-participant trials).

Types of participants

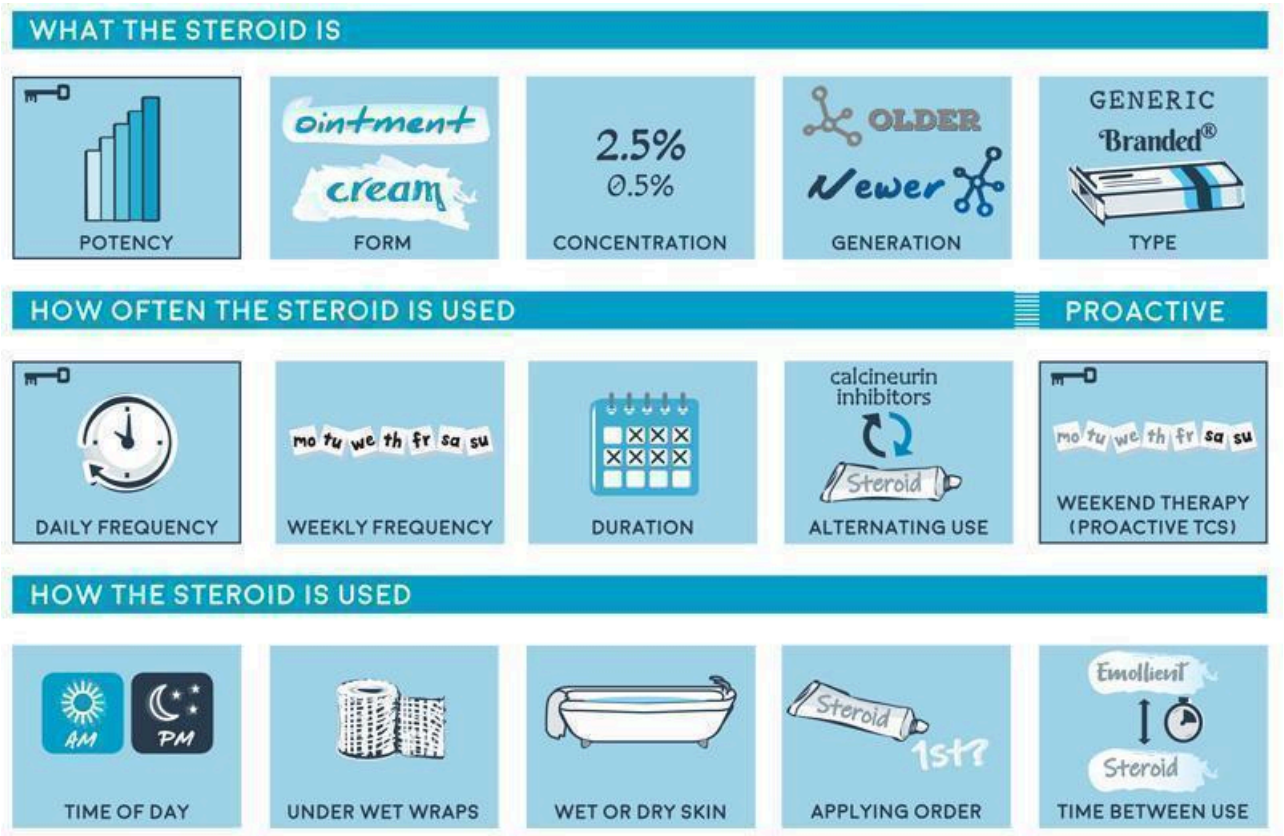
Participants of any age and gender with a diagnosis of eczema (also known as atopic dermatitis or atopic eczema) of any severity by a healthcare professional, or using established diagnostic criteria for eczema, e.g., the standardised diagnostic criteria of Hanifin and Rajka (Hanifin 1980) or the UK Working Party diagnostic criteria for atopic dermatitis (Williams 1994). We also accepted modified versions of standard diagnostic criteria. Where it was unclear whether a trial included participants with atopic eczema, a senior clinician (HCW) made a judgement as to whether the trial was to be included. This was primarily based upon the pattern of symptoms described in the paper.

We included trials that included participants with other types of eczema such as contact dermatitis, varicose eczema, and seborrhoeic eczema, or other inflammatory or 'steroid-responsive' skin conditions such as psoriasis, only if the trial also included people with eczema and the data were reported separately.

Types of interventions

The intervention was any topical corticosteroid of any preparation and potency in a trial where one strategy of using the topical corticosteroid was compared to a different strategy. This included the following strategies (see Figure 1).

Figure 1. Overview of strategies included in the review. Figure created by Dr Natasha Rogers, Centre of Evidence Based Dermatology, University of Nottingham



Which topical corticosteroid to use?

- Stronger-potency topical corticosteroid versus weaker-potency topical corticosteroid
  - Moderate- versus mild-potency topical corticosteroid
  - Potent versus mild-potency topical corticosteroid
  - Potent versus moderate-potency topical corticosteroid
  - Very potent versus potent topical corticosteroid
- Topical corticosteroid cream versus topical corticosteroid ointment
- Different concentrations of the same topical corticosteroid
- Second-generation topical corticosteroid (mometasone furoate and fluticasone propionate) versus older topical corticosteroid
- Branded topical corticosteroid versus generic topical corticosteroid

How often to apply topical corticosteroid?

- Twice or more versus once daily application of topical corticosteroid
- Daily application versus less frequent application per week
- Longer- (more than seven days) versus shorter-term (7 days) duration of use for induction of remission
- Topical corticosteroid alternating with topical calcineurin inhibitor versus topical corticosteroid alone
- Weekend therapy (proactive topical corticosteroid) versus no proactive topical corticosteroid (e.g. twice per week versus 'as required')

How to use the topical corticosteroid?

- Timing of application of topical corticosteroid
- Wet wrap versus no wet wrap
- Topical corticosteroid applied to wet versus dry skin
- Topical corticosteroid applied before emollient versus topical corticosteroid applied after emollient
- Time between application of emollient and steroid

We also included combinations of any of the strategies above (e.g. short burst of potent topical corticosteroids versus longer duration of mild topical corticosteroids).

Since the focus of this review was to compare different strategies of using topical corticosteroids, we excluded the following comparisons.

- Topical corticosteroid compared with either no treatment, vehicle or placebo (unless it was specifically assessing an alternative regimen such as weekend (proactive) therapy)
- Topical corticosteroid compared with another topical corticosteroid of the same potency and preparation but no differences in how they were used. We developed a hierarchy of sources to assign potency to each topical corticosteroid (Table 2). Potencies were most frequently determined using the British National Formulary 2018 and WHO 1997. If we could not establish the potency using these sources, we reviewed regional guidelines and the wider scientific literature, and consulted regional experts until we could reach a decision.
- Topical corticosteroid compared with different topical treatments such as calcineurin inhibitors or emollients
- Topical corticosteroid compared with systemic treatments
- Topical corticosteroid treatment in conjunction with an eczema treatment used for the most severe cases of eczema as defined by The National Institute for Health and Care Excellence (NICE); that is, phototherapy and systemic therapy (NICE 2018). This was because it would have been difficult to detect any differences in efficacy or safety between the topical corticosteroid strategies when such treatments were also used.

Types of outcome measures

We assessed both effectiveness and safety to reflect the overall aim of this review.

The effectiveness outcomes of interest for this review were focused on the two domains for which the international Harmonizing Outcome Measures for Eczema (HOME) initiative recommended core outcome measurement instruments, that is, clinician-reported signs and patient-reported symptoms of eczema (HOME).

There is currently no agreed standardised timing for effectiveness outcome assessments for eczema trials. Therefore, to assess treatment effects in a consistent way, we focused on short-term effectiveness outcomes reported between one and four weeks (taking the earliest available time point within that range), medium-term effectiveness outcomes between 12 and 16 weeks (taking the closest time point to 12 weeks), and long-term effectiveness as the longest time point longer than 16 weeks.

We also reported outcomes at baseline, end of treatment, and end of follow-up regardless of timing. We attempted to pool data at similar time points where possible.

Because many different instruments are used to assess effectiveness of treatments for eczema (Schmitt 2007), we used a hierarchical approach in which we initially extracted data from one instrument per outcome based on the priority order described below. We also made a note of the other instruments reported to maximise our ability to summarise data in pooled analyses of lower-priority instruments. We planned to compare effect sizes against minimal clinically important differences (MCID) from the literature where possible.

Throughout this review, we used the term 'effectiveness' to describe both 'efficacy' and 'effectiveness'. In many trials it was unclear whether the trial was primarily assessing efficacy or effectiveness and we preferred to avoid making inappropriate judgements.

Safety outcomes of interest reflected the side effects of topical corticosteroids. We defined 'relevant' adverse events as those previously identified as being of particular concern to patients (Li 2017), the side effects listed in the Summary of Product Characteristics for topical corticosteroids used to treat eczema, and original data submissions from the Eczema Priority Setting Partnership, outlining patients' and clinicians' concerns about the safety of topical corticosteroids (Batchelor 2013). We reported data on individual relevant adverse events and their relatedness to the trial drug where available. Where outcomes were assessed during post-treatment follow-up, we only included data where participants are retained in their randomised groups. We did not use long-term safety data from cross-over or within-participant trials due to the high likelihood of contamination.

For safety data, we reported adverse events at the end of treatment and the end of follow-up (where specified).

Primary outcomes

Two primary outcomes were included — effectiveness (clinician-reported signs of eczema) and safety — to reflect the overall aim of this review.

- Changes in clinician-reported signs of eczema (effectiveness). We extracted data based on the following priority order of instruments.
  - Eczema Area and Severity Index (EASI) – this is the HOME-recommended core outcome measurement instrument for clinician-reported signs of eczema (Hanifin 2001; Schmitt 2014).
  - Objective SCORing Atopic Dermatitis (ObjSCORAD) – measures similar aspects of the disease to EASI (Kunz 1997; Oranje 2007)
  - SCORing Atopic Dermatitis (SCORAD) – objective SCORAD plus itch and sleep loss (Kunz 1997; Oranje 2007)
  - Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score (Berth-Jones 1996)
  - Three Item Severity score (TIS) (Oranje 2007; Willemsen 2009; Wolkerstorfer 1999)
  - Investigator Global Assessment (IGA) – no validated instrument and little consistency between trials but commonly included (Futamura 2016)
  - Any other instruments
- Number of relevant local adverse events (safety). This included skin thinning, striae, telangiectasia, aging/wrinkling, changes in skin colour, sensitisation, skin bleaching, worsening or induction of acne, skin infections, folliculitis, perioral/periocular dermatitis, and application site reactions such as burning sensation/stinging. We only included local site reactions that resemble symptoms of eczema (e.g. itching), where they were indicated to be adverse events by the authors of the included trials. In our analyses, our primary focus was on the number of participants with at least one adverse event where this was possible (see: Measures of treatment effect).

Secondary outcomes

- Patient-reported symptoms of eczema (effectiveness). We extracted data based on the following priority order of instruments.
  - Patient-Oriented Eczema Measure (POEM) – recommended core instrument by HOME for the patient-reported symptoms of eczema (Charman 2004 Spuls 2017).
  - Patient-Oriented SCORAD (PO-SCORAD) (Vourc'h-Jourdain 2009)
  - Sleep and itch scales, as measured by Visual Analogue Scales (VAS) or Numerical Rating Scales (NRS)
  - Self-Administered EASI (SA-EASI) (Housman 2002)
  - Patient Global Assessment (PGA) – no validated instrument and little consistency between trials
  - Any other instruments
- Number of relevant systemic adverse events (safety). This included bone problems, impact on growth and development, effects on endocrine system, eye problems, and cancer. In our analyses, our primary focus was on the number of participants with at least one adverse event where this was possible (see: Measures of treatment effect).

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist searched the following databases up to 28 January 2021 using strategies based on the draft strategy for MEDLINE in our published protocol (Chalmers 2019).

- the Cochrane Skin Specialised Register (Cochrane Skin Specialised Register 2021) using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL); 2021, Issue 1, in the Cochrane Library using the strategy in Appendix 2;
- MEDLINE via Ovid (from 1946 onwards) using the strategy in Appendix 3; and
- Embase via Ovid (from 1974 onwards) using the strategy in Appendix 4.

We accessed the GREAT database (**G**lobal **R**esource for **E**czem**A** **T**rials (Centre of Evidence Based Dermatology) at www.greatdatabase.org.uk on 19 July 2018 (browsed to the Topical corticosteroids section and exported all relevant records). GREAT has not been updated since 2017 so we did not undertake any further searches of this database.

Trials registers

We (EA) searched the following trials registers using the search terms 'eczema' and 'atopic dermatitis'.

- ClinicalTrials.gov (www.clinicaltrials.gov) searched to 28 January 2021;
- The World Health Organization International Clinical Trials Registry Platform (ICTRP; trialsearch.who.int/) searched to 21 November 2018. It was unavailable in January 2021 so we were unable to update the search.

We searched the following three registries to 21 November 2018. We did not identify any unique records, therefore we did not search them when we updated our searches in January 2021.

- The ISRCTN register (www.isrctn.com);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au); and
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

Searching reference lists

We checked the bibliographies of included trials and any relevant systematic reviews identified for further references to relevant trials.

Correspondence with trial authors

We contacted trial authors for clarification and further data if trial reports were unclear (Table 3).

Correspondence with pharmaceutical companies

We emailed all of the pharmaceutical companies listed as manufacturers of topical corticosteroids in the British National Formulary 2020. Correspondence with pharmaceutical companies is listed in Table 4.

Correspondence with regulatory agencies

We contacted the Medicines and Healthcare products Regulatory Agency (MHRA) to request Public Assessment Reports prior to 2005; none were available. We checked the MHRA website for Public Assessment Reports published for topical corticosteroids after 2005; none were identified.

Adverse effects

We did not perform a separate search for adverse effects of the target interventions. We considered adverse effects described in included trials only.

Data collection and analysis

We used Covidence systematic review software to screen and manage the references, and a Microsoft Access database (designed by SJL; piloted by SJL, JH and EA) to record the data extracted from the included trials.

Selection of studies

Two review authors (of EA, JH and SJL) independently screened the titles and abstracts of each record identified in the searches. If a trial met our inclusion criteria, we analysed the full text to confirm its inclusion. A third review author (JRC or HCW) resolved any disagreement. We recorded reasons for exclusions in Characteristics of excluded studies. We presented the process of trial selection in a PRISMA flow diagram (Page 2021).

Data extraction and management

Two review authors (of EA, JH, LJH and SJL) independently extracted data from each included trial using a data extraction form. We piloted and modified the form, as necessary. We extracted the following data.

- Trial population (e.g. inclusion criteria, setting/country, severity of eczema, age, gender, ethnicity)
- Trial methods (e.g. trial design, blinding methods, funding source)
- Interventions and comparators (e.g. treatment name, frequency of use)
- Primary and secondary outcomes (including time points – both during treatment and during follow-up)

We entered trial characteristics into a Characteristics of included studies table and we analysed or narratively described extracted outcome data. We resolved any disagreements during the data extraction phase through discussion with a third review author (JRC or HCW).

We included multiple reports of a trial but chose a primary reference and listed the others as secondary references. In some cases, we included more than one trial from one publication. It should also be noted that, for trials with more than two arms, the arms appear as more than one instance of the same trial, enabling all the relevant data to be included in the review, taking care to avoid double counting.

We translated non-English language papers using Google Translate or asked a native speaker. If there were any serious ambiguities identified using Google Translate we consulted a native speaker.

We also extracted trial characteristics for ongoing trials to produce a Characteristics of ongoing studies table. We described trials awaiting classification in as much detail as possible in the Characteristics of studies awaiting classification where there was not enough information available for us to include or exclude the trial in the review.

Assessment of risk of bias in included studies

Two authors (of EA, JH, LJH and SJL) independently assessed the risk of bias of each included trial using the Cochrane risk of bias tool (RoB 1; Higgins 2011). We assessed the following domains.

- Selection bias (random sequence generation and allocation concealment)
- Performance bias (blinding of participants and trial personnel)
- Detection bias (blinding of outcome assessment)
- Attrition bias (completeness of data, missing data and losses to follow-up, intention-to-treat principle)
- Reporting bias (selective reporting of outcomes, assessed via comparing with the trial's protocol or clinical trial register entry)
- Other bias (including design-specific risks of bias, baseline imbalance, contamination, fraud, selective reporting of subgroups)

We assessed each domain as low, unclear or high risk of bias. We resolved disagreements by discussion with a third review author (JRC). We presented a risk of bias graph (Figure 2) and risk of bias summary figure (Figure 3) in the review.

Figure 2. Risk of bias graph: percentage of studies for which review authors' judgements were low, unclear, and high risk of bias by domain

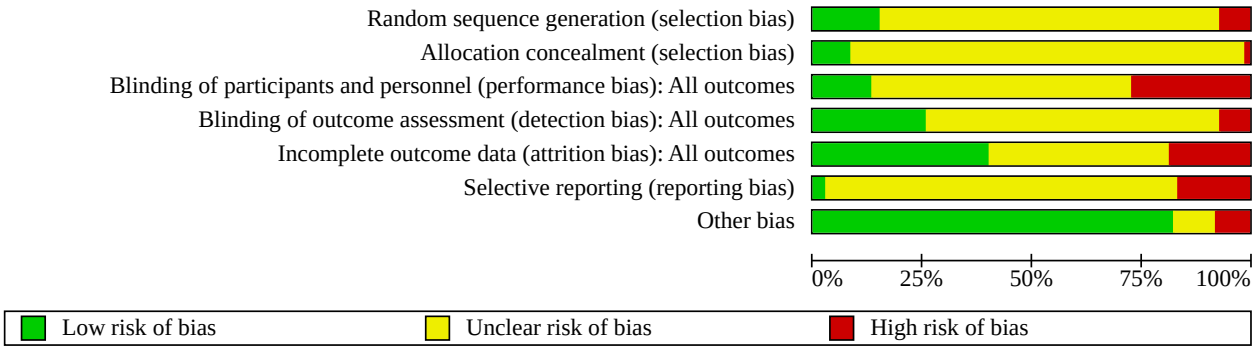


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

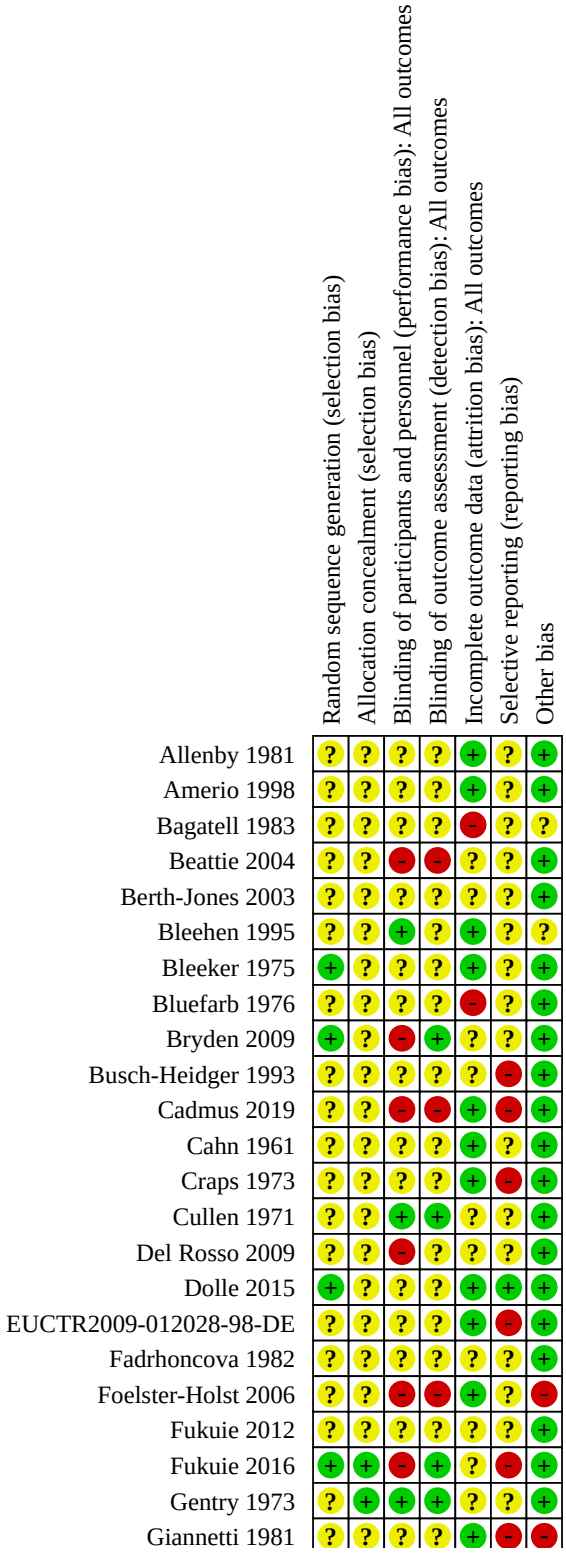


Figure 3. (Continued)

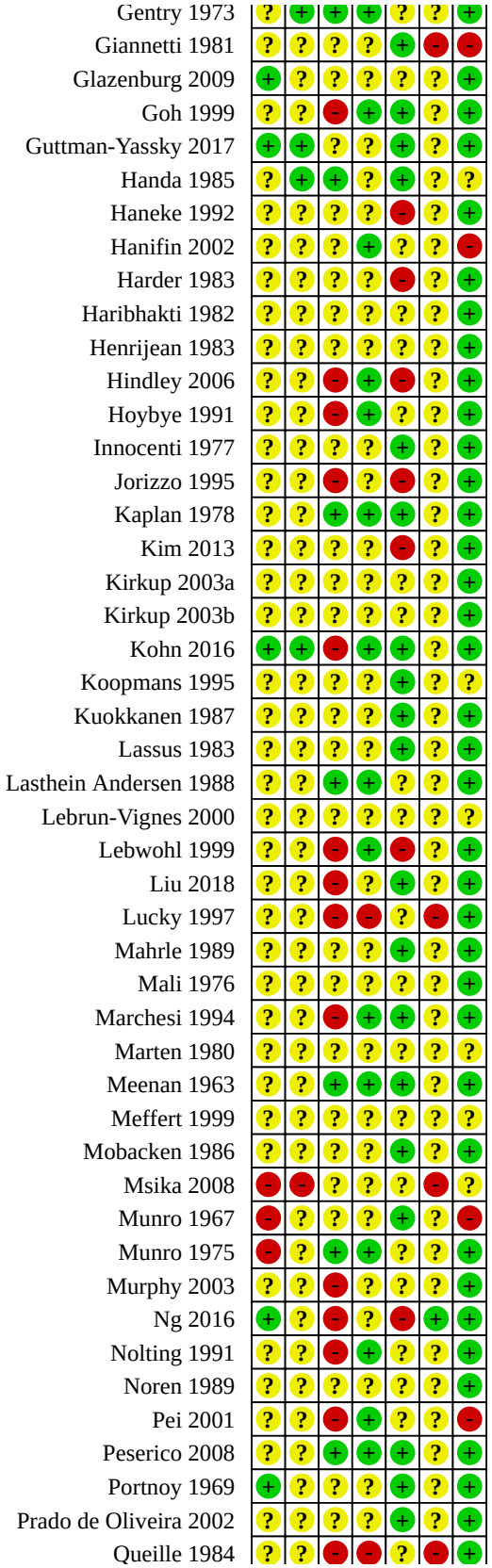
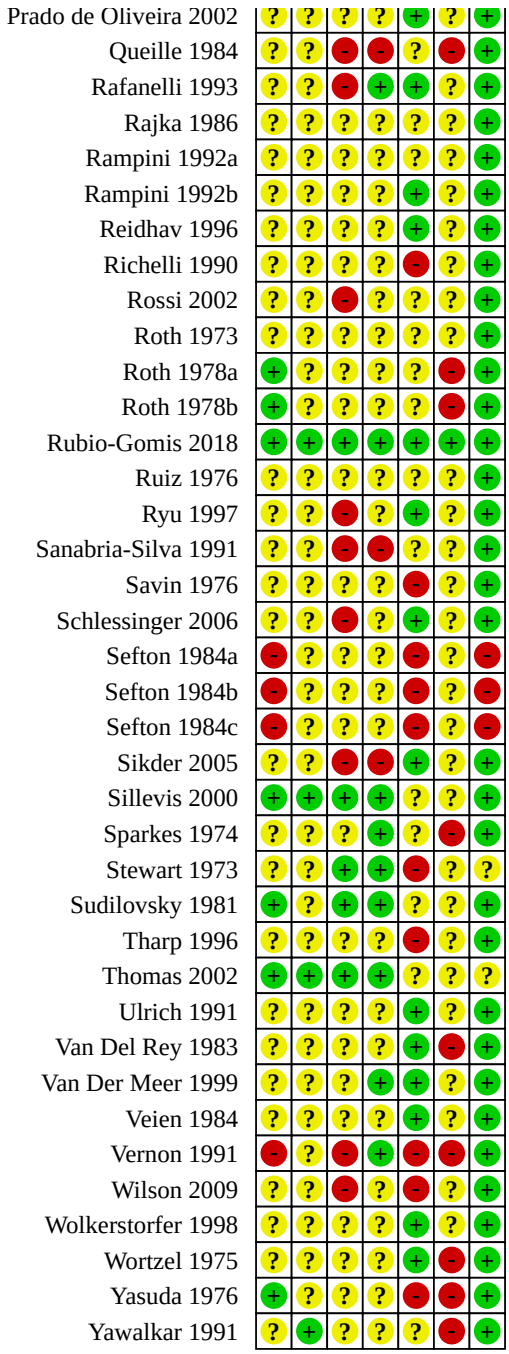


Figure 3. (Continued)



Measures of treatment effect

Many of our pooled analyses required a generic inverse variance (GIV) approach to enable parallel-group and within-participant trials to be pooled alongside one another. Therefore, we reported dichotomous data as odds ratios (OR) with associated 95% confidence intervals (CI). One exception was the weekend therapy comparison where we reported relapse risk as a risk ratio to extend the previous meta-analysis by Schmitt 2011.

We reported continuous data as mean differences (MD) with associated 95% confidence intervals (CIs), where trials used the same scale to measure an outcome. Where appropriate, we used a standardised mean difference (SMD) and associated 95% CI when trials used different instruments to measure effectiveness outcomes (i.e. clinician-reported signs and patient-reported symptoms).

Where trials reported time-to-relapse data based on a measure of effectiveness (e.g. EASI), we extracted hazard ratios (HR) from the trial reports. We pooled log-rank and Cox model estimates

using the GIV approach according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

For adverse event data, we reported the number of participants who experienced an event within the intervention and the control group, unless specified otherwise. We could not pool these data due to the low number of events. When judging whether a participant was deemed to have cortisol levels out of range, in the first instance we accepted what the trial report stated as the number of participants outside of the normal range whether they reported their reference range or not. If the trial did not tell us how many participants were deemed to be outside the normal range but did tell us cortisol test results, we used guidelines (referenced) to classify the participants. A clinical member of the author team reviewed these decisions.

We include contact with trial authors, where published data were ambiguous, in Table 3.

Unit of analysis issues

The unit of analysis was primarily the individual participant. To enable within-participant trials to be pooled alongside parallel-group trials we performed variance corrections using the Becker-Balagtas method (Elbourne 2002). We assumed an intra-class correlation coefficient (ICC) of 0.5 in our calculations, but also undertook sensitivity analyses using 0.25 and 0.75 to explore this choice (see Table 5). We used a continuity correction of 0.5 in the case of zero events (Sweeting 2004).

For within-participant trials where body parts received different interventions, we did not extract data on outcomes that affect the whole body (e.g. systemic adverse events), as it was not possible to determine which treatment caused the event.

For trials that included multiple intervention groups, we analysed each intervention group versus a comparator in a separate analysis, or combined groups to create a single pairwise comparison, if clinically appropriate (Higgins 2021a).

In order to generate clear summary statistics, where trials reported several signs of skin thinning, for example, telangiectasia, transparency, and thinning itself, we only collated the numbers of participants stated to have skin thinning. This was to avoid double counting.

For cross-over trials, we planned to only use data from the first part of the trial or to narratively describe the results. We had also planned to only meta-analyse cluster-RCTs with parallel RCTs if the data reported in the trial publication had been correctly analysed, taking into account the number of clusters, or if appropriate, estimating the intracluster correlation coefficient (Higgins 2021b). However, we did not meta-analyse any cluster or cross-over trials in the review.

Dealing with missing data

Where possible we conducted an intention-to-treat analysis, including all randomised participants where data were provided. If data were missing, we contacted trial authors and produced a table in the review detailing such contact (e.g. dates, information requested, whether they replied; Table 3). If it was not possible to obtain clarification, we discussed whether to assume the number randomised or an otherwise similarly sensible estimate. We have indicated clearly where we have done this, or we have reported the ambiguous data narratively.

We conducted sensitivity analyses, removing trials at high risk of attrition bias (see Table 6) and we also considered attrition bias when undertaking our quality assessments (Schünemann 2013).

For dichotomous data, we performed any calculations necessary to pool data divided by a similar threshold, for example, we combined results from multiple subclasses, or calculated exact numbers from reported percentages (rounding sensibly).

For continuous data, we attempted to calculate any missing statistics (e.g. standard deviations) using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). Where it was necessary to assume an ICC of 0.5 in our calculations we undertook sensitivity analyses using 0.25 and 0.75 to explore this choice (see: Table 7).

For time to event data, we performed calculations of missing HR from the statistics that were available according to Parmar 1998.

Assessment of heterogeneity

When pooling trials in a meta-analysis, we considered any methodological and clinical differences between trials, and only included trials in the same meta-analysis where it was considered appropriate. We assessed heterogeneity through forest plot inspection and the I^2 statistic (Higgins 2003), using the thresholds defined in the *Cochrane Handbook for Systematic Reviews of Interventions:* 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% represents considerable heterogeneity (Deeks 2021). If we identified substantial or considerable statistical heterogeneity, we attempted to determine reasons for this by examining the trial characteristics and performing subgroup and sensitivity analyses where appropriate.

Assessment of reporting biases

If we included 10 or more trials in a meta-analysis, we produced a funnel plot to explore publication bias (Sterne 2011). We described suspected reporting biases narratively and their potential effects on the overall results and conclusions.

Data synthesis

We narratively synthesised outcome data and conducted meta-analysis (where appropriate) in Review Manager 5.4, using the random-effects model (Review Manager 2020). We used the GIV model for meta-analyses, which included within-participant trials and displayed the effect sizes as ORs. We presented effect estimates, with 95% CIs and associated I^2 statistic and P values, for all pooled synthesis. For dichotomous outcomes, where a statistical evidence of an effect is reported we calculated an associated number needed to treat for an additional beneficial outcome (with associated 95% CIs).

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses.

- Children versus adults

- Anatomical site, for example, topical corticosteroid applied to sensitive sites (face/genitals) versus other body sites
- Baseline severity of eczema (mild disease versus moderate and severe, as specified in the trial report)

If there was substantial statistical heterogeneity (via forest plot inspection and using the I^2 statistic), we investigated additional clinical and methodological differences. Clinical differences could have included filaggrin (FLG) mutation status, age subgroups of children (0 to 4, 5 to 11, and 11+ years), chronic versus acute disease, and body surface area affected.

Sensitivity analysis

We performed a sensitivity analysis removing trials at high risk of bias from the meta-analysis (Table 6). We also performed sensitivity analyses where necessary, where we made assumptions or imputed data.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables for our main comparisons. We selected the following four most relevant and important comparisons, from both clinician and patient perspectives, to be included in the summary of findings tables.

- Stronger potency versus weaker potency for treatment of eczema flare-ups
- Twice daily versus once daily application for treatment of eczema flare-ups
- Longer- versus shorter-term application for induction of remission
- Twice weekly application to prevent relapse (weekend therapy) versus no application

We included both primary outcomes and secondary outcomes in each summary of findings table. We used the GRADE approach to assess the certainty of evidence for each primary and secondary outcome for our main comparisons. GRADE includes the assessment of five factors: trial limitations (risk of bias); inconsistency of results; indirectness of evidence; imprecision; and publication bias (Schünemann 2013). Each outcome can be downgraded by one or two levels for each domain, and we classed the overall certainty as high, moderate, low or very low. We used GRADEpro GDT to create our summary of findings tables and undertake our GRADE assessments.

RESULTS

Description of studies

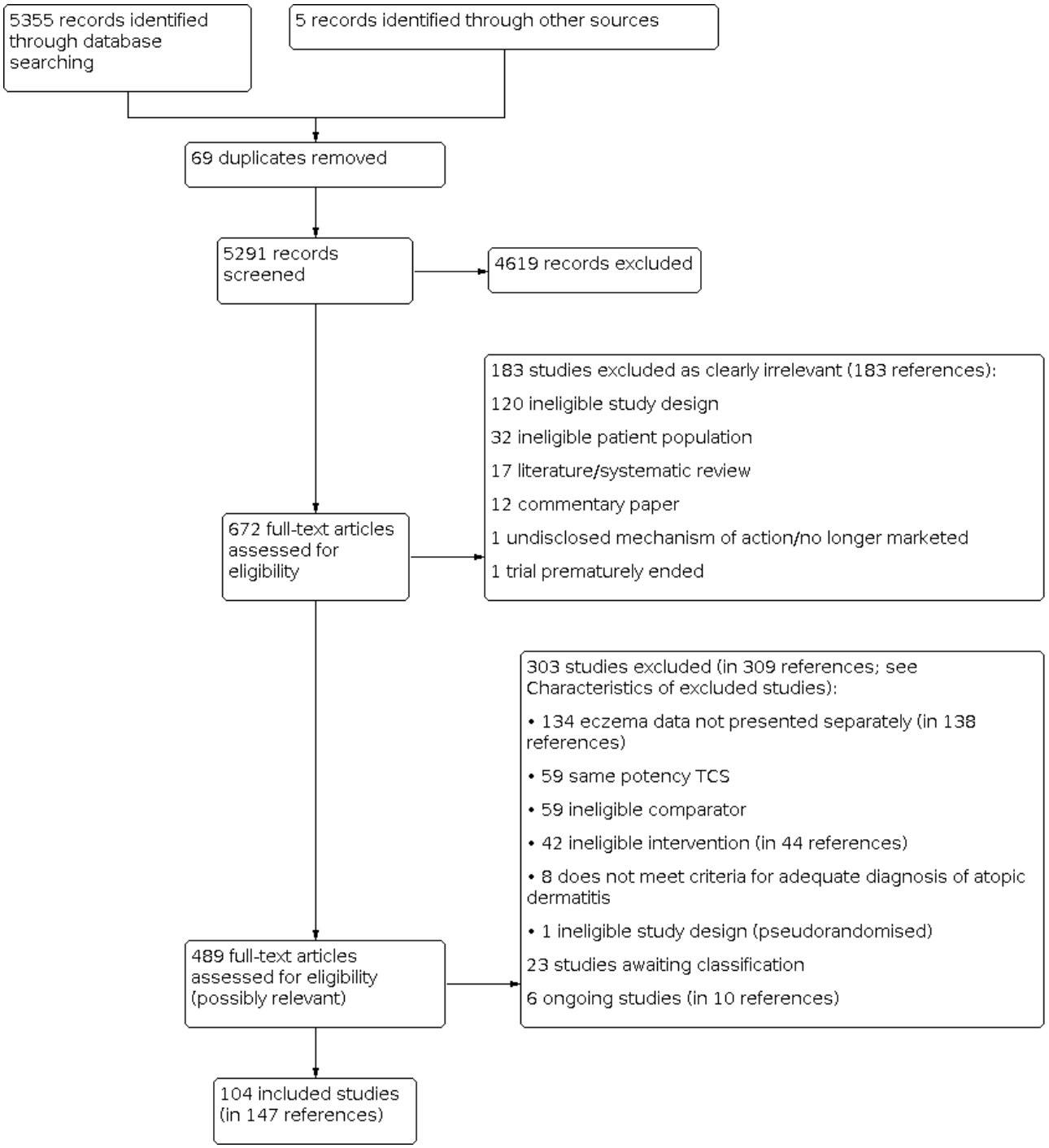
See: Characteristics of included studies, Characteristics of studies awaiting classification, Characteristics of ongoing studies, and Characteristics of excluded studies.

Results of the search

Our searches of the electronic databases and trials registers (see Electronic searches) retrieved 5355 records. The Cochrane Skin Information Specialist removed duplicates from this group, using EndNote's duplicate identification strategy. We found five additional records through handsearching. We removed a further 69 duplicate records and screened 5291 titles and abstracts for eligibility, and excluded 4619. We sought full texts associated with the remaining 672 records, over 150 of which required translation of key methods text into English. We found 183 to be clearly irrelevant, for example, because they were not RCTs, or were not conducted in people with eczema. We excluded a further 303 trials reported in 309 references, with reasons given in the Characteristics of excluded studies (mostly ineligible trial design); 23 are awaiting classification primarily because we could not obtain full texts (see: Characteristics of studies awaiting classification); and a further six trials reported in 10 references are ongoing (see: Characteristics of ongoing studies).

We included 104 trials reported in 147 references. Seventeen required translation into English from a number of other languages (see: Acknowledgements for where this was done outside the review team): Czech (Fadrhoncova 1982); Dutch (Sillevis 2000); French (Craps 1973; Lebrun-Vignes 2000); German (Busch-Heidger 1993; Harder 1983; Mahrle 1989; Meffert 1999; Nolting 1991; Ruiz 1976; Ulrich 1991); Italian (Amerio 1998; Giannetti 1981; Innocenti 1977); Korean (Ryu 1997); Portuguese (Van Del Rey 1983); and Spanish (Sanabria-Silva 1991). For a further description of our screening process, see the trial flow diagram (Figure 4).

Figure 4. Study flow diagram. Database searches last updated 28 January 2021



Sample size

We included 104 trials, with a total of 8443 participants (range 3 to 409; see: Characteristics of included studies). Over half were parallel-group trials (63/104); 39 were within-participant trials; two were cross-over trials (Dolle 2015; Kohn 2016).

Setting

Most trials were conducted in high-income countries (81/104): Europe (52); USA (22); Japan (2); South Korea (2); Canada (1); Hong Kong (1); Singapore (1). An additional two were conducted across multiple centres in both high- and upper-middle-income countries (Kirkup 2003a; Kirkup 2003b). Five were conducted in the following upper-middle-income countries: Brazil (2); China (1); Malaysia (1); and Mexico (1). Three were conducted in the following lower-middle-income countries: India (2); and Bangladesh (1). It was not possible to report or infer where the remaining 13 trials were conducted. We classified countries according to the current classification by World Bank.

Approximately half of the trials (51/104) were conducted in outpatient or other hospital settings, with an additional three trials working across both community and hospital settings (Kohn 2016; Rubio-Gomis 2018; Thomas 2002). Three trials were conducted in private dermatology clinics (Cullen 1971; Mali 1976; Noren 1989). The nature of the trial setting was unspecified in the remaining 47 trials, but is most likely be outpatient or other hospital settings.

Participants

Forty-three trials included children only, 16 included adults only, and 17 included both adults and children. Twenty-eight trials did not specify the age of participants. Sex was specified in 82/104 trials, with all including male and female participants, and with one trial noting that sex was not reported for one participant (Lasthein Andersen 1988).

Half the trials included participants with moderate or severe eczema (51/104) and 16/104 with mild to moderate eczema. Three trials included participants with mild to severe eczema. Thirty-four trials did not report participants' baseline severity of eczema.

Interventions and comparisons

See: Figure 1; overview of strategies included in the review.

Which topical corticosteroid to use?

- Moderate- versus mild-potency topical corticosteroid* (12 trials in 1184 participants)
- Potent versus mild-potency topical corticosteroid* (22 trials in 1010 participants)
- Potent versus moderate-potency topical corticosteroid* (25 trials in 1515 participants)
- Very potent versus potent topical corticosteroid* (6 trials in 730 participants)
- Topical corticosteroid cream versus topical corticosteroid ointment (7 trials in 677 participants)
- Different concentrations of the same topical corticosteroid (2 trials in 401 participants)
- Second-generation topical corticosteroid versus older topical corticosteroid (15 trials in 1248 participants)
- Branded topical corticosteroid versus generic topical corticosteroid (no trials)

How often to apply topical corticosteroid?

- Twice or more versus once daily application of topical corticosteroid* (25 trials in 2862 participants)
- Daily application versus less frequent application (4 trials in 327 participants)
- Longer- versus shorter-term duration of use for induction of remission* (no trials)
- Topical corticosteroid alternating with topical calcineurin inhibitor versus topical corticosteroid alone (1 trial in 30 participants)
- Weekend therapy (proactive topical corticosteroid) versus no proactive topical corticosteroid* (9 trials in 1344 participants)

How to use the topical corticosteroid?

- Timing of application of topical corticosteroid (2 trials in 158 participants)
- Wet wrap versus no wet wrap (6 trials in 221 participants)
- Topical corticosteroid applied to wet versus dry skin (1 trial in 45 participants)
- Topical corticosteroid applied before emollient versus topical corticosteroid applied after emollient (1 trial in 46 participants)
- Time between application of emollient and steroid (no trials)

*Key comparisons for which summary of findings tables are presented.

Several included trials tested a combination of the above, reflecting how topical corticosteroids might be used in clinical practice, therefore, are found in more than one results section. For instance, Rafanelli 1993 compares a newer, second-generation potent topical corticosteroid (mometasone furoate) applied once daily with a moderate-potency, older topical corticosteroid (clobetasone butyrate) used twice daily. As a result, Rafanelli 1993 is included in three separate meta-analyses; 1. potency versus moderate topical corticosteroid; 2. second-generation versus older topical corticosteroid; and 3. frequency of application, and the comparison of interest changes for each.

Trials that compared treatment strategies designed to treat eczema flares were generally short-term (range 1 to 6 weeks) and rarely conducted any follow-up. Trials included in the comparison of weekend (proactive) therapy with topical corticosteroid versus no topical corticosteroid, where the intervention aimed to prolong time to new flare (i.e. prevent relapse), were longer in duration. These trials involved a two- to four-week stabilisation phase where both groups received topical corticosteroid, followed by a 16- to 20-week maintenance phase, with the exceptions of Fukuie 2012 and Fukuie 2016, which observed participants at 6 and 12 months, respectively.

Outcomes

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

The number of included trials from which clinician-reported data have been used in this review is detailed below against the protocol-specified priority order of instruments.

- Eczema Area and Severity Index (EASI): five trials, one of which had factored patient assessment of itch into a composite score
- Objective SCORing Atopic Dermatitis (ObjSCORAD): three trials, one of which used objective local SCORAD
- SCORing Atopic Dermatitis (SCORAD): three trials
- Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score: three trials
- Three Item Severity score (TIS): two trials*
- Investigator Global Assessment (IGA): 62 trials, three of which had factored patient responses into the judgements
- Any other instruments: seven trials of weekend therapy versus no topical corticosteroid reported time to relapse and number of participants experiencing a relapse*; unnamed scales were used from 18 trials.
- No useable data: two trials

*One of these trials (Berth-Jones 2003), included TIS data from the end of the acute phase in short-term outcomes for topical corticosteroid cream versus topical corticoid steroid ointment,

different concentrations of the same topical corticoid steroid, and twice or more versus once daily topical corticoid steroid; relapse data from the end of the maintenance phase are included in weekend (proactive) therapy versus no topical corticoid steroid.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

The number of included trials from which patient-reported data have been used in this review is detailed below against the protocol-specified priority order of instruments.

- Patient-Oriented Eczema Measure (POEM): no trials
- Patient-Oriented SCORAD (PO-SCORAD): no trials
- Sleep and itch scales: eight trials reported itch; eight reported both itch and sleep separately; one trial reported itch and sleep in a composite score; and another reported EASI and itch as a composite score
- Self-Administered EASI (SA-EASI): no trials
- Patient Global Assessment (PGA): 15 trials, three of which were IGA factoring patient responses into the judgements.
- Any other instruments: two trials reported unnamed scales, one of which had an itch component.
- No useable data: 69 trials

Safety: number of relevant local adverse events (primary outcome)

The number of included trials that looked for relevant local adverse events incorporated into this review is detailed below, against the main groupings.

- Skin thinning: 33 trials
- Local site reactions: 39 trials, one of which did not report the data separately for the comparison of interest to this review.
- Skin infections: 23 trials, one of which did not report the data separately for the comparison of interest to this review.
- Other relevant local adverse events: four trials

Safety: number of relevant systemic adverse events (secondary outcome)

The number of included trials that looked for relevant systemic adverse events incorporated into this review is detailed below:

- Abnormal cortisol: 17 trials, only one of which looked for clinical signs of adrenal suppression.
- Other relevant systemic adverse events: 13 trials, one of which did not report the data separately for the comparison of interest to this review. Rarely was information given to the nature of the systemic adverse events looked for.

Funding sources

Fourteen trials were funded by pharmaceutical companies (Berth-Jones 2003; Bleehen 1995; Foelster-Holst 2006; Glazenburg 2009; Guttman-Yassky 2017; Hanifin 2002; Kirkup 2003a; Kirkup 2003b; Lebwohl 1999; Liu 2018; Schlessinger 2006; Van Der Meer 1999; Vernon 1991; Yawalkar 1991). Two trials were explicitly conducted in industry settings (EUCTR2009-012028-98-DE; Lucky 1997). Another trial not declaring funding source or conflicts of interest (Tharp 1996) is likely to be an industry-based trial as two of the four references in the bibliography of the article are to industry documentation and data on file. Three trials were funded by healthcare providers; two by the NHS Research and Development Fund (Hindley 2006; Thomas 2002), and another by Seton Healthcare (Cadmus 2019). Four trials received charitable or other public funding (Bryden 2009; Fukuie 2016; Kohn 2016; Rubio-Gomis 2018).

Eleven trials received treatments, other trial materials, or more general trial support from industrial partners (Cahn 1961; Cullen 1971; Handa 1985; Haribhakti 1982; Hoybye 1991; Meenan 1963; Pei 2001; Portnoy 1969; Sikder 2005; Stewart 1973; Wortzel 1975). One trial reported being sponsored by a pharmaceutical company (Koopmans 1995). Two further trials acknowledged the support of industrial partners but did not provide details regarding the nature of the support (Reidhav 1996; Wilson 2009).

Of the remainder, 22 trials did not report funding source, but declared interest in, or affiliation to, pharmaceutical companies. Neither funding source nor declarations of interest were reported by 44 trials.

Excluded studies

We excluded 302 trials reported in 309 references with reasons given in the Characteristics of excluded studies.

Risk of bias in included studies

We assessed each trial with regards to the seven criteria defined within the Cochrane risk of bias tool (RoB 1). For a summary of all the judgements see: Figure 2 and Figure 3. We judged only one trial, which assessed weekend (proactive) topical corticosteroid treatment versus no proactive treatment, to be at low risk of bias throughout all domains (Rubio-Gomis 2018). Of the remaining 103 trials, we assessed 55 as having at least one domain at high risk of bias. We did not judge any trials to be at high risk of bias in all domains. We assessed the remaining 48 trials as unclear in at least one domain.

Allocation

Although we selected only RCTs for this review, we judged only 16 of the 104 (15%) to be low risk of bias in the 'random sequence generation' domain and nine of the 104 (9%) to be low risk of bias in the 'allocation concealment' domain. Conversely, we judged seven of the 104 (7%) trials to be at high risk of bias for 'random sequence generation' and one of the 104 (1%) at high risk of bias for the 'allocation concealment' domain. Therefore, we judged most trials to be unclear in these domains. This was usually because they did not give a description of the method of randomisation and allocation at all or did not describe their methods in enough detail to allow assessment. Most of the trials that we assessed as being at low risk in the 'random sequence generation' domain used either random number tables or computer-generated methods of allocation. The trials that we judged at low risk of bias in the 'allocation concealment domain' explicitly stated that the investigator did not know the treatment allocation or mentioned that allocation was done by a third party.

Blinding

Performance bias

We assessed 14 out of the 104 trials as being adequately blinded in this domain. In contrast, we judged 28 out of the 104 trials to

be at high risk of bias within this domain. This meant that the we judged the majority of trials (62) to be unclear with regards to assessment of this domain. In some comparisons, due to the nature of the strategies, it would have been very difficult to blind the participants and the personnel, for example we judged all six of the trials that assessed the use of wet wrap therapy at risk of bias in this area and it would have been difficult to avoid this problem. This was also the case in other trials that assessed other strategies, for example in the trial that assessed ointment versus cream under wet wraps (1 trial), the trial that evaluated the application on dry skin versus wet skin (1 trial), and the trial that tested whether to apply topical corticosteroid first or emollient first (1 trial). An additional problem was that many trials did not specifically mention who was blinded. For example, the trial may have stated "single-blinded" or "double-blinded" but there was no mention of who the blinded parties were, or the paper did not mention blinding at all. There was also a number of trials, 10 out of the 28 judged at high risk of bias in this domain, where participants were applying treatments at different frequencies per day. In some cases, a placebo was not used at the same time as the other group were applying topical corticosteroid, though this may have been a conscious decision by the trial authors, due to the risk of the placebo acting as an active agent.

Detection bias

We assessed 27 out 104 trials as adequately blinded in this domain, seven at high risk of bias, and 70 trials where the information was unclear and so we could not make a judgement. Again, there were problems with the trials stating "single blinded" or "double-blinded" and then not stating which of the parties were blinded and problems with trials not providing any details as to whether any efforts were made to blind assessors.

Incomplete outcome data

We assessed 42 out of 104 trials as being at low risk of bias in this domain, 19 at high risk of bias and 43 trials as unclear. Trials were likely to have been marked as at high risk of bias in this domain because a large proportion of the participants were unaccounted for in the results of the trial, in some cases because participants were dropped from the trial when they achieved clearance of their eczema symptoms.

Selective reporting

Out of the 104 trials included in the review, we judged 84 at unclear risk of reporting bias. We judged only three trials to be at low risk and 17 at high risk. This was usually because, if there was not a trial protocol available for the trial, we were not able to compare the a priori outcomes, and so again we judged this domain as unclear. As around 80% of the trials included in this review were from before 2005, when registration was required for publication by a consensus statement from the International Committee of Medical Journal Editors (De Angelis 2004), this is probably the reason for this issue.

Other potential sources of bias

We judged most of the trials at low risk of bias in this domain (86 trials). For the eight trials that we judged at high risk of bias, the reasons were differences in co-interventions in the two groups (Foelster-Holst 2006), problems with selection of an unrepresentative population (Giannetti 1981), violations in the trial protocol (Hanifin 2002), trial potentially stopped prematurely (Munro 1967), mismatches in baseline severity (Pei 2001), and lack of information about methodologies (Sefton 1984a; Sefton 1984b; Sefton 1984c). We judged the 10 remaining trials to be unclear.

Effects of interventions

See: **Summary of findings 1** Moderate-potency compared to mild-potency topical corticosteroid; **Summary of findings 2** Potent compared to mild-potency topical corticosteroid ; **Summary of findings 3** Potent compared to moderate-potency topical corticosteroid; **Summary of findings 4** Very potent compared to potent topical corticosteroid; **Summary of findings 5** Twice daily or more compared to once daily topical corticosteroid; **Summary of findings 6** Longer-term compared to shorter-term duration of use of topical corticosteroid ; **Summary of findings 7** Weekend therapy compared to no topical corticosteroid

See Summary of findings 1: Moderate- versus mild-potency topical corticosteroid; Summary of findings 2: Potent versus mild-potency topical corticosteroid; Summary of findings 3: Potent versus moderate-potency topical corticosteroid; Summary of findings 4: Very potent versus potent topical corticosteroid; Summary of findings 5: Twice or more versus once daily topical corticosteroid; Summary of findings 6: Duration of use for induction of remission; and Summary of findings 7: Weekend therapy versus no topical corticosteroid.

We reported all relevant outcomes from the included trials for 18 pairwise comparisons. We considered seven of these the main comparisons in our review because of their relevance to clinical practice, and we rated the quality of evidence for these outcomes using GRADE.

We have performed subgroup analyses throughout, where there were sufficient data, with respect to age and baseline severity of eczema. As there were consistently insufficient data with which to compare effectiveness at different anatomical sites it was not possible to conduct subgroup analyses for any of the comparisons in this review.

Where possible, we did sensitivity analyses removing trials at high risk of bias. The results were generally consistent or based on insufficient trials (see: Table 6), and points of particular interest are highlighted under the relevant comparison. In addition, we examined the effects of Becker-Balagtas correction of the variance from within-participant trials, and imputation of missing standard deviations for a range of intraclass correlation coefficients (0.25, 0.5 and 0.75; Table 5 and Table 7).

Potency comparisons

Strategies in this review regarding potency were focused on clinically relevant comparisons that reflected the 'stepping-up' strategies for treating eczema, including moderate versus mild, potent versus mild, potent versus moderate, and very potent versus potent topical corticosteroid.

Moderate- versus mild-potency topical corticosteroid

See: Summary of findings 1.

This comparison comprises 12 trials; six parallel-group (Bagatell 1983; Jorizzo 1995; Lucky 1997; Mobacken 1986; Queille 1984; Rossi 2002) and six within-participant (Haribhakti 1982; Kuokkanen 1987;

Meenan 1963; Munro 1975; Portnoy 1969; Roth 1978a). In all trials only the potency of topical corticosteroid varied between groups, none compared multiple strategies.

Data were available for all outcomes relevant to this review.

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

Eleven trials included in this comparison measured clinician-reported signs of eczema. Taken together, we judged the certainty of evidence was judged to be moderate.

Pooled analyses: moderate- versus mild-potency topical corticosteroid

- **Investigator global assessment (IGA)**
- We pooled results from four trials for IGA as a short-term outcome (range 1 to 5 weeks; Bagatell 1983; Jorizzo 1995; Mobacken 1986; Roth 1978a), that included 420 participants; 391 from the parallel-group trials and 29 from the within-participant trial (Roth 1978a). The trials used a 5-, or 6-point scale and we pooled data from categories corresponding to 'cleared or marked improvement'. In the parallel-group trials, 86 of 195 participants who used moderate topical corticosteroid achieved cleared or marked improvement in the short-term compared to 60 of 196 participants who used mild topical corticosteroid. In the within-participant trial, 24 of 29 sides achieved cleared or marked improvement when treated with moderate topical corticosteroid compared to 17 of 29 sides treated with mild topical corticosteroid (OR 2.07, 95% CI 1.41 to 3.04; P = 0.0002; I^2 = 0%; 4 trials, 449 participants or sides treated; Analysis 1.1), indicating that moderate-potency topical corticosteroid is more effective than mild-potency topical corticosteroid. It is expected that one additional person will achieve success for every six participants receiving moderate topical corticosteroid rather than mild topical corticosteroid (95% CI 4 to 12).
- We were unable to perform subgroup analyses of trials in adults compared to children owing to the lack of trials in adults only, so we restricted the previous analysis to children only. Two parallel-group trials (Jorizzo 1995; Mobacken 1986), reported IGA as a short-term outcome (day 7 to 10), with 169 participants. The OR for achieving cleared or marked improvement was 2.11 (95% CI 1.08 to 4.13; P = 0.03; I^2 = 0%; 2 trials, 169 participants; Analysis 1.2), in favour of moderate topical corticosteroid.
- The three trials that reported baseline severity of eczema were all different severities, therefore subgroup analyses were not appropriate with respect to severity.
- We found similar results at end of treatment both overall (range 3 to 5 weeks; Bagatell 1983; Jorizzo 1995; Mobacken 1986; Roth 1978a; OR 2.74. 95% CI 1.47 to 5.11; P = 0.002; I^2 = 53%; 4 trials, 427 participants or sides treated; Analysis 1.3); and in children only (range 3 to 5 weeks; OR 3.90, 95% CI 1.84 to 8.25; P = 0.0004; I^2 = 6%; 2 trials, 169 participants; Jorizzo 1995; Mobacken 1986; Analysis 1.4).
- **Investigator assessment of clinical signs**
  - We pooled results from two trials (Haribhakti 1982; Queille 1984), for investigator assessment of clinical signs as a short-term outcome in children with moderate to severe eczema. There were 30 participants; nine from the parallel-group trial (Queille 1984), and 21 from the within-participant trial (Haribhakti 1982). The standardised mean difference (SMD) at day 6 to 7 was a decrease of 0.15 (95% CI −0.27 to 0.56; P = 0.49; I^2 = 0%; 2 trials, 51 participants or sides treated; Analysis 1.5), suggesting no difference between groups in contrast to the pooled IGA data. We found similar results for end of treatment (range 1 to 3 weeks; SMD 0.43, 95% CI 0.00 to 0.86; P = 0.05; I^2 = 0%; 2 trials, 51 participants or sides treated; Analysis 1.6).
  - Subgroup analysis was not possible because all trials included in SMD Analysis 1.5 and Analysis 1.6 included children with moderate to severe eczema only.
- **Number of participants with a greater investigator global assessment (IGA)/patient global assessment (PGA) compared to the other group**
  - We pooled data from three within-participant trials (Meenan 1963; Munro 1975; Portnoy 1969), that included 472 participants, for IGA, in the form of the number of participants for which each topical corticosteroid was judged to be better than the other, as a short-term outcome and at end of treatment. Two of the trials (Meenan 1963; Portnoy 1969; 64 participants), combined patient judgement with clinician judgement. Moderate topical corticosteroid was judged to be better in 180 participants; mild topical corticosteroid was judged to be better in 106 participants. The OR for the clinician judging one topical corticosteroid to be superior to the other was 3.14 (95% CI 1.39 to 7.13; P = 0.006; I^2 = 91%; 3 trials, 472 participants; Analysis 1.7). This suggests that moderate topical corticosteroid was more effective than mild-potency topical corticosteroid in line with the pooled IGA analysis, although this result has a high degree of imprecision and statistical heterogeneity. The increasing concentration of moderate topical corticosteroid used in the moderate arms of Munro 1975 is reflected in how they increasingly favour moderate topical corticosteroid; Meenan 1963 appears as an outlier because none of the participants favoured the mild topical corticosteroid; an artefact of using the generic inverse variance approach to enable consistent pooling of within-participant trials across this review. Removing the trials judged high risk of bias inflated the result and expanded the 95% confidence interval to include 1 (see: Table 6); OR = 37.51 (95% CI 0.34 to 4133.15).
  - Only Meenan 1963 specified they investigated children only (Analysis 1.7), and none of the trials reported baseline severity, therefore no subgroup analyses were possible.
- **Data not included in the meta-analyses**
  - We could not include two trials in the meta-analyses because the numerical data were incomplete. We have summarised these in Analysis 1.8. They did not show any difference between moderate and mild-potency topical corticosteroid.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Five trials reported this outcome in 356 participants (range 1 to 5 weeks). Taken together, we judged the certainty of evidence to be low.

We combined parent or participant judgements with investigator assessments in two within-participant trials (Meenan 1963 in children with unspecified disease severity; Portnoy 1969 in participants with unspecified age and disease severity; 64 participants), and pooled the data (Analysis 1.7). Results favoured moderate over mild-potency topical corticosteroid. Three additional parallel-group trials in 292 participants (263 from parallel-group trials and 29 from a within-participant trial),

summarised in Analysis 1.9, were also in favour of moderate topical corticosteroid (Jorizzo 1995; Rossi 2002; Roth 1978a).

Safety: number of relevant local adverse events (primary outcome)

Five trials reported on local adverse events (Bagatell 1983; Haribhakti 1982; Jorizzo 1995; Kuokkanen 1987; Roth 1978a), that included 446 participants; 362 from the parallel-group trials and 84 from the within-participant trials (range 2 to 5 weeks). Taken together, we judged the certainty of evidence to be low.

Skin thinning and related signs

Four trials that compared moderate and mild topical corticosteroid of two to five weeks' duration assessed skin thinning and related signs; no cases were reported (Bagatell 1983; Haribhakti 1982; Jorizzo 1995; Kuokkanen 1987; 417 participants). No cases were reported in a subgroup of 36 participants treated for up to 25 weeks in Jorizzo 1995.

Local site reactions

Four trials that compared moderate and mild topical corticosteroid of two to five weeks' duration reported the number of participants who experienced local site reactions (Bagatell 1983; Jorizzo 1995; Kuokkanen 1987; Roth 1978a; Analysis 1.10). Some trials described adverse events as "brief" and "slight". The trial with the largest number of participants that reported local site reactions was Bagatell 1983 (4/127 with moderate topical corticosteroid and 3/122 with mild topical corticosteroid).

Skin infections

A three-week trial that compared moderate (127 participants) and mild (122 participants) topical corticosteroid found no cases of folliculitis (Bagatell 1983).

Other adverse events are described under ‘Unspecified adverse events (safety)’.

Safety: number of relevant systemic adverse events (secondary outcome)

Three parallel-group trials assessed systemic adverse events in 282 participants (range 1 to 4 weeks; Bagatell 1983; Lucky 1997; Queille 1984). Taken together, we judged the certainty of evidence to be very low.

Two trials reported the number of participants with abnormal cortisol levels. Lucky 1997 included children with unspecified eczema severity. Morning serum cortisol samples (obtained before 9 am) were taken at baseline and days 14 and 28, and serum cortisol values 30 and 60 minutes after adrenocorticotropic hormone (ACTH) stimulation were also taken at baseline and day 28. Queille 1984 included children with severe eczema. Plasma cortisol samples were taken at any visit up to day 6. For this review, we converted individual measurements to number of participants with levels outside a reference range (6 to 23 µg/dL or 170 to 635 nmol/L; Royal College, Canada). No cases were reported in either trial (Lucky 1997; Queille 1984; 33 participants).

Bagatell 1983 reported that no systemic adverse events occurred up to week 3 (249 participants).

Unspecified adverse events (safety)

Mobacken 1986 reported that no adverse events occurred in either group (up to day 25; 29 participants), and Rossi 2002 stated that both topical corticosteroids were “safe and well tolerated” up to 3 weeks (152 participants).

Potent versus mild-potency topical corticosteroid

See: Summary of findings 2.

This comparison comprises 22 trials; 15 parallel-group trials (Gentry 1973; Kaplan 1978; Kirkup 2003a; Lebrun-Vignes 2000; Mali 1976; Marten 1980; Noren 1989; Prado de Oliveira 2002; Queille 1984; Ryu 1997; Sanabria-Silva 1991; Savin 1976; Thomas 2002; Vernon 1991; Wortzel 1975), and seven within-participant trials (Cahn 1961; Fadrhoncova 1982; Giannetti 1981; Handa 1985; Roth 1973; Veien 1984; Yasuda 1976). In 16 trials only the potency of topical corticosteroid varied between groups (single strategy), whilst the remaining six trials were a combination of multiple different strategies of topical corticosteroid use.

Of the six trials that tested multiple strategies, one trial compared a potent cream with a mild-potency ointment (Kaplan 1978; age and severity unspecified). Two trials compared a second-generation potent topical corticosteroid to an older mild-potency topical corticosteroid (Kirkup 2003a; Prado de Oliveira 2002; both in children with moderate to severe eczema). A further two trials were similar, but the second-generation potent topical corticosteroid was applied once daily compared to twice daily application of the older mild topical corticosteroid (Vernon 1991, in children with moderate to severe eczema; Ryu 1997, in adults and children over three years with mild- to moderate-severity eczema). One trial compared a three day ‘pulse’ of potent topical corticosteroid with seven days of mild topical corticosteroid for management of flares in children with mild to moderate eczema (Thomas 2002).

Data were available for all outcomes relevant to this review.

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

All trials included in this comparison measured clinician-reported signs of eczema. Taken together, we judged the certainty of evidence to be moderate.

Pooled analyses: potent versus mild-potency topical corticosteroid

- **Investigator global assessment (IGA)**
  - We pooled IGA, as a short-term outcome (range 1 to 4 weeks), from nine trials (Gentry 1973; Giannetti 1981; Handa 1985; Kirkup 2003a; Mali 1976; Ryu 1997; Savin 1976; Veien 1984; Wortzel 1975), that included 392 participants; 326 from the parallel-group trials and 66 from the within-participant trials. Most trials used a 4-, 5-, or 6-point scale and we pooled data from categories corresponding to ‘cleared or marked improvement’ where possible. In the parallel-group trials, 131 of 165 participants who used potent topical corticosteroid achieved cleared or marked improvement compared to 73 of 161 who used mild topical corticosteroid. In the within-participant trials, 25 of 66 participants achieved cleared or marked improvement on the side treated with potent topical corticosteroid compared to 16 of 66 on the side treated with mild topical corticosteroid (OR 3.71, 95% CI 2.04 to 6.72; P < 0.00001; I^2 = 39%; 9 trials, 458

participants or sides treated; Analysis 2.1), indicating that potent topical corticosteroid is more effective than mild-potency topical corticosteroid. This corresponds to a need to treat 3.2 people with potent topical corticosteroid to achieve an additional treatment success compared to mild topical corticosteroid (95% CI 2.4 to 5.7). We observed this effect in analyses of trials of a single strategy only, potent versus mild topical corticosteroid (Analysis 2.1.1; Analysis 2.1.2), as well as in multiple strategies including a second-generation potent topical corticosteroid (Analysis 2.1.3), and a second-generation potent topical corticosteroid applied once daily versus twice daily application of mild-potency topical corticosteroid (Analysis 2.1.4). The short-term time point was the end of treatment for over half of the trials; therefore, we did not carry out a separate end of treatment meta-analysis.

- We were unable to perform subgroup analyses of adults and children owing to the lack of trials in adults only, so we restricted the previous short-term IGA analyses to three trials in children (Giannetti 1981; Kirkup 2003a; Veien 1984). The OR for achieving cleared or marked improvement in the short term was 2.21 (95% CI 1.39 to 3.51; P = 0.0008; I^2 = 0%; 3 trials, 245 participants or sides treated; Analysis 2.2), in favour of potent topical corticosteroid, consistent with the overall finding.
- We then pooled IGA as a short-term outcome from three trials that included participants with moderate to severe eczema (Kirkup 2003a; Savin 1976; Veien 1984). The OR for achieving cleared or marked improvement was 2.69 (95% CI 1.34 to 5.39; P = 0.005; I^2 = 35%; 3 trials, 232 participants or sides treated; Analysis 2.3.1), in favour of potent topical corticosteroid. Two trials included participants with mild to moderate eczema (Giannetti 1981; Ryu 1997). The OR for achieving cleared or marked improvement was 4.84 (95% CI 0.33 to 71.44; P = 0.25; I^2 = 80%; 2 trials, 63 participants or sides treated; Analysis 2.3.2). We observed no difference between the two groups when we pooled only trials in mild- to moderate-severity eczema, however, the test for subgroup differences for Analysis 2.3 was not statistically significant, with a P value of 0.68, suggesting that potent topical corticosteroids are more effective than mild-potency topical corticosteroids regardless of baseline severity of eczema.

- **Investigator assessment of clinical signs**
  - We pooled investigator assessment of clinical signs as a short-term outcome (day 5 to 6) from two parallel-group trials in 46 children with severe eczema (Lebrun-Vignes 2000; Queille 1984). The SMD was a decrease of 0.63 (95% CI −0.95 to 2.21; P = 0.43; I^2 = 82%; 2 trials, 46 participants; Analysis 2.4) and therefore did not reflect the difference between potent and mild-potency topical corticosteroid seen in the main pooled IGA analysis. The statistical heterogeneity is high; Queille 1984 favours potent topical corticosteroid while Lebrun-Vignes 2000 shows no difference, but the number of participants is small, and the confidence intervals do overlap. The short-term time point was the end of treatment for one of the trials, therefore we did not carry out a separate end of treatment meta-analysis.
  - Both trials included in SMD Analysis 2.4 included children with severe eczema only, therefore no further restricted analyses were required.
- **Number of participants with a greater IGA compared to the other group**
  - We pooled IGA, in the form of the number of participants for whom each topical corticosteroid was judged to be better than the other, as a short-term outcome (week 1), from three within-participant trials in 67 participants (Cahn 1961; Roth 1973; Yasuda 1976). Roth 1973 included participants aged 18 months to 59 years with moderate to severe eczema; Cahn 1961 and Yasuda 1976 did not specify age and severity. The clinician-reported potent topical corticosteroid to be superior to mild in 39 participants and mild to be superior in six (OR 11.70, 95% CI 5.67 to 24.15; P < 0.00001; I^2 = 0%; 3 trials, 67 participants; Analysis 2.5) in favour of potent topical corticosteroid. The short-term time point was the end of treatment for two of the trials, therefore we did not carry out a separate end of treatment meta-analysis.
  - None of the trials included in Analysis 2.5 were in either adults or children only, and only one trial reported participants' baseline severity (Roth 1973; moderate to severe eczema); therefore, no further subgroup or restricted analyses were possible.
- **Data not included in the meta-analyses**
  - We could not include nine trials in the meta-analyses, either because we could not pool the instrument used to measure clinician-reported signs of eczema alongside those included (Thomas 2002), because the duration was too long relative to the short-term outcomes pooled (Prado de Oliveira 2002), or because the numerical data were incomplete (Fadrhoncova 1982; Kaplan 1978; Kirkup 2003a; Marten 1980; Noren 1989; Sanabria-Silva 1991; Vernon 1991), and are summarised in Analysis 2.6. Five trials suggest potent topical corticosteroid to be more effective than mild-potency topical corticosteroid in line with the meta-analyses favouring potent topical corticosteroid, but most are difficult to interpret with any certainty due to lack of information about the scale used or lack of dispersion data. The remaining four trials did not show any difference between the two potencies, including Thomas 2002, which compared mild topical corticosteroid used daily with short, three-day bursts of potent topical corticosteroid.
  - One trial (Sanabria-Silva 1991), looked for 'rebound', defined as "reactivation of lesions with greater intensity than their pre-treatment state" in the 10 days after the cessation of topical corticosteroid treatment (end of treatment was 4 weeks). No participants in either the potent topical corticosteroid group (assumed 15 participants) or mild topical corticosteroid group (assumed 15 participants) were reported as having experienced rebound.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Six trials reported this outcome, but none of the data were suitable for pooling. The findings are summarised in Analysis 2.7. Taken together, we judged the certainty of evidence to be moderate.

Four trials measured patient-reported itch, including 198 participants receiving potent topical corticosteroid and 205 who used mild topical corticosteroid over a range of 1 to 18 weeks (Giannetti 1981; Kirkup 2003a; Noren 1989; Thomas 2002). Although two trials were suggestive of modest improvement in itch with potent compared to mild topical corticosteroid, overall, there

appeared to be little difference between the two different potencies. Similarly, there was no clinically important difference in sleep disturbance between potent and mild topical corticosteroid in two trials that included 285 participants (Kirkup 2003a; Thomas 2002), or in one trial with PGA presented as a comparison between groups (Veien 1984).

Safety: number of relevant local adverse events (primary outcome)

Nineteen trials reported local adverse events and event rates were generally low. Taken together, we judged the certainty of evidence to be low.

Skin thinning and related signs

Five trials that compared potent and mild topical corticosteroid of 2 to 18 weeks' duration reported the number of participants with skin thinning and related signs (Kirkup 2003a; Prado de Oliveira 2002; Ryu 1997; Thomas 2002; Vernon 1991; Analysis 2.8). Four participants of 221 who used potent topical corticosteroid reported skin thinning compared to two of 219 who used mild topical corticosteroid. Just one of the five trials, which compared daily application of a second-generation potent topical corticosteroid to daily application of an older, mild topical corticosteroid in children with moderate to severe eczema over 42 days reported all events (Prado de Oliveira 2002).

Local site reactions

Eight trials that compared potent and mild topical corticosteroid of 2 to 18 weeks' duration reported the number of participants with local site reactions (Cahn 1961; Fadrhoncova 1982; Kaplan 1978; Kirkup 2003a; Prado de Oliveira 2002; Ryu 1997; Thomas 2002; Vernon 1991; Analysis 2.9). Nine of 295 participants who used potent topical corticosteroid reported local site reactions (burning, stinging, irritation, rash, itch) compared to three of 293 who used mild topical corticosteroids. One event in the mild topical corticosteroid group resulted in discontinuation from the trial (Kaplan 1978; unspecified age and severity).

Skin infections

Four trials that compared potent and mild topical corticosteroid of 2 to 16 weeks' duration reported the number of participants with a skin infection (Kirkup 2003a; Marten 1980; Ryu 1997; Vernon 1991; Analysis 2.10). Four of 115 participants who used potent topical corticosteroid reported skin infections (ringworm, folliculitis, eczema herpeticum, scalp infection) compared to one of 111 who used mild topical corticosteroid (secondary infection). The one *Staphylococcus aureus* infection of the scalp in the potent group resulted in discontinuation from the trial (Vernon 1991; children with moderate to severe eczema).

Other local adverse events

Two trials of six and 18 weeks' duration each reported hair growth in one participant who used potent topical corticosteroid (Prado de Oliveira 2002; Thomas 2002; 232 participants).

Safety: number of relevant systemic adverse events (secondary outcome)

Of the 16 parallel-group trials included within this comparison, six reported on relevant systemic adverse events. Taken together, we judged the certainty of evidence to be very low.

Four trials of six days' to six weeks' duration reported the number of participants with abnormal cortisol levels (Lebrun-Vignes 2000; Marten 1980; Queille 1984; Vernon 1991; Analysis 2.11). In the three trials that reported the number of cases, 11 of 43 children with moderate to severe eczema who used potent topical corticosteroid had abnormal cortisol levels compared to 4 of 39 children who used mild topical corticosteroid. Two trials reported that no relevant systemic adverse events occurred (Thomas 2002; Prado de Oliveira 2002; 232 participants).

Unspecified adverse events (safety)

An additional seven trials of short duration looked for adverse events but provided no information on which adverse events, specifically they investigated or whether the adverse events were local or systemic (Gentry 1973; Giannetti 1981; Sanabria-Silva 1991; Savin 1976; Veien 1984; Wortzel 1975; Yasuda 1976; Analysis 2.12), and most reported no adverse events or no serious adverse events.

Potent versus moderate-potency topical corticosteroid

See: Summary of findings 3.

This comparison comprises 25 trials; 12 parallel-group (Bluefarb 1976; Busch-Heidger 1993; Lassus 1983; Lebwohl 1999; Nolting 1991; Queille 1984; Rafanelli 1993; Rampini 1992a; Rampini 1992b; Ulrich 1991; Van Del Rey 1983; Wolkerstorfer 1998) and 13 within-participant (Allenby 1981; Craps 1973; Cullen 1971; Henrijean 1983; Innocenti 1977; Munro 1967; Rajka 1986; Roth 1978b; Ruiz 1976; Sefton 1983a; Sefton 1983b; Sefton 1983c; Stewart 1973). In 19 trials only the potency of topical corticosteroid varied between groups (single strategy), whilst the remaining six trials were a combination of different strategies of topical corticosteroid use.

Of the six trials that tested multiple strategies, one trial compared a potent lipocream with moderate-potency ointment (Rajka 1986). One trial compared once daily potent topical corticosteroid with twice daily moderate topical corticosteroid (Rampini 1992a). Three trials compared once daily potent second-generation topical corticosteroid to twice daily older, moderate-potency topical corticosteroid (Lebwohl 1999; Rafanelli 1993; Wolkerstorfer 1998). A further trial also compared once daily application of a second-generation potent topical corticosteroid to twice daily application of an older, moderate topical corticosteroid (Nolting 1991).

Data were available for all outcomes relevant to this review.

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

All trials included in this comparison measured clinician-reported signs of eczema. Taken together, we judged the certainty of evidence to be moderate.

Pooled analyses: potent versus moderate-potency topical corticosteroid

- **Investigator global assessment (IGA)**
  - We pooled IGA as a short-term outcome (range 1 to 3 weeks) from 15 trials (Bluefarb 1976; Craps 1973; Cullen 1971; Innocenti 1977; Lassus 1983; Lebwohl 1999; Nolting 1991; Rafanelli 1993; Rajka 1986; Rampini 1992a; Rampini 1992b; Roth 1978b; Ruiz 1976; Ulrich 1991; Van Del Rey 1983), that included 1053 participants; 933 from the parallel-group trials and 120 from the within-participant trials. Most trials used a 4-, 5-, or 6-point scale and we pooled data from categories

corresponding to 'cleared or marked improvement' where possible. In the parallel-group trials, 217 of 467 participants who used potent topical corticosteroid achieved cleared or marked improvement in IGA compared to 218 of 466 in those who used moderate topical corticosteroid. In the within-participant trials, 63 of 120 achieved cleared or marked improvement on the side treated with potent topical corticosteroid compared to 49 of 120 on the side treated with moderate topical corticosteroid. The OR was 1.33 (95% CI 0.93 to 1.89; P = 0.12; I^2 = 11%; 15 trials, 1173 participants or sides treated; Analysis 3.1). This is insufficient evidence to show that potent topical corticosteroid are better than moderate-potency topical corticosteroid in the short term. The short-term time point was the end of treatment for most trials; therefore, we did not carry out a separate end of treatment meta-analysis.

- We then pooled IGA as a short-term outcome from three trials in adults only (Nolting 1991; Rajka 1986; Ruiz 1976). The OR for achieving cleared or marked improvement in the short term was 3.43 (95% CI 0.79 to 14.86; P = 0.10; I^2 = 43%; 3 trials, 131 participants or sides treated; Analysis 3.2.1), indicating no evidence of a difference between potent and moderate-potency topical corticosteroid as the 95% CI is wide and includes 1. The same analysis from six trials in children only (Lassus 1983; Lebwohl 1999; Rafanelli 1993; Rampini 1992a; Rampini 1992b; Ruiz 1976), also showed no difference (OR 1.12, 95% CI 0.50 to 2.51; P = 0.79; I^2 = 10%; 6 trials, 482 participants or sides treated; Analysis 3.2.2).
- As limited IGA data were available in participants with moderate eczema only (Cullen 1971), and severe eczema only (Cullen 1971; Ulrich 1991), and these subgroups overlapped with 9 trials in participants with moderate and severe eczema (Bluefarb 1976; Cullen 1971; Innocenti 1977; Lassus 1983; Lebwohl 1999; Rafanelli 1993; Rajka 1986; Ulrich 1991; Van Del Rey 1983), we performed a restricted analysis of IGA as a short-term outcome including only trials of participants with moderate to severe eczema. The OR for achieving cleared or marked improvement was 1.39 (95% CI 0.86 to 2.23; P = 0.18; I^2 = 11%; 9 trials, 770 participants or sides treated; Analysis 3.3), in line with the overall analysis.

- **Investigator assessment of clinical signs**
  - We pooled investigator assessment of clinical signs as a short-term outcome (range 6 to 7 days) from three small trials (Henrijean 1983; Queille 1984; Wolkerstorfer 1998), that included 36 participants; 33 from the parallel-group trials and three from the within-participant trial. The SMD was a decrease of 0.01 (95% CI −0.70 to 0.72; P = 0.98; I^2 = 16%; 3 trials, 39 participants or sides treated; Analysis 3.4), indicating no difference between potent and moderate-potency topical corticosteroid. Similar results were seen at end of treatment (SMD 0.29, 95% CI −0.62 to 1.20; P = 0.54; I^2 = 0%; 3 trials, 21 participants or sides treated; Analysis 3.5).
  - Two trials included children only (Queille 1984; Wolkerstorfer 1998), and none included adults only, therefore no subgroup analysis was possible with respect to age. In children, the SMD in the short term (day 6 to 7) was 0.23 (95% CI −1.14 to 1.60; P = 0.74; I^2 = 58%; 2 trials, 33 participants; Analysis 3.4.1); end of treatment (maximum week 4) was 0.49 (95% CI −0.87 to 1.85; P = 0.48; I^2 = 20%; 2 trials, 17 participants; Analysis 3.5.1). No difference was observed between groups at either time point.
  - All three trials in Analysis 3.4 and Analysis 3.5 included participants with different eczema severities therefore no further subgroup analysis was possible.
- **Number of participants with a greater IGA compared to the other group**
  - We pooled IGA, in the form of the number of participants for which each topical corticosteroid was judged to be better than the other, as a short-term outcome (after 1 week) from two within-participant trials in 100 participants (Munro 1967; Stewart 1973; unspecified age and severity of eczema). The clinician judged potent topical corticosteroid to be superior in 46 of 100 participants compared and moderate-potency topical corticosteroid to be superior in 19 of 100. The OR was 3.86 (95% CI 2.42 to 6.14; P < 0.00001; I^2 = 0%; 2 trials, 100 participants; Analysis 3.6). The short-term time point was the end of treatment for one of the two trials; therefore, we did not carry out a separate end of treatment meta-analysis.
  - Neither trial included in Analysis 3.6 specified participants' age or baseline eczema severity, therefore no subgroup analyses were possible.
- **Data not included in the meta-analyses**
  - We were unable to include four within-participant trials in the meta-analyses because the numerical data were incomplete. They are summarised in Analysis 3.7 (Allenby 1981; Sefton 1983a; Sefton 1983b; Sefton 1983c; 164 participants). In all trials, participants in both groups saw a clinically meaningful improvement in clinician-reported signs, but there were no clear differences between potent and moderate-potency topical corticosteroids. One trial that we included in SMD Analysis 3.4 and Analysis 3.5 also reported very limited follow-up data (Wolkerstorfer 1998, included in Analysis 3.7).

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Two trials reported this outcome (Munro 1967; Rafanelli 1993), and are summarised in Analysis 3.8. Taken together, we judged the certainty of evidence to be low.

Rafanelli 1993 reported that potent topical corticosteroid was more effective than moderate topical corticosteroid, although gave no numerical data support this. There appeared to be no difference between groups in Munro 1967.

Ruiz 1976 consulted patients when judging the IGA (see Analysis 3.1).

Safety: number of relevant local adverse events (primary outcome)

Seventeen trials looked for local adverse events (Bluefarb 1976; Busch-Heidger 1993; Cullen 1971; Innocenti 1977; Lassus 1983; Lebwohl 1999; Nolting 1991; Rafanelli 1993; Rajka 1986; Rampini 1992a; Rampini 1992b; Roth 1978b; Sefton 1983a; Sefton 1983b; Sefton 1983c; Ulrich 1991; Van Del Rey 1983). Taken together, we judged the certainty of evidence to be low.

Skin thinning and related signs

Ten trials that compared potent and moderate topical corticosteroid of one to three weeks' duration looked for the number of participants with skin thinning and related signs (Cullen 1971; Innocenti 1977; Lebwohl 1999; Nolting 1991; Rafanelli 1993; Sefton 1983a; Sefton 1983b; Sefton 1983c; Ulrich 1991; Van Del Rey

1983; Analysis 3.9). There were four reports (2 per group) of skin thinning (541 participants).

Local site reactions

Thirteen trials that compared potent and moderate topical corticosteroid of two to five weeks' duration looked for the number of participants with local site reactions (Bluefarb 1976; Busch-Heidger 1993; Cullen 1971; Lassus 1983; Lebwohl 1999; Rajka 1986; Rampini 1992a; Rampini 1992b; Roth 1978b; Sefton 1983a; Sefton 1983b; Sefton 1983c; Van Del Rey 1983; Analysis 3.10). The most frequently reported local site reaction was burning, reported by nine of 307 participants who used potent topical corticosteroid and six of 306 who used moderate topical corticosteroid.

Skin infections

Six trials that compared potent and moderate topical corticosteroid of two to three weeks' duration looked for the number of participants with skin infection (Cullen 1971; Rampini 1992a; Rampini 1992b; Sefton 1983a; Sefton 1983b; Sefton 1983c; Van Del Rey 1983; 372 participants; Analysis 3.11). One participant in each group reported secondary infection (Sefton 1984c; 31 participants; unspecified age; mild to moderate eczema). In Rampini 1992a, in children with unspecified severity eczema, one participant reported impetigo in the potent topical corticosteroid group (55 participants) compared to none in the moderate topical corticosteroid group (53 participants).

Other adverse events are described under 'Unspecified adverse events (safety)'.

Safety: number of relevant systemic adverse events (secondary outcome)

Six parallel-group trials looked for systemic adverse events (Queille 1984; Rafanelli 1993; Rampini 1992a; Rampini 1992b; Ulrich 1991; Wolkerstorfer 1998). Taken together, we judged the certainty of evidence to be very low.

Three trials of children with moderate to severe eczema, of six days' to four weeks' duration, reported the number of participants with abnormal cortisol levels (Queille 1984; Rafanelli 1993; Wolkerstorfer 1998; Analysis 3.12). Nine of 55 children who used potent topical corticosteroid had abnormal cortisol levels compared to one of 44 who used moderate topical corticosteroid. All nine events in the potent topical corticosteroid group were reported by Queille 1984, in which 13 children were treated with potent topical corticosteroid once daily for six days then alternate days until discharged.

Rampini 1992a, Rampini 1992b, and Ulrich 1991 reported that no systemic adverse events occurred (351 participants; week 2 to 3).

Unspecified adverse events (safety)

An additional three trials of two to five weeks' duration looked for adverse events (Busch-Heidger 1993; Henrijean 1983; Ruiz 1976), but provided no information on specifically which adverse events they investigated or whether they were local or systemic. Two within-participant trials reported no adverse events (Ruiz 1976 in adults and children with unspecified severity eczema; Henrijean 1983 in participants with unspecified age and severity eczema; 9 participants). Busch-Heidger 1993 reported no serious adverse events (unspecified) up to five weeks (75 participants).

In addition to skin thinning reported above, Nolting 1991 looked for adverse events, however the trial authors report that no other significant adverse events occurred.

Very potent versus potent topical corticosteroid

See: Summary of findings 4.

This comparison comprises six trials; two parallel-group (Harder 1983; Yawalkar 1991), and four within-participant (Bleeker 1975; Goh 1999; Guttman-Yassky 2017; Sparkes 1974). In four trials, only the potency of topical corticosteroid varied between groups (single strategy), whilst the remaining two trials were a combination of multiple different strategies of topical corticosteroid use.

Harder 1983 compared once daily very potent topical corticosteroid with three times daily older potent topical corticosteroid. Goh 1999 compared twice daily very potent topical corticosteroid with once daily second-generation potent topical corticosteroid, which contrasts with most multi-strategy trials where the higher-potency topical corticosteroid is used less frequently, reflecting clinical practice, and so has been excluded from the meta-analyses.

Data were available for all outcomes relevant to this review.

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

All trials included in this comparison measured clinician-reported signs of eczema. Taken together, we judged the certainty of evidence to be low.

Pooled analyses: very potent versus potent topical corticosteroid

- **Investigator global assessment (IGA)**
  - We pooled IGA as a short-term outcome (range 1 to 2 weeks) from three trials (Bleeker 1975; Harder 1983; Yawalkar 1991), that included 216 participants; 189 from the parallel-group trials and 27 from the within participant trial (Bleeker 1975). These trials used a 4-, 5-, or 6-point scale and we pooled data from categories corresponding to 'cleared or marked improvement' where possible. In the parallel-group trials, 79 of 96 participants who used very potent topical corticosteroid achieved cleared or marked improvement compared to 87 of 93 who used potent topical corticosteroid. In the within-participant trial, 25 of 27 sides achieved cleared or marked improvement with both very potent and potent topical corticosteroid. The OR was 0.53 (95% CI 0.13 to 2.09; P = 0.37, I^2 = 52%; 3 trials, 243 participants or sides treated; Analysis 4.1), suggesting no difference between very potent and potent topical corticosteroid. The short-term time point was the end of treatment for two of the three trials; therefore, we did not carry out a separate end of treatment meta-analysis.
  - We considered repeating this analysis with the alternative threshold of 'any improvement' where available, to address the fact that people with severe eczema may also be interested in more modest effects. However, only one trial presented data in this way and we did not do a separate meta-analysis.
  - Only one trial included in Analysis 4.1 specified participants' age and baseline eczema severity (Yawalkar 1991; adults with moderate and severe eczema), therefore no subgroup analyses were possible.

- **Number of participants with a greater IGA compared to the other group**
  - We pooled IGA, in the form of the number of participants for which each topical corticosteroid was judged to be better than the other, as a short-term outcome (one week) from four distinct sets of participants from a single within-participant trial that included 398 participants (Sparkes 1974; age and severity unspecified). Very potent topical corticosteroid was judged to be better in 127 participants; potent topical corticosteroid was judged to be better in 83 participants. The OR for the clinician judging very potent topical corticosteroid to be superior to potent topical corticosteroid was 1.68 (95% CI 1.00 to 2.83; P = 0.05; I^2 = 80%; 398 participants; Analysis 4.2), suggesting very potent topical corticosteroid was more effective than potent topical corticosteroid. There was no obvious reason for the high statistical heterogeneity. There were no additional end of treatment data in this trial.
  - The trial included in Analysis 4.2 (Sparkes 1974) did not report participants' age or baseline eczema severity, therefore no subgroup analyses were possible.
- **Data not included in the meta-analyses**
  - A further two within-participant trials were unsuitable for pooling (87 participants). One showed no difference between treatments (Guttman-Yassky 2017); another favoured very potent topical corticosteroid (Goh 1999). However, the latter was thought clinically irrelevant as very potent topical corticosteroid was applied twice daily and potent topical corticosteroid was a second-generation topical corticosteroid applied once daily. Results are provided in Analysis 4.3.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

One within-participant trial measured patient-reported effectiveness in a comparison of twice daily application of a very potent topical corticosteroid to once daily application of a second-generation potent topical corticosteroid in 58 adults with moderate to severe eczema (Goh 1999). At day 8, the number of participants reporting an excellent response on the side treated with very potent topical corticosteroid was nine compared to three for the side treated with potent topical corticosteroid (OR 3.37, 95% 1.22 to 9.29; 1 trial, 58 participants). At day 22, 25 participants reported an excellent response on the side treated with very potent topical corticosteroid compared to six treated with potent topical corticosteroid (OR 6.57, 95% CI 3.14 to 13.74; 1 trial, 58 participants; Analysis 4.4). we judged the certainty of evidence to be very low.

Safety: number of relevant local adverse events (primary outcome)

Two trials looked for local adverse events (Goh 1999; Yawalkar 1991). Bleeker 1975 also reported local adverse events, however they did not present results for participants with atopic eczema separately for this outcome. Taken together, we judged the certainty of evidence to be very low.

Skin thinning and related signs

Two trials in adults with moderate and severe eczema that compared very potent and potent topical corticosteroids of two to three weeks' duration looked for the number of participants with skin thinning and related signs; none were reported (Goh 1999; Yawalkar 1991; 175 participants; Analysis 4.5).

Local site reactions

Yawalkar 1991 reported five local adverse events in the group that received very potent topical corticosteroid (58 participants) and two in the group that received potent topical corticosteroid (59 participants), which included dryness and itching. One participant per group discontinued because of severe dryness. Goh 1999 also stated that "no side effects were observed on any of the treated sites" (58 participants). See Analysis 4.6.

Other adverse events are described under 'Unspecified adverse events (safety)'.

Safety: number of relevant systemic adverse events (secondary outcome)

One parallel-group trial stated that they looked for systemic adverse events and found none (Yawalkar 1991; 117 adults with severe eczema). We judged the certainty of evidence to be very low (Analysis 4.7).

Unspecified adverse events (safety)

An additional two trials of two to three weeks' duration looked for adverse events (Harder 1983; Guttman-Yassky 2017). Harder 1983 stated that "side effects such as intolerance have never been observed" (72 participants; unspecified age and severity of eczema; week 3). Guttman-Yassky 2017 did not report any relevant adverse events (22 adults; mild- to moderate-severity eczema; up to week 2).

Topical corticosteroid cream versus topical corticosteroid ointment

This comparison comprises seven trials; four parallel-group (Berth-Jones 2003; EUCTR2009-012028-98-DE; Kaplan 1978; Wilson 2009), and three within-participant trials (Cadmus 2019; Lasthein Andersen 1988; Rajka 1986). In four trials, the only comparison of interest was ointment versus cream; three used the same topical corticosteroid in both the cream and the ointment arms (Cadmus 2019; Lasthein Andersen 1988; Wilson 2009), and one compared an ointment topical corticosteroid with a different topical corticosteroid in a cream preparation (EUCTR2009-012028-98-DE). The remaining trials included multiple strategy comparisons. Berth-Jones 2003 compared a cream and ointment of the same potent topical corticosteroid at different concentrations (0.05% cream and 0.005% ointment fluticasone), either once daily or twice daily. Two trials compared different potency topical corticosteroid in ointment or cream; Kaplan 1978 compared a potent topical corticosteroid cream with a mild topical corticosteroid ointment, and Rajka 1986 compared a potent topical corticosteroid lipocream with a moderate topical corticosteroid ointment.

Data were available for all primary outcomes and for the secondary outcome: patient-reported symptoms of eczema (effectiveness). No data were available for the secondary outcome: number of relevant systemic adverse events (safety).

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

All trials included in this comparison measured clinician-reported signs of eczema.

Pooled analyses: topical corticosteroid cream versus topical corticosteroid ointment

- **Investigator global assessment (IGA)**
  - We pooled IGA as a short-term outcome (week 4) from two within-participant trials (Lasthein Andersen 1988; Rajka 1986), that included 122 participants. The trials used 5- and 6-point scales, and we pooled data from categories corresponding to 'cleared or marked improvement'. The OR was 1.65 (95% CI 0.41 to 6.60; P = 0.48; I^2 = 63%; 2 trials 244 sides treated; Analysis 5.1). This suggests no difference in effectiveness between cream and ointment, but there is a high degree of imprecision. As both trials only presented data for up to 4 weeks, we did not perform a separate analysis for end of treatment.
  - We pooled only two trials that reported IGA (Analysis 5.1), therefore subgroup analyses were not possible.
- **Data not included in the meta-analyses**
  - We did not include five trials in the meta-analysis, either because we could not pool the instrument used to measure clinician-reported signs of eczema alongside those included (Berth-Jones 2003; Cadmus 2019; EUCTR2009-012028-98-DE), or because the numerical data were incomplete (Kaplan 1978; Wilson 2009), and are summarised in Analysis 5.2. In Berth-Jones 2003, the OR for the 9-point, 3-item severity score (TIS) of achieving remission of 1 or less between the cream and ointment was 1.19 (95% CI 0.60 to 2.37) for the once daily topical corticosteroid (195 participants) and 2.06 (95% CI 1.00 to 4.22) for twice daily topical corticosteroid (181 participants). There was no clinically significant difference in EASI or IGA in any of four further trials, although all were small, with a maximum of 58 participants.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Two within-participant trials reported PGA as a comparison between groups in children (Cadmus 2019; Lasthein Andersen 1988). Lasthein Andersen 1988 did not report any difference between lipocream and ointment by (92 participants at week 2; 88 at week 4; P = 0.5). In Cadmus 2019, nine participants thought cream was more effective compared to 16 who preferred ointment (OR 0.43, 95% CI 0.21 to 0.87; 1 trial, 39 participants; day 3-5).

Safety: number of relevant local adverse events (primary outcome)

Six trials looked for local adverse events (Berth-Jones 2003; Cadmus 2019; EUCTR2009-012028-98-DE; Kaplan 1978; Lasthein Andersen 1988; Rajka 1986).

Skin thinning and related signs

There were no cases of skin thinning in a three-week trial in adults (EUCTR2009-012028-98-DE; Analysis 5.3). Related signs were reported in one trial at four weeks (Berth-Jones 2003; Analysis 5.3) with one participant in each group reporting telangiectasia, and one participant who used ointment reporting striae; two of these events preceded the trial treatment, but it is unclear which (426 participants).

Local site reactions

Four trials that compared cream and ointment of one to four weeks' duration reported the number of participants with local site reactions (Cadmus 2019; EUCTR2009-012028-98-DE; Kaplan 1978; Rajka 1986; Analysis 5.4). The most frequently observed local site reaction was burning, reported in a within-participant trial by five participants treated with cream, two of whom also reported burning with ointment (Cadmus 2019; 39 participants). Burning was also reported by a participant in a parallel-group trial, treated with ointment (Kaplan 1978). Eight participants who used cream reported other local site reactions compared to two who used ointment (55 participants from parallel-group trials; 69 participants from within-participant trials), one of which resulted in discontinuation from the trial (Kaplan 1978; unspecified age and severity).

Skin infection

Three trials that compared cream and ointment of one to four weeks' duration reported the number of participants with skin infection (Cadmus 2019; EUCTR2009-012028-98-DE; Lasthein Andersen 1988; Analysis 5.5). No participants reported skin infection using cream (156 participants or sides treated) compared to one who used ointment (156 participants or sides treated).

Safety: number of relevant systemic adverse events (secondary outcome)

Relevant systemic adverse events were not reported in the included parallel-group trials for this comparison.

Unspecified adverse events (safety)

One parallel-group trial that included adults with mild- to moderate-severity disease reported no adverse events (Wilson 2009; up to week 2; 6 participants in the ointment group; 8 in the lipocream group; 8 in the cream group).

Different concentrations of the same topical corticosteroid

We included two trials that compared different concentrations of the same topical corticosteroid. One trial (Dolle 2015), compared two concentrations of an experimental potent topical corticosteroid, GW870086. This cross-over trial in 25 adults with moderate to severe eczema compared 2% (15 sites treated) versus 0.2% (20 sites treated) versions of the cream in specified lesions. An additional four-week, multi-arm, parallel-group trial in adults and children with moderate to severe eczema compared 0.05% cream and 0.005% ointment preparations of the same potent topical corticosteroid (fluticasone; Berth-Jones 2003 once daily application and Berth-Jones 2003 twice daily application).

Different concentrations of the same topical corticosteroid

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

Dolle 2015 assessed clinical signs using the TIS, a clinical signs scale of 0 to 9, where an increase represents worsening eczema. There was no significant difference between the 0.2% and 2% GW870086 groups in the mean change in TIS from baseline at day 7 or 22, although an improvement in the signs of eczema was seen in both groups. At day 7 the mean change in the 2% group was −1.78 (95% CI −2.64 to −0.92; 15 sites treated) versus −1.43 (95% CI −2.18 to −0.67; 20 sites treated) in the 0.2% group. A further reduction by day 22 was seen, mean change of −2.49 (95% CI −3.49 to −1.49; 15 sites treated) in the 2% group and −1.99 (95% CI −2.86 to −1.12; 20 sites treated) with 0.2%. The number of treatment responses (TIS score

1 or less, irrespective of baseline score) at day 22 was 7 with 0.2% and 6 with 2%.

Berth-Jones 2003 reported that 76 of 95 participants achieved remission (TIS ≤ 1) using 0.05% fluticasone cream compared to 77 of 100 who used 0.005% fluticasone ointment applied once daily (OR 1.19, 95% CI 0.60 to 2.37; 195 participants). When applied twice daily, 76 of 91 participants achieved remission using 0.05% fluticasone cream compared to 94 of 90 who used 0.005% fluticasone ointment (OR 2.06, 95% CI 1.00 to 4.22; 181 participants) when applied twice daily.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

None of the three trials reported patient-reported symptoms.

Safety: number of relevant local adverse events (primary outcome)

Dolle 2015 stated that, up to week five (7 to 14 days' follow-up), "GW870086 showed no clinical signs of atrophogenic effects in AD patients," although no values were given.

Berth-Jones 2003 reported one case each of striae and telangiectasia in the 0.005% ointment groups (190 participants) and one case of telangiectasia in the 0.05% cream group (186 participants).

Safety: number of relevant systemic adverse events (secondary outcome)

Neither of the trials reported systemic adverse events in this strategy comparison.

Second-generation topical corticosteroid versus older topical corticosteroid

The term 'second-generation' refers to newer topical corticosteroids, primarily fluticasone propionate and mometasone furoate, developed in the 1990s with the intention of minimising adverse events whilst preserving effectiveness. They are marketed as once daily alternatives to standard topical corticosteroids, which were typically applied twice a day. This is reflected in the regimens and the choice of older topical corticosteroid comparators used in the included trials. There is significant overlap between this comparison and the trials included in the once versus twice daily application comparison. This comparison comprises 15 trials; 12 parallel-group trials (Amerio 1998; Hoybye 1991; Kirkup 2003a; Kirkup 2003b; Lebwohl 1999; Marchesi 1994; Nolting 1991; Prado de Oliveira 2002; Rafanelli 1993; Ryu 1997; Vernon 1991; Wolkerstorfer 1998) and three within-participant trials (Goh 1999; Kim 2013; Reidhav 1996).

Seven trials compared a potent second-generation topical corticosteroid applied once daily with an older topical corticosteroid of a different potency (usually mild/moderate) used more frequently (usually twice daily; Goh 1999; Lebwohl 1999; Nolting 1991; Rafanelli 1993; Ryu 1997; Vernon 1991; Wolkerstorfer 1998). Three trials compared a potent second-generation topical corticosteroid used once daily with the same potency older topical corticosteroid used twice daily (Amerio 1998; Hoybye 1991; Marchesi 1994). A further two trials compared the second-generation potent topical corticosteroid with a mild-potency older topical corticosteroid, both used once daily (Kirkup 2003a; Prado de Oliveira 2002). Only three trials were single strategy, that is, a second-generation potent topical corticosteroid versus an older topical corticosteroid of the same potency and both applied the same number of times per day (Kim 2013; Kirkup 2003b; Reidhav 1996).

Data were available for all outcomes relevant to this review.

Second-generation topical corticosteroid versus older topical corticosteroid

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

All trials included in this comparison measured clinician-reported signs of eczema.

Pooled analyses: second-generation topical corticosteroid versus older topical corticosteroid

- **Dichotomous investigator global assessment (IGA)**
  - We pooled IGA as a short-term outcome (range 1 to 4 weeks) from nine parallel-group trials (Amerio 1998; Hoybye 1991; Kirkup 2003a; Kirkup 2003b; Lebwohl 1999; Marchesi 1994; Nolting 1991; Rafanelli 1993; Ryu 1997), involving 824 participants. Most trials used a 4-, 5-, or 6-point scale and we pooled data from categories corresponding to 'cleared or marked improvement' where possible. Overall, 251 of 383 participants achieved cleared or marked improvement when using second-generation topical corticosteroid compared to 196 of 408 participants who used older topical corticosteroids. The OR across all single-strategy and multiple-strategy trials that compared a second-generation topical corticosteroid with an older topical corticosteroid was 2.52 (95% CI 1.47 to 4.30; P = 0.0007; I^2 = 27%; 9 trials, 824 participants; Analysis 6.1), in favour of second-generation topical corticosteroid. This corresponds to a need to treat 4.6 people with a second-generation topical corticosteroid to achieve an additional treatment success compared to older topical corticosteroid (95% CI 3.1 to 10.4).
  - We then pooled IGA from three trials in adults only (Hoybye 1991; Marchesi 1994; Nolting 1991). The OR for achieving cleared or marked improvement in adults was 1.70 (95% CI 0.88 to 3.31; P = 0.12; I^2 = 0%; 3 trials, 221 participants; Analysis 6.2.1), showing no difference between groups. We included four trials in children, as a short-term outcome (Kirkup 2003a; Kirkup 2003b; Lebwohl 1999; Rafanelli 1993). The OR for achieving cleared or marked improvement in children was 2.68 (95% CI 1.07 to 6.76; P = 0.04; I^2 = 40%, 4 trials, 483 participants; Analysis 6.2.2), favouring second-generation topical corticosteroid. The test for subgroup differences for Analysis 6.2 had a P value of 0.43, suggesting that the effect of second-generation topical corticosteroid was not dependent on age.
  - We were unable to perform subgroup analyses based on severity due to the lack of trials in participants with milder disease, which is reasonable considering that the second-generation topical corticosteroids are potent topical corticosteroids. We restricted the previous analyses to the seven trials that reported IGA in participants with moderate to severe eczema as a short-term outcome (range 1 to 4 weeks; Amerio 1998; Hoybye 1991; Kirkup 2003a; Kirkup 2003b; Lebwohl 1999; Marchesi 1994; Rafanelli 1993). The OR for achieving cleared or marked improvement in moderate to severe eczema was consistent with the overall estimate

(OR 2.40, 95% CI 1.53 to 3.79; P = 0.0002; I^2 = 0%; 7 trials, 734 participants; Analysis 6.3).

- We also found similar results at end of treatment overall (Amerio 1998; Hoybye 1991; Lebwohl 1999; Marchesi 1994; Nolting 1991; Prado de Oliveira 2002; Rafanelli 1993; Ryu 1997); 2.79 (95% CI 1.71 to 4.56; P < 0.0001; I^2 = 5%; 8 trials, 580 participants; Analysis 6.4); in adults versus children (Hoybye 1991; Lebwohl 1999; Marchesi 1994; Nolting 1991; Prado de Oliveira 2002; Rafanelli 1993; P = 0.41; Analysis 6.5); and in moderate to severe eczema (range 1 to 6 weeks; Amerio 1998; Hoybye 1991; Lebwohl 1999; Marchesi 1994; Prado de Oliveira 2002; Rafanelli 1993); OR 2.74 (95% CI 1.64 to 4.58; P = 0.0001; I^2 = 0%; 6 trials, 490 participants; Analysis 6.6).
- As we had noted at data extraction that several trials were industry-sponsored, we repeated both short-term and end-of-treatment analyses of IGA data in a post-hoc sensitivity analysis to exclude trials with obvious links to industry (Hoybye 1991; Kirkup 2003a; Kirkup 2003b; Lebwohl 1999; Marchesi 1994). The OR in the short term was 4.11 (95% CI 1.15 to 14.63; P = 0.03; I^2 = 40%; 247 participants; Table 8), and at end of treatment was 3.46 (95% CI 1.32 to 9.06; P = 0.01; I^2 = 39%; 271 participants). Removing several trials judged high risk of bias expanded the 95% CI to include 1 (see: Table 6); OR 2.12 (95% CI 0.51 to 8.81).

- **Mean investigator global assessment (IGA)**
  - We pooled mean IGA in two trials (range 14 to 16 weeks that included a two- to four-week acute treatment phase) in 193 children with moderate to severe eczema (Kirkup 2003a; Kirkup 2003b). MD was −1.63 (95% CI −2.57 to −0.69; P = 0.0007; I^2 = 0%; 2 trials, 193 participants; Analysis 6.7) in favour of second-generation topical corticosteroid. The single strategy trial was consistent with the multiple strategy trial.
  - As both trials that reported mean IGA at end of treatment (Analysis 6.7) included children with moderate to severe eczema only, no further restricted analysis was possible.
- **Investigator-assessed clinical signs**
  - We pooled investigator assessment of clinical signs as a short-term outcome (range 7 to 15 days) from two trials (Kim 2013; Wolkerstorfer 1998), in 180 participants; 21 from the parallel-group trial and 159 from the within-participant trial. The SMD was 0.16 (95% CI −0.45 to 0.77; P = 0.61; I^2 = 56%; 2 trials, 339 participants or sides treated; Analysis 6.8), suggesting no difference between treatments. The short-term time point was the end of treatment for Kim 2013; therefore we did not do a separate end of treatment meta-analysis.
  - As we included only two trials in SMD Analysis 6.8, subgroup analyses were not possible.
- **Data not included in the meta-analyses**
  - We did not include two small trials in any meta-analyses because the numerical data were incomplete (Reidhav 1996; Vernon 1991). We have summarised these in Analysis 6.9, and neither demonstrated a difference between the second-generation and older topical corticosteroid. We did not include another in the meta-analyses because it was thought to be clinically incomparable owing to the use of a more potent topical corticosteroid more frequently than the less potent topical corticosteroid, however we also include the results narratively (Goh 1999). One trial that was included in SMD Analysis 6.8 also reported some limited follow-up data (Wolkerstorfer 1998), also included in Analysis 6.9.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Pooled analyses: second-generation topical corticosteroid versus older topical corticosteroid

- **Itch**
  - We pooled the number of participants who judged itch to be better as a short-term outcome (week 2 to 4) from two parallel-group trials that included 243 children with moderate to severe eczema (Kirkup 2003a; Kirkup 2003b). The OR at week 2 to 4 was 2.26 (95% CI 1.24 to 4.14; P = 0.008; I^2 = 0%; 2 trials, 243 participants; Analysis 6.10). The single strategy trial was similar to the multiple strategy trial, although the multiple strategy trial was not statistically significant. However, when we pooled the same two trials at end of treatment (week 14 to 16) the significance between groups was not maintained (OR 1.16, 95% CI 0.60 to 2.25; P = 0.67; I^2 = 0%; 2 trials, 193 participants; Analysis 6.11).
- **Sleep disturbance**
  - We pooled the number of participants who judged sleep disturbance to be better as a short-term outcome (week 2 to 4) from two parallel-group trials that included 242 children with moderate to severe eczema (Kirkup 2003a; Kirkup 2003b). The OR at week 2 to 4 was 2.09 (95% CI 1.15 to 3.81; P = 0.02 I^2 = 0%; 2 trials, 242 participants; Analysis 6.12). The single-strategy trial was consistent with the multiple-strategy trial. We found similar results at end of treatment (week 14 to 16; Kirkup 2003a; Kirkup 2003b; OR 2.41, 95% CI 1.03 to 5.65; P = 0.04; I^2 = 19%; 2 trials, 193 participants; Analysis 6.13).
  - Both trials that reported the number of participants who judged itch and sleep disturbance to be better (Analysis 6.10; Analysis 6.11; Analysis 6.12; Analysis 6.13), included children with moderate to severe eczema only, therefore no further restricted analysis was possible.
- **Data not included in the meta-analyses**
  - Six additional trials included in this comparison measured patient-reported symptoms of eczema in some way, most were of a reasonable size (Amerio 1998; Goh 1999; Hoybye 1991; Kim 2013; Rafanelli 1993; Reidhav 1996), and are summarised in Analysis 6.14. The results are mixed, however most trials reported little or no difference between groups in itch or patient global assessment.

Safety: number of relevant local adverse events (primary outcome)

Thirteen trials looked for local adverse events (Amerio 1998; Goh 1999; Hoybye 1991; Kim 2013; Kirkup 2003a; Kirkup 2003b; Lebwohl 1999; Marchesi 1994; Nolting 1991; Prado de Oliveira 2002; Rafanelli 1993; Ryu 1997; Vernon 1991). Overall, the rate of local adverse events was low.

Skin thinning and related signs

Eleven trials that compared second-generation topical corticosteroid versus older topical corticosteroid for two to six weeks reported the number of participants with skin thinning (Amerio 1998; Goh 1999; Hoybye 1991; Kirkup 2003a; Kirkup 2003b; Lebwohl 1999; Nolting 1991; Prado de Oliveira 2002; Rafanelli 1993; Ryu 1997; Vernon 1991; Analysis 6.15). Six out of 513 participants who used second-generation topical corticosteroid reported skin

thinning compared to four out of 501 participants who used older topical corticosteroid. Two trials reported all the events (Nolting 1991; Prado de Oliveira 2002), one in children and the other in adults. One trial reported related signs; there were no events in either group (Prado de Oliveira 2002; 25 participants).

Local site reactions

Eight trials that compared second-generation topical corticosteroid versus older topical corticosteroid for two to 16 weeks reported the number of participants with local site reactions: burning, itching, stinging, rashes (Prado de Oliveira 2002; Kim 2013; Kirkup 2003a; Kirkup 2003b; Lebwohl 1999; Marchesi 1994; Vernon 1991; Ryu 1997; Analysis 6.16). Ten out of 497 participants who used second-generation topical corticosteroid reported local site reactions compared to twelve out of 491 participants who used older topical corticosteroid.

Skin infections

Four trials that compared second-generation topical corticosteroid versus older topical corticosteroid for two to 16 weeks' duration reported the number of participants with skin infections (Kirkup 2003a; Kirkup 2003b; Ryu 1997; Vernon 1991; Analysis 6.17). There were three reports of skin infections across the second-generation topical corticosteroid compared with four in the control, older topical corticosteroid groups (464 participants) and there was no more than one participant per arm in each trial with an adverse event. One *Staphylococcus aureus* infection of the scalp in the second-generation group resulted in discontinuation from the trial (Vernon 1991; children with moderate to severe eczema).

Other local adverse events

One trial, of 42 days' duration, reported hair growth in one participant who used second-generation potent topical corticosteroid (Prado de Oliveira 2002; 25 participants).

Safety: number of relevant systemic adverse events (secondary outcome)

Seven trials reported on systemic adverse events.

Four trials of three to six weeks' duration reported on the number of participants with abnormal cortisol levels (Hoybye 1991; Rafanelli 1993; Vernon 1991; Wolkerstorfer 1998; Analysis 6.18). In the trials that provided exact numbers of participants (Rafanelli 1993; Vernon 1991; Wolkerstorfer 1998), none had abnormal cortisol in the second-generation topical corticosteroid group (65 participants) compared to two in the older topical corticosteroid group (63 participants).

Three trials reported that no relevant systemic adverse events occurred (Kirkup 2003b; Marchesi 1994; Prado de Oliveira 2002).

Unspecified adverse events (safety)

Nolting 1991 looked for adverse events, in addition to skin thinning reported above, however, the trial authors report that no other significant adverse events occurred.

Also in addition to the skin thinning data reported above, Hoybye 1991 found that "Treatment-related side effects were few, and these were similar in both patient groups." These adverse events were reported to be stinging, burning, itching, dryness, acne, folliculitis, and hair growth.

Branded topical corticosteroid versus generic topical corticosteroid

We found no trials that involved the use of this strategy.

Twice or more versus once daily topical corticosteroid

See: Summary of findings 5.

This comparison comprises 25 trials; 22 parallel-group trials (Amerio 1998; Beattie 2004; Berth-Jones 2003; Bleehen 1995; Bryden 2009; Del Rosso 2009; Harder 1983; Hoybye 1991; Koopmans 1995; Lebwohl 1999; Marchesi 1994; Meffert 1999; Msika 2008; Nolting 1991; Rafanelli 1993; Rampini 1992a; Richelli 1990; Ryu 1997; Schlessinger 2006; Tharp 1996; Vernon 1991; Wolkerstorfer 1998), and three within-participant trials (Goh 1999; Haneke 1992; Sudilovsky 1981). In 11 trials only the daily frequency of topical corticosteroid application varied between groups, whilst the other 14 trials included multiple strategies, for example, once daily potent topical corticosteroid versus twice daily moderate-potency topical corticosteroid.

Nine of these 14 trials compared a newer, second-generation potent topical corticosteroid (mometasone furoate or fluticasone propionate) applied once daily versus older topical corticosteroid applied twice daily - either potent (Amerio 1998; Hoybye 1991; Marchesi 1994), moderate potency (Lebwohl 1999; Nolting 1991; Rafanelli 1993; Wolkerstorfer 1998), or mild potency (Ryu 1997; Vernon 1991). One trial compared the once daily, second-generation potent topical corticosteroid with a stronger topical corticosteroid applied twice daily (very potent; Goh 1999), and we did no include it in any meta-analyses on the basis that it was not clinically comparable; the more potent topical corticosteroid was used more frequently rather than less frequently. Two further trials compared either three times daily potent topical corticosteroid with once daily very potent topical corticosteroid (Harder 1983), or twice daily moderate-potency topical corticosteroid with once daily use of a potent topical corticosteroid (Rampini 1992a); both used older topical corticosteroid. The remaining two trials compared once daily mild topical corticosteroid applied under wet wraps with twice daily application without occlusion (Beattie 2004; Bryden 2009 which used twice daily application in the control group in the first week).

Data were available for all outcomes relevant to this review.

Twice or more versus once daily topical corticosteroid

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

All trials included in this comparison measured clinician-reported signs of eczema. Taken together, we judged the certainty of evidence to be moderate.

Pooled analyses: twice or more versus once daily topical corticosteroid

- **Investigator global assessment (IGA)**
  - We pooled IGA as a short-term outcome (range 1 to 4 weeks) from 15 trials (Amerio 1998; Bleehen 1995; Del Rosso 2009; Harder 1983; Hoybye 1991; Koopmans 1995; Lebwohl 1999; Marchesi 1994; Nolting 1991; Rafanelli 1993; Rampini 1992a; Ryu 1997; Schlessinger 2006; Sudilovsky 1981; Tharp 1996), that included 1821 participants; 1672 from the parallel-group trials and 149 from the within-participant trial. Most trials used a 4-, 5-, or 6-point scale

and we pooled data from categories corresponding to 'cleared or marked improvement' where possible. In the parallel-group trials, 538 of 824 participants who applied topical corticosteroid twice daily achieved cleared or marked improvement compared to 553 of 848 in the once daily group. In the within-participant trial, 87 of 149 achieved cleared or marked improvement on the side treated with twice daily topical corticosteroid compared to 80 of 149 on the side treated with once daily topical corticosteroid. The OR across all single-strategy and multiple-strategy trials in which frequency of daily application differed between groups was 0.97 (95% CI 0.68 to 1.38; P = 0.86; I^2 = 45%; 15 trials, 1970 participants or sides treated; Analysis 7.1), indicating no benefit in applying topical corticosteroid more than once daily. Meta-analysis of trials where the only difference between the groups was the frequency of application also showed no benefit of more frequent application (Analysis 7.1.1 and Analysis 7.1.2). However, there was more variation across trials comparing multiple strategies. As for the single strategy trials, twice daily moderate-potency topical corticosteroid versus once daily potent topical corticosteroid (either newer second-generation or older; Analysis 7.1.5 and 7.1.6) showed no difference between once and twice daily application. However, once daily potent second-generation topical corticosteroid was more effective than twice daily application of equivalent potency older topical corticosteroid (Analysis 7.1.3). Ryu 1997 found once daily potent second-generation topical corticosteroid was more effective than mild topical corticosteroid applied twice a day (Analysis 7.1.4; 23 participants) whilst Harder 1983 found that very potent topical corticosteroid applied once daily was less effective than potent topical corticosteroid applied three times daily (Analysis 7.1.7). Both Ryu 1997 and Harder 1983 were small trials with wide confidence intervals.

- The short-term time point was the end of treatment for most trials; therefore, we did not do a separate end of treatment meta-analysis.
- We then pooled IGA from four trials in adults only (Del Rosso 2009; Hoybye 1991; Marchesi 1994; Nolting 1991), and four trials in children only (Lebwohl 1999; Rafanelli 1993; Rampini 1992a; Schlessinger 2006). The OR for achieving cleared or marked improvement in the short term in adults was 0.77 (95% CI 0.51 to 1.17; P = 0.23; I^2 = 0%; 4 trials, 432 participants; Analysis 7.2.1) and in children 0.79 (95% CI 0.32 to 1.94; P = 0.61; I^2 = 0%, 4 trials, 478 participants; Analysis 7.2.2).
- We were unable to perform subgroup analyses based on severity owing to the lack of trials in participants with milder disease. Therefore, we performed a restricted analysis of nine parallel-group trials that reported IGA in participants with moderate to severe eczema as a short-term outcome (Amerio 1998; Bleehen 1995; Del Rosso 2009; Hoybye 1991; Lebwohl 1999; Marchesi 1994; Rafanelli 1993; Schlessinger 2006; Tharp 1996). The OR for achieving cleared or marked improvement was 0.93 (95% CI 0.65 to 1.34; P = 0.71; I^2 = 19%; 9 trials, 1254 participants; Analysis 7.3), indicating that for people with more severe eczema, there is no benefit in applying topical corticosteroid more than once daily.
- IGA data were available after two weeks' follow-up from two parallel-group trials, with 163 participants included in the twice daily topical corticosteroid group and 170 included in the once daily group (Del Rosso 2009; Schlessinger 2006). Ninety-eight of 163 participants who applied topical corticosteroid twice daily achieved cleared or marked improvement compared to 83 of 170 in the once daily group. The OR was 1.58 (95% CI 0.80 to 3.10; P = 0.19; I^2 = 41%; 2 trials, 333 participants; Analysis 7.4), in line with the lack of difference between groups during treatment.

- **Investigator assessment of clinical signs**
  - We pooled investigator assessment of clinical signs as a short-term outcome (week 1) from two trials in 40 children with moderate-severity eczema (Wolkerstorfer 1998; Beattie 2004). The once daily group in Beattie 2004 applied the mild topical corticosteroid under wet wraps. The SMD in the short term (week 1) was a decrease of 0.40 (95% CI −0.23 to 1.03; P = 0.21; I^2 = 0%; 2 trials, 40 participants; Analysis 7.5), indicating no benefit from applying topical corticosteroid more than once daily in children with moderate to severe eczema. Similar results were found at end of treatment (2 to 4 weeks; SMD 0.51, 95% CI −0.32 to 1.33; P = 0.23; I^2 = 0%; 2 trials, 24 participants; Analysis 7.6).
  - As all trials included in SMD Analysis 7.5 and Analysis 7.6 included children with moderate-severity eczema only, no further subgroup analyses were possible.
- **Data not included in the meta-analyses**
  - Eight trials were not included in any meta-analyses either because the instrument used to measure clinician-reported signs of eczema could not be pooled with those included (Berth-Jones 2003; Bryden 2009), because the numerical data were incomplete (Haneke 1992; Meffert 1999; Msika 2008; Richelli 1990; Vernon 1991), or because the trial was judged not clinically comparable owing to the more potent topical corticosteroid being used more frequently than the less potent topical corticosteroid (Goh 1999). These have been summarised in Analysis 7.7 and are generally consistent with no difference between groups (879 participants). Two trials that were included in SMD Analysis 7.5 and Analysis 7.6 also reported some limited follow-up data (Beattie 2004; Wolkerstorfer 1998), also included in Analysis 7.7.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Eleven trials included in this comparison measured patient-reported symptoms of eczema. Taken together, we judged the certainty of evidence to be low.

Pooled analyses: twice or more versus once daily topical corticosteroid

We pooled PGA as a short-term outcome (range 1 to 4 weeks) from two trials (Koopmans 1995; Tharp 1996). The trials used a 4- or 6-point scale and we pooled data from categories corresponding to 'cleared or marked improvement' where possible. In the group treated with twice daily topical corticosteroid 128 of 151 achieved cleared or marked improvement; 114 of 149 participants achieved cleared or marked improvement in the once daily topical corticosteroid group. The OR was 1.91 (95% CI 0.62 to 5.83; P = 0.26; I^2 = 67%; 2 trials, 300 participants; Analysis 7.8). The short-term time point was the end of treatment for one of the two trials; therefore, we did not do a separate end of treatment meta-analysis.

Both trials that reported PGA included adults and children, and only one of these gave baseline severity of eczema; therefore, no subgroup or restricted analyses were possible.

Data not included in the meta-analyses

We did not include nine trials in the meta-analyses, either because the instrument used to measure clinician-reported signs of eczema could not be pooled alongside those included, because the numerical data were incomplete, or because we judged the comparison not clinically comparable. We have summarised these in Analysis 7.9 and they are generally consistent with no difference between groups.

Safety: number of relevant local adverse events (primary outcome)

Nineteen trials looked for local adverse events (Amerio 1998; Beattie 2004; Berth-Jones 2003; Bleehen 1995; Del Rosso 2009; Goh 1999; Haneke 1992; Hoybye 1991; Koopmans 1995; Lebwohl 1999; Marchesi 1994; Nolting 1991; Rafanelli 1993; Rampini 1992a; Ryu 1997; Schlessinger 2006; Sudilovsky 1981; Tharp 1996; Vernon 1991). Meffert 1999 also reported local adverse events, however, they did not present data separately for the comparison of interest. Taken together, we judged the certainty of evidence to be low.

Skin thinning and related signs

Twelve trials that compared twice or more versus once daily application of topical corticosteroid for two to six weeks reported skin thinning or related signs (Amerio 1998; Berth-Jones 2003; Del Rosso 2009; Goh 1999; Haneke 1992; Hoybye 1991; Lebwohl 1999; Nolting 1991; Rafanelli 1993; Ryu 1997; Schlessinger 2006; Vernon 1991; Analysis 7.10). Trials reported skin thinning in 10 participants in both the twice or more times daily group (706 participants) and the once daily topical corticosteroid group (717 participants; Analysis 7.10.1). Eight of these were reported in two trials, which both used very potent topical corticosteroid (Del Rosso 2009; Schlessinger 2006). Three trials reported on clinical signs relating to skin thinning although it is unclear whether multiple signs were experienced by the same participants. Berth-Jones 2003 reported that one participant experienced striae and two reported telangiectasia. However, two of the three events preceded the start of trial treatment, and it is unclear which, so we have not included this trial in any subsequent summary statistics.

Local site reactions

Eight trials that compared twice or more versus once daily application of topical corticosteroid for four to six weeks reported the number of participants with local site reactions (Bleehen 1995; Koopmans 1995; Lebwohl 1999; Marchesi 1994; Rampini 1992a; Sudilovsky 1981; Tharp 1996; Vernon 1991; Analysis 7.11). Haneke 1992 also reported local site reactions, however, they did not present data separately for each comparison of interest. Across the trials that gave exact numbers of participants, almost all trials reported at least one event, with the largest number of participants reporting irritation in Bleehen 1995 (2/133 in the twice daily group; 5/137 in the once daily group, both treated with second-generation topical corticosteroid). Overall, 651 participants were treated with twice (or more) daily topical corticosteroid and 655 with once daily topical corticosteroid.

Skin infection

Five trials that compared twice or more versus once daily application of topical corticosteroid for two to six weeks' duration reported the number of participants with skin infection (Beattie 2004; Koopmans 1995; Rampini 1992a; Ryu 1997; Vernon 1991; Analysis 7.12). Haneke 1992 also reported skin infections, however, they did not present data separately for each comparison of interest. One participant who used twice daily topical corticosteroid reported folliculitis (174 participants) compared to seven participants who reported folliculitis and one who reported impetigo contagiosa in the once daily group (175 participants). One *Staphylococcus aureus* infection of the scalp in the once daily topical corticosteroid group was stated to have resulted in discontinuation from the trial (Vernon 1991; children with moderate to severe eczema).

Other local adverse events

In addition, Goh 1999 reported no other local adverse events up to day 22 (within-participant trial; 58 participants). Other adverse events are described under 'Unspecified adverse events (safety)'.

Safety: number of relevant systemic adverse events (secondary outcome)

Ten parallel-group trials looked for systemic adverse events. Meffert 1999 also reported systemic adverse events, however, they did not present data separately for each group. Taken together, we judged the certainty of evidence to be very low.

Seven trials of one to six weeks' duration measured abnormal cortisol levels (Del Rosso 2009; Hoybye 1991; Rafanelli 1993; Richelli 1990; Schlessinger 2006; Vernon 1991; Wolkerstorfer 1998; Analysis 7.13). Across the four trials that gave exact numbers of participants, five events were reported in 124 children with moderate to severe eczema who used twice daily topical corticosteroid compared to none in 125 who used once daily topical corticosteroid. Three trials reported that no relevant systemic adverse events occurred (Berth-Jones 2003; Marchesi 1994; Rampini 1992a; 544 participants).

Unspecified adverse events (safety)

An additional trial (Harder 1983), looked for adverse events. None were reported (up to week 3; 72 participants).

Nolting 1991 looked for adverse events, in addition to skin thinning reported above, however the trial authors report that no other significant adverse events occurred. Also, in addition to the skin thinning data reported above, Hoybye 1991 found that "Treatment-related side effects were few, and these were similar in both patient groups." These adverse events were reported to be stinging, burning, itching, dryness, acne, folliculitis, and hair growth.

Daily application versus less frequent application

This comparison is focused on comparing different number of days per week topical corticosteroids are applied for treating eczema. This differs from the daily frequency comparison, which compared different number of applications per day, assuming daily application, and from the weekend (proactive) therapy comparison, in which a defined two days per week of treatment is used for preventing flares. This comparison comprises four trials; three parallel-group trials (Msika 2008; Sillevis 2000; Thomas 2002), and one within-participant trial (Mahrle 1989). Two trials compared daily application with application only on alternate days, two-day intervals between applications, or three-day intervals (Mahrle 1989; Msika 2008). Two trials compared daily application with application only on three to four consecutive days of each week (Sillevis 2000; Thomas 2002). Thomas 2002 compared mild topical corticosteroid used for seven days to a three-day 'pulse' of potent topical corticosteroid for management of flares.

Data were available for all primary outcomes and for the secondary outcome: patient-reported symptoms of eczema (effectiveness). No data were available for the secondary outcome: number of relevant systemic adverse events (safety).

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

All four included trials for this comparison reported this outcome and we summarised the results narratively in Analysis 8.1. There was no difference in clinical signs of eczema between daily and less frequent application (i.e. one day in every 2 to 3 days) although this was across a low number of participants; 44 in a within-participant trial (Mahrle 1989), and 36 in a parallel-group trial (Msika 2008). However, there were clinically significant improvements in signs of eczema in both groups. Of the two trials that compared daily application with a three- to four-day 'pulse', one suggested that pulse treatment with moderate or potent topical corticosteroid is as effective as everyday use of moderate or mild topical corticosteroid, and that both strategies result in clinically significant improvements signs of eczema (Thomas 2002; 87 participants in both groups), and one suggested that 'pulse' treatment might be more beneficial, however this trial was very small (Sillevis 2000; 20 participants).

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

One trial in children with mild to moderate eczema showed no difference in itch between seven days of mild topical corticosteroid and a three-day 'pulse' of potent topical corticosteroid (Thomas 2002). The median number of scratch-free days was 118 (interquartile range (IQR) 99.8 to 124.0; 98 participants) and 117.5 (IQR 99.3 to 125.0; 100 participants) respectively, a difference of 0.5 days (95% CI −3.0 to 2.0, P = 0.68) over 18 weeks. Furthermore, there was no significant difference in sleep a subgroup of participants. The median number of undisturbed nights was 123 (IQR 109.5 to 126.0; 81 participants) in the daily topical corticosteroid group compared to 121 (IQR 101.3 to 126.0; 84 participants) in the 'pulse' group, a difference of two nights (95% CI 0.0 to 2.0, P = 0.53) over 18 weeks.

Safety: number of relevant local adverse events (primary outcome)

Thomas 2002 reported no cases of clinically significant skin thinning in either group up to 18 weeks (daily mild topical corticosteroid 104 participants; 3-day potent topical corticosteroid 'pulse' 103 participants). Two participants in the 'pulse' group, who used potent topical corticosteroid for three days per week, reported spots/rash, and one reported hair growth. No other adverse events were reported.

Safety: number of relevant systemic adverse events (secondary outcome)

None of the trials included in this comparison reported any relevant systemic adverse events.

Unspecified adverse events (safety)

One small trial (27 participants) of moderate-potency topical corticosteroid in children with moderate to severe eczema reported 20 non-specified, non-serious adverse events in both the daily application and the four-days-per-week groups up to week 12 (Sillevis 2000; unpublished data).

Longer- versus shorter-term duration of use for induction of remission

See: Summary of findings 6.

We did not find any trials that involved the use of this strategy.

Topical corticosteroid alternating with topical calcineurin inhibitor versus topical corticosteroid alone

We included only one trial (Sikder 2005), that compared topical corticosteroid alternating with topical calcineurin inhibitor (15 participants) versus topical corticosteroid alone (15 participants). This parallel-group, short-term trial in children aged 7 to 15 years old with moderate to severe eczema compared a moderate-potency topical corticosteroid in the morning and 0.03% tacrolimus ointment in the evening (alternating group) versus a moderate-potency topical corticosteroid applied twice daily. Treatment for continued for four weeks, with two weeks' follow-up.

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

This trial combined EASI (scale of 0 to 72, increase represents worsening eczema) with a patient assessment of itching. Both groups showed significant improvement in eczema at week 4 in this composite outcome; median reduction (representing an improvement) in modified EASI from baseline was 98.7% in the alternating group (15 participants) compared to 95.1% in the group who received topical corticosteroid alone (14 participants). Median increase in adjusted EASI score at two weeks after treatment was stopped was 7.9% in the alternating group (14 participants) compared to 20.6% in the group who received topical corticosteroid alone (14 participants).

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Sikder 2005 incorporated the patient-reported outcome of itch into the clinician-reported adjusted EASI score above and did not report it separately.

Safety: number of relevant local adverse events (primary outcome)

Two cases of burning were identified in the alternating group (15 participants) compared to one in the topical corticosteroid alone group (15 participants). One case of itching was reported in the alternating group (15 participants) compared to two in the topical corticosteroid alone group (15 participants).

Safety: number of relevant systemic adverse events (secondary outcome)

There was one case of fever in each group and the trial authors stated, "This event did not suggest a relationship with treatment regimes". No other systemic adverse events were reported over the six-week trial period.

Weekend therapy versus no topical corticosteroid/reactive application

See: Summary of findings 7.

This comparison comprises nine parallel-group trials (Berth-Jones 2003; Fukuie 2012; Fukuie 2016; Glazenburg 2009; Hanifin 2002; Liu 2018; Peserico 2008; Rubio-Gomis 2018; Van Der Meer 1999). Most trials used fluticasone propionate in the topical corticosteroid strategy arm; Peserico 2008 used methylprednisolone aceponate; Fukuie 2016 used betamethasone valerate. All trials were long term; each had a two- to four-week acute treatment phase for flare control and most then proceeded to a 16- to 20-week maintenance phase. In Fukuie 2012, maintenance was six months (assuming participants were treated throughout) and in Fukuie 2016, maintenance was 12 months. Two trials included a follow-up phase: Liu 2018 for an additional 12 weeks and Hanifin 2002 for 24 weeks (although this was only in participants in the weekend therapy group who did not relapse).

Data were available for all outcomes relevant to this review.

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

Eight trials included in this comparison measured clinician-reported signs of eczema. Taken together, we judged the certainty of evidence to be moderate.

Pooled analyses: weekend therapy versus no topical corticosteroid/reactive application

- **Time to relapse**
  - We included seven trials that reported time to relapse (Berth-Jones 2003; Glazenburg 2009; Hanifin 2002; Liu 2018; Peserico 2008; Rubio-Gomis 2018; Van Der Meer 1999), with 621 participants in the weekend therapy group and 528 in the no topical corticosteroid/reactive application group. Definitions of relapse are included in Analysis 9.11. The hazard ratio (HR) for time to relapse was 2.28 (95% CI 1.88 to 2.76; P < 0.00001; I^2 = 0%; 7 trials, 1149 participants; Analysis 9.1), in favour of weekend therapy.
  - We were unable to perform subgroup analyses of trials in adults compared to children owing to the lack of trials in adults only, so we restricted the previous analysis to children. We pooled time to relapse from three trials (Glazenburg 2009; Liu 2018; Rubio-Gomis 2018), with 119 participants in the weekend therapy group and 112 in the no topical corticosteroid/reactive application group. The HR was 2.87 (95% CI 1.90 to 4.34; P < 0.00001; I^2 = 0%; 3 trials, 231 participants; Analysis 9.2), in favour of weekend therapy.
  - We then pooled time to relapse from five trials in 993 participants with moderate to severe eczema (Berth-Jones 2003; Glazenburg 2009; Hanifin 2002; Peserico 2008; Van Der Meer 1999). The HR was 2.12 (95% CI 1.73 to 2.60; P < 0.00001; I^2 = 0%; 5 trials, 993 participants; Analysis 9.3.1), in favour of weekend therapy. We also pooled two trials in 156 participants with mild- to moderate-severity eczema (Liu 2018; Rubio-Gomis 2018). The HR was 3.50 (95% CI 2.04 to 6.00; P < 0.00001; I^2 = 0%; 2 trials, 156 participants; Analysis 9.3.2), also in favour of weekend therapy.
- **Number of participants with one or more relapses**
  - We included seven trials that reported the number of participants with one or more relapses (Berth-Jones 2003; Glazenburg 2009; Hanifin 2002; Liu 2018; Peserico 2008; Rubio-Gomis 2018; Van Der Meer 1999), with 621 participants in the weekend therapy group and 528 in the no topical corticosteroid/reactive application group. The risk ratio (RR), the statistic chosen to be comparable with the previous analysis by Schmitt 2011, for relapse was 0.43 (95% CI 0.32 to 0.57; P < 0.00001; I^2 = 67%; 7 trials, 1149 participants; Analysis 9.4), in favour of weekend therapy. This corresponds to a number needed to treat for an additional beneficial outcome of 3.0 with weekend therapy to prevent a relapse compared to no topical corticosteroid/reactive application (95% CI 2.6 to 4.0).
  - Two trials reported number of participants with one or more relapses in 171 adults (Hanifin 2002; Van Der Meer 1999). The RR was 0.42 (95% CI 0.24 to 0.75; P = 0.003 I^2 = 59%; 2 trials, 171 adults; Analysis 9.5.1). Four trials reported number of participants with one or more relapses in 462 children (Glazenburg 2009; Hanifin 2002; Liu 2018; Rubio-Gomis 2018). The RR was 0.39 (95% CI 0.24 to 0.62; P < 0.00001; I^2 = 68%; 4 trials, 462 children; Analysis 9.5.2).
- We then pooled number of participants with one or more relapses from five trials that included 993 participants with moderate to severe eczema (Berth-Jones 2003; Glazenburg 2009; Hanifin 2002; Peserico 2008; Van Der Meer 1999). The RR was 0.46 (95% CI 0.35 to 0.61; P < 0.00001; I^2 = 61%; 5 trials, 993 participants; Analysis 9.6.1), in favour of weekend therapy. Two trials in 156 participants with mild- to moderate-severity eczema were also included (Liu 2018; Rubio-Gomis 2018). The RR was 0.23 (95% CI 0.04 to 1.24; P = 0.09; I^2 = 84%; 2 trials, 156 participants; Analysis 9.6.2), also in favour of weekend therapy.
- We noted at data extraction that several trials were industry-sponsored. However, we did not conduct a post-hoc sensitivity analysis excluding trials with obvious links to industry as this resulted in insufficient trials for pooling. Five trials were sponsored by Glaxo Wellcome (Berth-Jones 2003; Glazenburg 2009; Hanifin 2002; Liu 2018; Van Der Meer 1999), and one was sponsored by Intendis GmbH (Peserico 2008).
- **Data not included in the meta-analyses**
  - Fukuie 2016 reported median change in SCORAD, so we were unable to pool it. They made observations after three months and again after 12 months in children with moderate to severe eczema (30 children; 15 in each arm). After three months, median change was 42.6 (IQR 31.7 to 50.7) in the weekend therapy arm compared to 28.5 (IQR 18.3 to 39.7) in the reactive application arm. After 12 months, median change was 46.9 (IQR 38.7 to 57.2) in the weekend therapy arm compared to 36.1 (IQR 16.1 to 41.8) in the reactive application arm (P = 0.018). We extracted data using WebPlotDigitizer.
  - Liu 2018 reported follow-up data at week 32 in children with mild to moderate eczema. Risk of relapse was 5.0 higher (2.4 to 10.1; 54 children vs 53; P < 0.0001) in children just using emollient.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Four trials reported this outcome, summarised in Analysis 9.7. Trials reported results for itch (Peserico 2008; Rubio-Gomis 2018), sleep (Peserico 2008; Rubio-Gomis 2018), and PGA (Hanifin 2002; Liu 2018). The two trials that reported itch measures both favoured weekend therapy (270 participants). One trial that reported a sleep measure gave unclear findings (Rubio-Gomis 2018; 49 participants), whilst another stated that it favoured weekend therapy (Peserico 2008; 221 participants).

One trial (Hanifin 2002), reported the number of participants who judged their eczema to be excellent or good: 163 of 225 judged their eczema to be excellent or good in the weekend therapy group; 38 of 118 judged their eczema to be excellent or good in the vehicle group. The risk ratio for adults and children at end of treatment (week 20 + 4 weeks acute phase) was 2.25 (95% CI 1.71 to 2.96; 343 participants). One further trial that reported PGA (Liu 2018), was unsuitable for pooled analysis (107 participants) as it was unclear what statistic they reported.

Taken together, we judged the certainty of evidence to be moderate.

Safety: number of relevant local adverse events (primary outcome)

Eight trials looked for local adverse events (Berth-Jones 2003; Fukuie 2016; Glazenburg 2009; Hanifin 2002; Liu 2018; Peserico 2008; Rubio-Gomis 2018; Van Der Meer 1999). Taken together, we judged the certainty of evidence to be low.

Skin thinning and related signs

Seven trials looked for the number of participants with skin thinning and related signs and reported no cases (1050 participants; 572 with weekend therapy and 478 without; Analysis 9.8). Glazenburg 2009 reported one participant with telangiectasia, described as “pre-atrophy”, in each group (75 participants).

Skin infection

Two trials of participants with moderate to severe eczema reported the number of participants with skin infection (Fukuie 2016; Hanifin 2002; Analysis 9.9). Hanifin 2002 reported one participant with acne in the weekend therapy group (229 adults and children; up to 20 weeks) and none in the placebo group (119 participants). Fukuie 2016 reported one participant with eczema herpeticum in both groups (both groups with 15 participants; children only; up to 12 months). Fukuie 2016 also reported four cases of impetigo contagiosa in the weekend therapy group compared to three in the ‘as required’ group. It might be speculated that such a high number in both arms could be due to occlusive properties of the emollient used.

Other local adverse events

Two additional trials in children with mild to moderate eczema reported no local adverse events (Liu 2018, 106 participants; Rubio-Gomis 2018, 49 participants). Rubio-Gomis 2018 looked for hypertrichosis and found no cases.

Safety: number of relevant systemic adverse events (secondary outcome)

Eight trials looked for systemic adverse events. We judged the certainty of evidence to be very low.

Five trials reported the number of participants with abnormal cortisol levels (Fukuie 2012; Fukuie 2016; Glazenburg 2009; Hanifin 2002; Van Der Meer 1999; Analysis 9.10). Hanifin 2002 reported one participant in each group with abnormal cortisol levels, however it was unclear how many participants in each group they assessed for this outcome, and they stated that both were not newly observed.

Three trials reported no relevant systemic adverse events (Berth-Jones 2003; Liu 2018; Rubio-Gomis 2018; 531 participants).

Timing of application of topical corticosteroid

Two trials investigated whether the time of day that topical corticosteroids are applied had any effect. One trial in adults and children with at least moderate-severity eczema was nested within a larger trial of twice versus once daily application (Bleehen 1995); the once daily group were also randomised to morning or night topical corticosteroid application (137 participants). Another trial of seven days' duration (Richelli 1990), in children with eczema of unspecified severity, compared application of moderate-potency topical corticosteroid twice daily at 8 am and 3 pm (13 participants; morning/afternoon group) to application at 3 pm and 8 pm (8 participants; afternoon/evening group).

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

Bleehen 1995 reported no difference between morning and evening topical corticosteroid application at week 4, however they did not provide any numerical data (137 participants). Richelli 1990 reported investigator-assessed signs on a scale of 0 (none) to 3 (severe) at baseline and end of treatment (day 7). At baseline, the mean was 1.27 in the morning/afternoon group and 1.24 in the afternoon/evening group. At day 7, these decreased to 0.25 in the morning/afternoon group, and 0.14 in the afternoon/evening group; dispersion data were given.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Richelli 1990 reported mean score of symptoms of eczema as judged by participants at baseline and end of treatment (day 7). Mean score decreased from 1.17 to 0.3 in the morning/afternoon group and from 0.96 to 0.36 in the afternoon/evening group. Bleehen 1995 did not report patient-reported data with respect to timing of topical corticosteroid application.

Safety: number of relevant local adverse events (primary outcome)

Richelli 1990 did not report this outcome, and Bleehen 1995 did not report local adverse events with respect to timing of topical corticosteroid application.

Safety: number of relevant systemic adverse events (secondary outcome)

Bleehen 1995 did not report this outcome. Richelli 1990 measured cortisol and ACTH concentrations at baseline and day 7, 8 am and 4 pm. Trial authors reported no difference in serum cortisol and ACTH after treatment relative to baseline in any of the three groups, however there was insufficient information to judge changes in individual participants' levels (assumed 30 participants; children; unclear severity of eczema).

Wet wrap versus no wet wrap

This comparison relates to the use of topical corticosteroid under occlusion (wet wrap) compared with no occlusion. It comprises six trials; five parallel-group (Beattie 2004; Bryden 2009; Hindley 2006; Murphy 2003; Pei 2001), and one within-participant trial (Foelster-Holst 2006). In four trials, the only variation between groups was whether they used wet wraps (Foelster-Holst 2006; Hindley 2006; Murphy 2003; Pei 2001), whilst the remaining two trials also varied the frequency of topical corticosteroid application (Beattie 2004; Bryden 2009). Most trials used mild topical corticosteroid in both

arms; one trial used moderate topical corticosteroid (Foelster-Holst 2006); one used a second-generation potent topical corticosteroid (Pei 2001).

Data were available for all primary outcomes and for the secondary outcome: patient-reported symptoms of eczema (effectiveness). No data were available for the secondary outcome: number of relevant systemic adverse events (safety).

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

All trials included in this comparison measured clinician-reported signs of eczema.

Pooled analyses: wet wrap versus no wet wrap

We pooled investigator assessment of clinical signs as a short-term outcome (range 2 to 3 days to 4 weeks) from three trials that used SCORAD or SASSAD (Beattie 2004; Foelster-Holst 2006; Hindley 2006). Two parallel-group trials included 64 participants; one within-participant trial included 24 participants. The SMD in the short term (ranging from day 2 to week 4) was −0.26 (95% CI −0.92 to 0.41; P = 0.45; I^2 = 71%; 3 trials, 112 participants or sides treated; Analysis 10.1), suggesting no clinically significant benefit from using wet wraps. The high statistical heterogeneity prompted an exploration of the trial characteristics; Hindley 2006 reported several withdrawals from the wet-wraps group (5/28) relative to the group that did not use wet wraps (0/22), and discontinued recruitment earlier than planned owing to an interim analysis concluding "clinically significant adverse differences between the two groups". It might be speculated that this relates to the number of participants who required antibiotics in the group using wet wraps (5/23), assumed to be treating skin infections. When removing Hindley 2006, the statistical heterogeneity falls (I^2 = 0%) and the SMD becomes −0.60 (95% CI −1.00 to −0.21; P = 0.003), favouring topical corticosteroid use without wet wraps. The short-term time point was the end of treatment for two of the trials, therefore we did not do a separate end of treatment meta-analysis.

We then restricted the analysis to two trials in children only (Beattie 2004; Hindley 2006). The SMD in the short term was 0.00 (95% CI −0.79 to 0.80; P = 1.00; I^2 = 54%; 2 trials, 64 participants; Analysis 10.2), in line with the analysis of adults and children.

As there was overlap in the severity bandings for the trials that had specified baseline severity of eczema, no subgroup analysis relating to severity was possible.

Data not included in the meta-analyses

We did not include three trials in any meta-analyses because the numerical data were unsuitable for pooling (Bryden 2009; Murphy 2003; Pei 2001), and are summarised in Analysis 10.3. In line with the Analysis 10.1, Bryden 2009 found no significant difference in SASSAD between groups in a small trial of 51 children with moderate to severe eczema. One multiple arm trial of 40 children with moderate to severe eczema, who used a newer, second-generation potent topical corticosteroid (Pei 2001), showed improvement in clinical signs in all groups, but baseline severity differed significantly between the groups making it difficult to draw any meaningful conclusion. One trial suggested an improvement in clinical signs in the wet-wraps group but provided no numerical data to support this statement (Murphy 2003).

One trial in children with moderate-severity eczema reported limited follow-up data (Beattie 2004). At one week of follow-up (week 3), SASSAD had increased in the twice daily, without wet-wraps group to 22.8 (9 participants) and to 21.9 in the once daily, wet-wrap group (10 participants). Beattie 2004 did not report dispersion data at this time point.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Two trials reported itch and sleep data and we have summarised them in Analysis 10.4 (Beattie 2004; Hindley 2006). These trials included a very low number of participants (19 and 45 respectively) but there were no relevant differences suggestive of benefit in using wet wraps.

Safety: number of relevant local adverse events (primary outcome)

Two small short-term trials in children with moderate and severe eczema (Beattie 2004; Hindley 2006; Analysis 10.5), found that seven of 33 participants treated with wet wraps reported skin infections or required antibiotics whilst none were reported in the group that did not use wet wraps (31 participants).

None of the trials included under this comparison reported skin thinning and related signs, and local site reactions.

Safety: number of relevant systemic adverse events (secondary outcome)

Relevant systemic adverse events were not reported.

Unspecified adverse events (safety)

Foelster-Holst 2006 reported that no adverse events occurred up to end of treatment (48 to 72 hours) in the 14-day follow-up period (adults and children; mild to moderate eczema; 24 participants).

Topical corticosteroid applied to wet versus dry skin

Only one parallel-group trial (Kohn 2016), compared the application of topical corticosteroid to wet skin versus dry skin. This two-week trial in children aged two weeks to 18 years with mild to severe eczema (baseline EASI 2.8 to 34.95), compared a potent topical corticosteroid ointment applied twice daily to either dry skin (23 participants) at least 15 minutes after a bath or shower or wet skin (22 participants) immediately after a bath. This was a cross-over trial and we have included only data from the first treatment phase.

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

A similar decrease in mean EASI scores at week 2 from baseline was seen in both groups (scale of 0 to 72, increase represents worsening eczema). Mean decrease in the wet-application group was 13.3 (SD 7.95) compared to 12.5 (SD 6.04) in the dry-application group. The MD between groups at end of treatment was 0.80 (95% CI −3.34 to 4.94; P = 0.70; 45 participants) showing no difference.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

In both groups, the mean itch score measured on a numerical rating scale (0 = no itch to 10 = severe itch) decreased at week 1 and 2 compared to baseline. Mean decrease in the wet-application group

was 3.4 (SD 2.65) compared to 2.7 (SD 2.86) in the dry-application group at week 1. The MD between groups was 0.70 (95% CI −0.91 to 2.31; P = 0.39; 45 participants) showing no difference.

At week 2, mean decrease in the wet-application group was 4.7 (SD 2.55) compared to 3.5 (SD 2.91) in the dry-application group. The MD between groups was 1.20 (95% CI −0.40 to 2.80; P = 0.14; 45 participants) showing no difference.

There was an improvement in sleep in both groups reported on a numerical scale (0 = slept well to 3 = slept poorly). At week 1, mean decrease from baseline in the wet-application group was 0.7 (SD 0.98) compared to 0.6 (SD 0.96) in the dry-application group. The MD between groups was 0.10 (95% CI −0.47 to 0.67; P = 0.73; 45 participants); showing no difference.

At week 2, mean decrease in the wet-application group was 0.8 (SD 0.96) compared to 0.6 (SD 0.98) in the dry-application group. The MD between groups was 0.20 (95% CI −0.37 to 0.77; P = 0.49; 45 participants; showing no difference.

Safety: number of relevant local adverse events (primary outcome)

Three participants in the wet-application group (22 participants) experienced folliculitis compared to five participants in the dry-application group (23 participants) over two weeks. There were no cases of skin thinning in either group.

Safety: number of relevant systemic adverse events (secondary outcome)

The trial authors stated, "no patients developed clinical signs of systemic suppression of the hypothalamic pituitary adrenal axis, such as moon faces, fat redistribution, signs or symptoms of glucose intolerance or immunosuppression" measured up to week 2. Mean morning serum cortisol at day 14 was 15 micrograms/dL in the wet-application group (4 participants) and 12 micrograms/dL for the dry-application group (6 participants), with one participant having levels of less than 5 micrograms/dL.

Topical corticosteroid applied before emollient versus topical corticosteroid applied after emollient

We included only one trial (Ng 2016) that compared topical corticosteroid applied before emollient (20 participants) with topical corticosteroid applied after emollient (26 participants). This parallel-group, two-week trial in children with moderate to severe eczema compared a moderate-potency steroid applied twice daily, either 15 minutes before or after applying emollient.

Effectiveness: changes in clinician-reported signs of eczema (primary outcome)

There was a reduction in eczema severity in both groups after two weeks' treatment with topical corticosteroid, measured by EASI, scale of 0 to 72, where an increase represents worsening eczema. In the topical corticosteroid first group, median EASI decreased from 15.5 (IQR 7.3 to 22.0; 20 participants) at baseline to 10.6 (IQR 3.3 to 14.9; 16 participants) at week 1, and 10.4 (IQR 4.9 to 16.1; 12 participants) at week 2. In the emollient-first group, median EASI decreased from 13.3 (IQR 6.8 to 19.2; 26 participants) at baseline to 7.7 (IQR 3.6 to 13.5; 24 participants) at week 1, and 4.6 (IQR 2.7 to 11.5; 19 participants) at week 2.

Effectiveness: patient-reported symptoms of eczema (secondary outcome)

Both groups saw some reduction in itch measured on an unspecified scale by week 2. In the topical corticosteroid-first group, median itch was 6.0 (IQR 5.0 to 8.0; 20 participants) at baseline, 6.0 (IQR 3.0 to 8.0; 17 participants) at week 1, and 4.0 (IQR 2.5 to 7.0; 12 participants) at week 2. In the emollient-first group, median itch was 6.0 (IQR 5.0 to 8.0; 26 participants) at baseline, 4.0 (IQR 3.0 to 6.0; 23 participants) at week 1, and 4.0 (IQR 3.0 to 6.0; 19 participants) at week 2.

Safety: number of relevant local adverse events (primary outcome)

Local site reactions were reported up to week 2 (see Analysis 11.1). The most frequent event was pruritus, reported in 6 of 20 participants in the topical corticosteroid-first group compared to four of 26 participants in the topical corticosteroid after group. Overall, there was little difference between groups in local site reactions.

Safety: number of relevant systemic adverse events (secondary outcome)

Systemic adverse events were not reported.

Time between application of emollient and steroid

We did not find any trials that involved the use of this strategy.

Overall effectiveness and safety

Whilst it is important to view the data for each strategy individually, through pairwise comparisons, to answer the specific review questions, there is also merit in considering the overall effectiveness and safety data from this cohort regardless of the strategy for topical corticosteroid use employed. When all trials reporting on IGA are taken together, the number of participants who achieved cleared or marked improvement on IGA was 59% after one to four weeks (Analysis 12.1) and 71% by end of treatment (Analysis 12.2), although it should be noted that there was significant variation between trials in the proportion of participants who achieved cleared or marked improvement, with no obvious reason for the variation. This is coupled with the observation that a minority of trials reported cases of skin thinning, but most reported none. Across all strategies and comparisons, 26 cases of skin thinning were reported in 3574 participants (less than 1%; Analysis 12.3). Sixteen of these were reported when using very potent topical corticosteroid in trials that had not excluded participants with signs of skin atrophy at baseline (Analysis 12.4).

DISCUSSION

A total of 104 trials and 8443 participants were included in this review. These covered a wide range of clinically plausible strategies for using topical corticosteroids in treating eczema, which fell into three broad categories:

1. which topical corticosteroid to use;
2. how often and how long to use topical corticosteroid for; and
3. how best to apply the topical corticosteroid.

Summary of main results

The main findings, for which we have drawn up summary of findings tables, address 1. which topical corticosteroid to use, and 2. how often and how long to use topical corticosteroid for.

Which topical corticosteroid to use

See: Summary of findings 1, Summary of findings 2, Summary of findings 3, Summary of findings 4.

Our review focused on four comparisons of topical corticosteroid of one **potency** with another topical corticosteroid of a different potency (moderate versus mild topical corticosteroid, potent versus mild topical corticosteroid, potent versus moderate topical corticosteroid, and very potent versus potent topical corticosteroid) for treating eczema flare-ups, which reflects clinical practice decision making based on a stepped approach. In mainly moderate to severe eczema, potent and moderately potent topical corticosteroid probably result in an increased number of participants achieving clinician-reported treatment success compared to mild-potency topical corticosteroid (moderate-certainty evidence), with insufficient data to determine whether this applied to people with mild disease. There was also insufficient evidence of a benefit of potent topical corticosteroid compared to moderate-potency topical corticosteroid (moderate-certainty evidence). Again, the trials were mainly in moderate to severe eczema but perhaps more representative of the population that may be offered these higher-potency topical corticosteroids There was insufficient evidence to demonstrate any advantage of very potent over potent topical corticosteroid, with only three small trials included in the meta-analysis (low-certainty evidence). These trials usually included more children than adults. The number of reported cases of skin thinning was very low, with a relatively even spread across groups but tending towards more events with increasing potency of topical corticosteroid. Most trials were of short duration so may not detect longer-term adverse events (low-certainty evidence for local adverse events, except for the comparison of very potent versus potent topical corticosteroid which we assessed as very low-certainty.)

In six trials involving 188 participants, 16 participants had levels of cortisol outside of the normal range (very low-certainty evidence). There were minimal data on whether the levels returned to normal once the topical corticosteroids were stopped, minimal data on clinically relevant adrenal suppression, and no data regarding impact on growth (see: Completeness of outcomes; safety).

How often to apply topical corticosteroid?

See: Summary of findings 5; Summary of findings 6; and Summary of findings 7.

Applying topical corticosteroid **twice daily** probably does not increase the proportion of participants (adults and children) who achieve clinician-reported treatment success for treating a flare (1 to 4 weeks) compared to once daily application (moderate-certainty evidence).This still applied when restricting to trials where the same topical corticosteroid was used in both arms; however, most of those trials were in participants with moderate to severe eczema, using a potent or very potent topical corticosteroid. It also applied in the trials that spanned more than one strategy, comparing higher-potency, often newer, second-generation topical corticosteroid applied once a day with lower-potency topical corticosteroid applied more frequently.

The evidence suggests that frequency of application results in little to no difference between strategies in the risk of developing skin thinning (low-certainty evidence). The number of reported cases was low, and more than three-quarters of cases were seen in participants using very potent topical corticosteroid. The evidence addressing whether using topical corticosteroids more than once daily affects cortisol levels is very uncertain and there were no data on clinically relevant effects.

No trials looked at longer- versus shorter-term **duration of treatment** for induction of remission from a flare.

Weekend, or 'proactive' therapy, in which topical corticosteroids are applied twice a week for two consecutive days in between flares, aims to prevent rather than treat eczema flares. Weekend therapy likely results in a large decrease in the likelihood of experiencing a new flare compared to no topical corticosteroid application, with moderate-certainty evidence. This effect was seen in children and adults and across all eczema severities, although most evidence was in moderate to severe eczema. With regard to safety, no cases of skin thinning, or new cases of abnormal cortisol levels were reported (low- or very low-certainty evidence), but there were no data on clinically relevant adrenal suppression or impact on growth. The trials of weekend therapy were significantly longer in duration (16 weeks to 12 months) than trials identified for other strategies, primarily because of the need to detect the number of new flares rather than treating the existing flare. Whilst these trials may be better designed to detect adverse events that take longer to manifest, such as skin thinning, it should be noted that the data are not necessarily comparable with the other strategy comparisons as the topical corticosteroid use was intermittent (two days per week) rather than daily as is normal for treating a flare.

Other strategies examined

Newer, **second-generation** topical corticosteroids, fluticasone propionate and mometasone furoate, are probably more effective than older topical corticosteroids; use of second-generation topical corticosteroid is approximately two and a half times more likely to result in cleared or marked improvement on IGA compared to older topical corticosteroid in adults and children with moderate or severe eczema when used in the short term for treating a flare. Most trials tested once daily application of the second-generation topical corticosteroid in line with the marketing strategy compared to twice-a-day use of the older topical corticosteroid, supporting the conclusion that these newer topical corticosteroids are probably more effective. However, given many of these trials were industry funded, an independent trial would be beneficial.

Whether a **cream or ointment** preparation of the topical corticosteroid is used may have little to no effect on clinical signs of eczema, but the evidence is very uncertain with a high degree of imprecision. Similarly, the data from three trials that compared different **concentrations** of the same topical corticosteroid was not conclusive. We found no evidence comparing the **branded versus a generic** version of the same topical corticosteroid.

The **frequency** that topical corticosteroid is applied **each week** (i.e. every day or less frequently) may have little to no effect on clinical signs of eczema and safety, but the evidence is

very uncertain. **Substituting** an evening application of topical corticosteroid with a topical calcineurin inhibitor may have little to no effect on effectiveness in children with moderate to severe eczema compared to applying topical corticosteroid twice a day, but the evidence is very uncertain from only one very small trial, with no data on skin thinning or adrenal suppression.

Using topical corticosteroid under **wet wraps** may have little to no effect on investigator-assessed signs, but the evidence is very uncertain with a high degree of imprecision, and when we addressed the heterogeneity in the limited meta-analysis, the results favoured topical corticosteroid without wet wraps. Minimal safety data meant that we could not draw firm conclusions, however, skin infections did occur with wet wraps without corresponding events reported in the participants who did not use wet wraps. The **time of day** that the topical corticosteroid is applied, whether topical corticosteroid is applied to **wet or dry** skin, or **order of application** of topical corticosteroid and emollients may have little to no effect on clinician-reported signs of eczema or implications for safety, but the evidence is very uncertain from only one or two small trials for each comparison. No trials looked at the optimum **time to leave** between emollient and topical corticosteroid application.

Overall completeness and applicability of evidence

Completeness of participants

Most of the included trials were conducted in high-income countries and did not report detailed information on the ethnicity of participants; where ethnicity was reported, participants were predominantly white. Eczema in dark skin may present differently to eczema in white skin, for example lichenification is more common in those with darker skin tones and erythema may be underestimated when conducting skin assessments. As a result, it is unclear how the findings of this review inform treatment for people with darker skin tones, as they have been under-represented in eczema trials to date.

Almost all trials that stated information about location were conducted in outpatient or other hospital settings, and the severity of the eczema in the trial populations does not accurately reflect eczema in the general population. Whilst most people have mild or very mild eczema, trials more commonly included people with moderate and severe eczema. This is particularly relevant for this review as people with moderate or severe eczema are likely to be offered additional treatments over and above topical corticosteroid in practice, making trials of only topical corticosteroid potentially less relevant to this population. That said, the choice of topical corticosteroid for these populations was usually sensible, that is, a more potent topical corticosteroid for more severe eczema.

Most comparisons included trials of adults and children, but due to the overall number of trials per comparison, there were rarely enough trials to conduct meaningful subgroup analyses. Therefore, for many comparisons, it is not possible to clearly determine whether the effect is the same or different in adults and children. This could be significant due to the differences in skin between different age groups. There was also insufficient data with which to compare effectiveness at different anatomical sites.

We excluded some trials because it was not possible to extract the data on only participants with atopic eczema, as these trials had included people with a range of skin diseases or different types of eczema, or both.

Completeness of interventions

Our search included all topical corticosteroids and had no date restrictions. Therefore, it is likely that some of the topical corticosteroids tested are either no longer commonly used or are used in some areas of the world more than others. However, we grouped topical corticosteroids by potency for the purposes of this review, rather than looking at individual topical corticosteroids, which minimises the impact of this.

Owing to the lack of trials that met the inclusion criteria, we did not find sufficient evidence addressing several comparisons of interest. In particular, there were no trials addressing our key comparison of longer- compared to shorter-term duration of use of topical corticosteroids to treat flare-ups. More generally, of the three broad categories of comparison of 1. which topical corticosteroid to use, 2. how often to apply topical corticosteroids, and 3. how to use the topical corticosteroid, only 10 of 104 trials addressed the third category, how to use the topical corticosteroid. One trial in 45 participants looked at topical corticosteroid applied to wet versus dry skin; one trial in 46 participants looked at whether topical corticosteroid should be applied before emollient versus after emollient; and no trials looked at the optimum time between application of emollient and application of topical corticosteroid. Furthermore, when considering strategies for treatment of a flare (getting control) versus flare-prevention (keeping control), only one comparison addressed the latter in nine trials of weekend therapy (proactive topical corticosteroid) versus no proactive topical corticosteroid in 1344 participants. We discuss evidence gaps highlighted by this review further under Implications for research.

In this review we included a comparison of concentrations of topical corticosteroid where we included a trial that compared 0.05% fluticasone cream with 0.005% fluticasone ointment (Berth-Jones 2003). As the vehicle in which the topical corticosteroid is delivered influences the solubility (Oakley 2021), and therefore the effectiveness, then this could be the reason for the difference in concentrations within the formulation. Therefore, the comparison of concentrations within this trial may not be applicable to formulations of the same type.

Completeness of outcomes

Effectiveness

Because there are more than 20 different instruments for measuring signs of eczema (Schmitt 2007), we prespecified a hierarchy of outcome measures. EASI was highest on the list as it is recommended as the core outcome for clinical signs by HOME, however only five trials reported it. IGA was sixth in the list, but it was by far the most reported effectiveness outcome instrument, used in 62 of 104 trials, and therefore most meta-analyses in this review were conducted using IGA data. As there is no accepted and validated international standard instrument for measuring IGA, to enable synthesis of the data we abstracted the IGA results into a dichotomous outcome of treatment success (cleared or markedly improved) versus not successful (all remaining categories) where possible, reflecting the presentation of these data in most trials. This approach may be less relevant for people with severe or

very severe eczema who may be less likely to achieve cleared or markedly improved with only topical corticosteroid.

Patient-reported outcomes were our secondary effectiveness outcome. Again, we prespecified a hierarchy of preferred outcome measures, with POEM at the top of the list as it has been tested adequately for validity and reliability (Schmitt 2007), and is included in the HOME Core Outcome Set, however none of the included trials reported it. Patient-reported outcomes that we included were sleep and itch scales, and patient global assessments (15/104). Only a third of trials reported these, and rarely sufficiently to enable meta-analyses, but where there were data available, they generally supported the conclusions based on clinician-reported outcomes.

Most of the trials included in this review were short term (1 to 4 weeks' duration) as they were comparing strategies designed to get control of an eczema flare. Trials of weekend (proactive) therapy addressed keeping control of eczema once remission had been achieved. We discuss the need for longer-term trials with adequate follow-up under Implications for research.

Safety

Extraction of individual adverse events was restricted to known adverse events of topical corticosteroid, which are well-established drugs, identified from the Summary of Product Characteristics and prioritised with patient and clinician input. Although reported in this review where finer detail was unavailable, the overall number of adverse events gives no information on the type of adverse event and is not generally helpful in clinical decision making.

Data on individual adverse events were limited and often poor quality. Two of the key adverse events that are of concern to patients and parents are skin thinning and adrenal suppression, however trial authors rarely specified how they had measured skin thinning and there was little information on resolution of adverse events after stopping the topical corticosteroid.

Clinically relevant adrenal suppression was rarely looked for in the included trials; an exception being Kohn 2016, that compared topical corticosteroid application to wet versus dry skin. Some trials did measure and report cortisol levels, but the certainty of this evidence was consistently very low. Trials used different methods for measuring cortisol, often with little or no interpretation regarding whether the levels were abnormal and without specifying the reference ranges used. Some trials only tested a small subset of participants and reporting was often poor, lacking key numerical data. Furthermore, there were minimal data on whether this biochemical measurement returned to normal levels when topical corticosteroid was stopped, which would have provided an indication of the clinical relevance of such measurements. Additionally, the relatively small size of most trials (median 44.5 participants; range 3 to 409) means they are unlikely to be able to detect all but the most common adverse events. As a result, we are unable to draw conclusions from these data.

As many of the included trials were short term, of just a few weeks' duration with no post-treatment follow-up, this limited the ability to detect adverse events that take months or years to develop, such as skin thinning or hypopigmentation. This can lead to interpretation as evidence of no effect when in fact it could be no evidence of an effect. These short trials are a snapshot of a patient's eczema journey involving many years of treatment, which further hampers the ability to detect potential adverse events. Trials of weekend (proactive) therapy provide some data on prolonged use of topical corticosteroid over several months albeit with less frequent use than the current standard daily application for the management of flares.

We excluded one large, notable trial (PETITE) from this review because it did not compare different strategies of using topical corticosteroid (Sigurgeirsson 2015). The PETITE trial randomised 2418 children to receive topical corticosteroid (mild/moderate) or topical calcineurin inhibitors, used as required, and followed them for five years. This trial reports that clinical skin thinning occurred in one of 1213 participants (0.08%) who used mild to moderate topical corticosteroid over five years. We mention the trial here for context as it is the only large trial of normal topical corticosteroid use over a long period.

Quality of the evidence

We GRADE assessed almost all clinician-reported effectiveness outcomes as moderate, with only one judged very low. The reason for downgrading the effectiveness outcomes was due to issues identified by the risk of bias assessment and in the comparison classed as low, imprecision. Only half of the comparisons from the summary of findings table reported complete numerical data for the most reported patient-reported outcome; patient global assessment. Of those that did, one provided moderate-quality evidence, one low, and one very low. The reason for downgrading the data obtained from this analysis was again issues from the risk of bias assessment, and in the trials assessed as low, unexplained heterogeneity. In the comparison classed as very low, small numbers of events and participants meant we downgraded the comparison twice for this outcome in addition to the risk of bias concerns.

We judged all but one comparison low with regards to the data concerning skin thinning. This was again due to issues highlighted by the risk of bias assessment and imprecision. The comparison in which we classed the skin thinning data as very low was downgraded twice for imprecision due to low numbers of events and participants.

In all assessments of the evidence associated with abnormal cortisol assessment, we judged the certainty of the evidence as very low. This was due to risk of bias issues and low numbers of events and participants. One comparison also demonstrated inconsistency.

Where we sought further information from authors relating to risk of bias assessments, our requests for further data did not always get a response (see Table 3). In many cases, this is likely owing to the age of the included trials.

We did not downgrade any GRADE assessments due to publication bias. However, only two analyses that included assessment of short-term IGA from the potent versus moderate and twice or more versus once daily topical corticosteroid comparisons, included enough trials to allow the generation of valid funnel plots. Both showed no clear asymmetry (Figure 5 relating to Analysis 3.1; Figure 6 relating to Analysis 7.1).

Figure 5. Funnel plot of comparison 3. Potent versus moderate potency topical corticosteroid, outcome: 3.1: cleared or marked improvement on IGA (short term); all ages; all severities

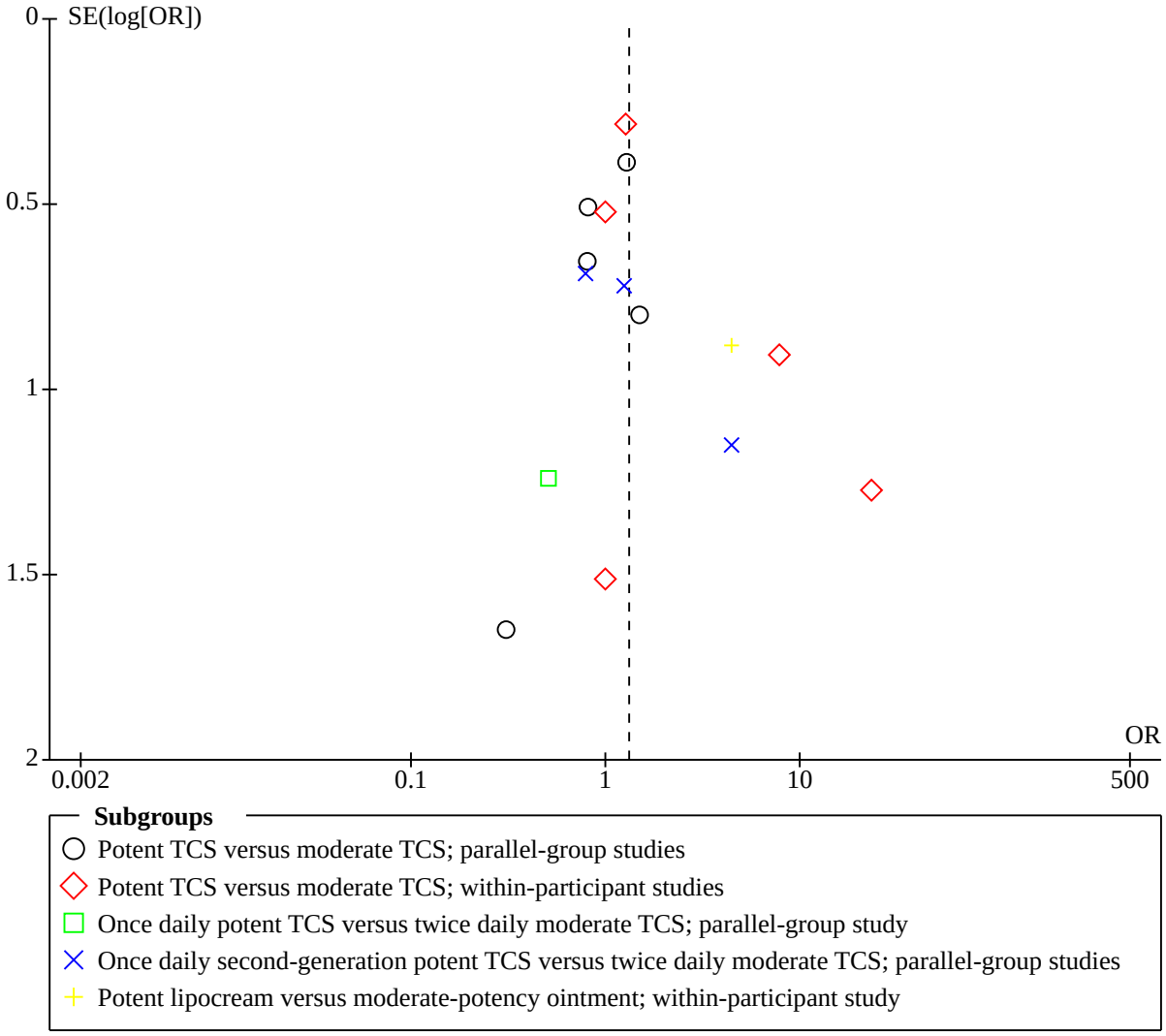
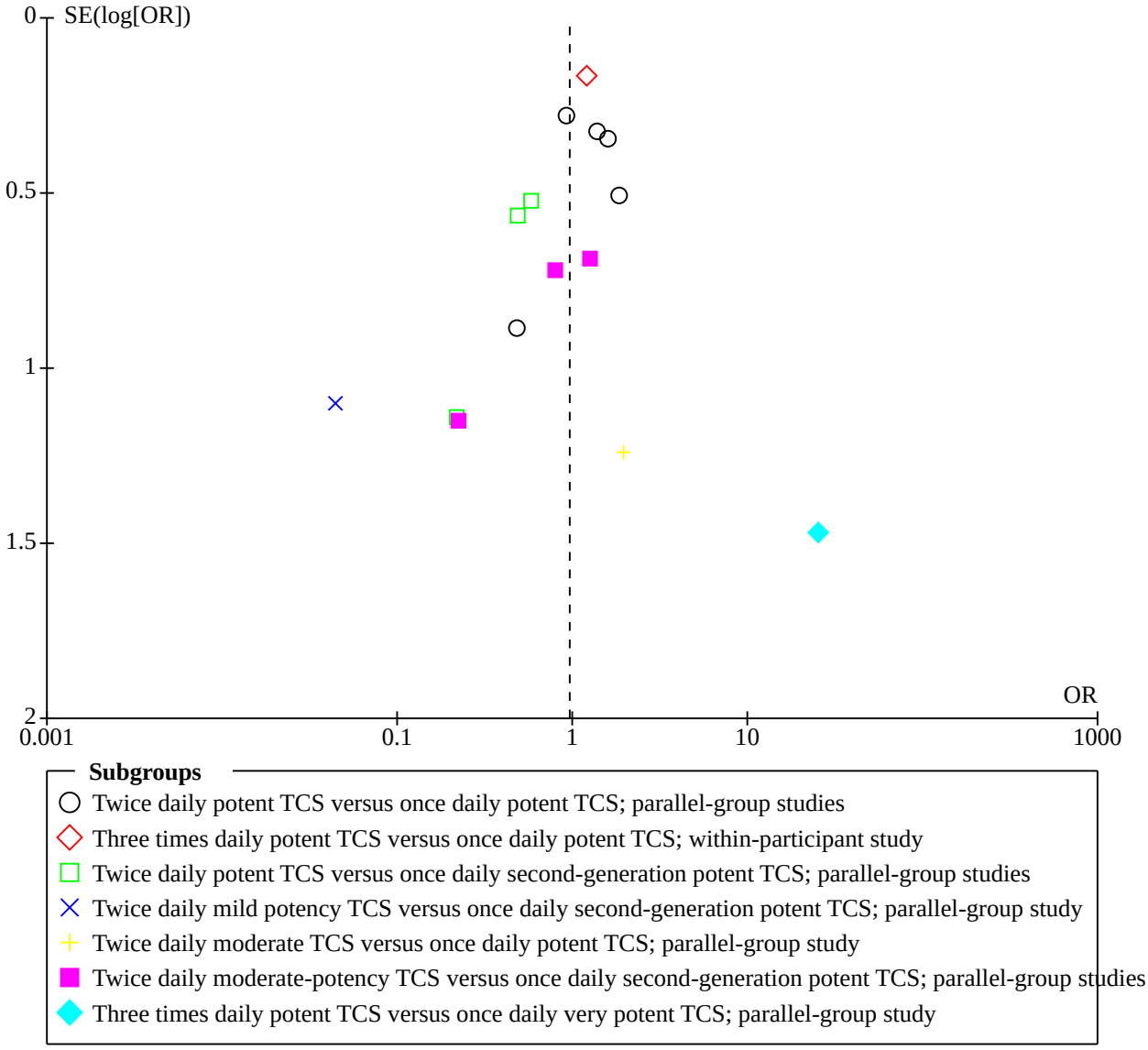


Figure 6. Funnel plot of comparison 7. Twice or more versus once daily topical corticosteroid, outcome 7.1: cleared or marked improvement (unless stated) on IGA (short term); all ages; all severities



Potential biases in the review process

The categorisation of topical corticosteroid potency is contentious. There is no one source of potency categorisation, and there are discrepancies between the different sources. Therefore, to ensure transparency and minimise bias, we developed a hierarchy of sources to assign potency to each topical corticosteroid (Table 2). We most frequently determined potencies using the British National Formulary 2018 and WHO 1997. If we could not establish potency using these sources, we reviewed regional guidelines and the wider scientific literature, and consulted regional experts until we could reach a decision. Although these sources are the most appropriate choice for this review, the evidence behind each potency classification is not always clear and manufacturers do not always state the potency of products in the Summary of Product characteristics.

Although the search included the terms for topical corticosteroids, it also included a comprehensive list of generic topical corticosteroid names. It is possible that this list was incomplete and therefore some trials missed from the search if they had not also included the term topical corticosteroids.

We have presented odds ratios (OR) rather than risk ratios (RR) for dichotomous analyses because for some comparisons a high proportion of the trials (up to 50% in some cases) had a within-participant design, and presenting a RR is inappropriate when the generic inverse variance method (GIV) with Becker-Balagtas correction is used to incorporate these within-participant trials. To ensure consistency across comparisons, we presented all meta-analyses as OR including those with no within-participant trials. The exception to this is the comparison of weekend (proactive) therapy versus no topical corticosteroid, where meta-analyses of

dichotomous data were reported as RR to be comparable to a previous systematic review (Schmitt 2011).

It was not always clear how the total number of participants in the analyses had been arrived at in some trials and this was compounded by the design of trials in which participants withdrew when the flare was controlled. Where the number of participants at later time points was unclear, we have assumed the number randomised, or the sample size reported for the previous visit if available, which may have resulted in overestimation in some instances.

We dichotomised the IGA data into cleared or almost cleared versus those who did less well. Some trials used an IGA with different response options, so we had to make a judgement regarding which categories best corresponded to cleared or marked improvement in some cases.

Where a trial stated in the methods that they looked for adverse events, but did not report data in the results, we assumed there were no cases. This ought to be a reasonable assumption, as trials ought to be more likely to report adverse events where they occur, however, we acknowledge this may be inaccurate. Furthermore, it was not always clear in the trial reports where adverse event data were reported as number of participants or number of events; in these instances, we have assumed number of participants as a conservative approach to over-estimate, rather than potentially underestimate, number of adverse events. However, where trials reported on multiple adverse events, and especially when skin thinning was reported separately to signs of skin thinning, for example, telangiectasia, such numbers were not combined to avoid double counting of individuals. Signs of skin thinning have not been included in summary of findings tables; however, they are reported in full in a separate sub-table under the skin thinning tables (e.g. Analysis 7.10).

We attempted to conduct a comprehensive search for trials, but the fact that 24 trials have not yet been incorporated may be a source of potential bias.

Agreements and disagreements with other studies or reviews

The recommendations for the use of topical corticosteroids related to the main comparisons reported within this review, (results reported in the summary of findings tables), were extracted from four international guidelines for the management of atopic dermatitis (from the UK, USA, Europe and Japan). The recommendations are reported in Table 9 with a summary of the results of the review.

All but one of the guidelines consulted recommended a specific potency or potencies for different severities of atopic dermatitis, however the potency or potencies that were recommended for a particular severity varied between guidelines. This is likely to be related to the different severity and potency classifications used in different countries. Most guidelines suggested topical corticosteroids could be applied once or twice daily, but three out of the four guidelines mentioned twice daily use first and then said once daily use "can" be used. All of the guidelines recommended weekend (proactive) use of topical corticosteroid, however the level of support for this approach varied between the regions. This may have been related to the age of the different guidelines. Most of the guidelines, (3 out of 4), suggested patients should be monitored for cutaneous effects. With regards to systemic effects, most guidelines did not specifically mention the need for monitoring, but usually included either restrictions on the use of certain potencies in some circumstances, or warnings about the need to consider the potential for adverse effects when using certain potencies.

We used the Centre of Evidence Based Dermatology map and an overview of systematic reviews (Axon 2021), to identify key literature. Below, the results of this review are compared to UK guidelines and relevant systematic reviews:

UK National Institute for Health and Care Excellence (NICE)

Key areas where this review supports NICE guidance (NICE 2007).

- **NICE says do not use very potent preparations in children without specialist dermatological advice.** Most cases of skin thinning collated into this review were in participants using very potent steroids. We assessed the evidence found within this review relating to the rates of skin thinning using GRADE as low or very low certainty.
- **NICE says start with mild steroids for those with mild eczema.** Within the potent versus mild topical corticosteroid comparison, there was no difference between mild and potent topical corticosteroid in participants with mild to moderate eczema, suggesting that mild steroids may work well enough for this group, however this only considered 43 participants from two trials and the confidence interval was wide compared to the data in moderate to severe eczema, which favoured potent topical corticosteroid. Furthermore, as there were more reports of skin thinning in more potent steroids, the trade-off of more effectiveness from higher potency does not seem necessary for this group unless it fails to control the flare. The evidence for potency in relation to specific disease severities was not GRADE-assessed independently from the overall analysis of potency.
- **NICE says healthcare professionals should discuss risks and benefits, emphasising that the benefits outweigh possible harms when topical corticosteroid are applied correctly.** Most participants had a good response to topical corticosteroids, these results were taken from within trials usually GRADE-assessed to be of moderate certainty. Rates of adverse events such as skin thinning were generally very low, though we GRADE-assessed this evidence as low or very low certainty.
- **NICE says prescribe according to lowest acquisition cost.** We did not find any data that compared generic and branded topical corticosteroids.
- **NICE says healthcare professionals should consider treating problem areas of atopic eczema with topical corticosteroids for two consecutive days per week to prevent flares, instead of treating flares as they arise, in children with frequent flares (2 or 3 per month) once the eczema has been controlled. This strategy should be reviewed within three months to six months to assess effectiveness.** This review supports weekend (proactive) therapy for the prevention of eczema flares, including in children, however more trials are needed to verify for how long this should be continued (effectiveness evidence for weekend (proactive) therapy GRADE-assessed as moderate certainty).
- This review confirms the research gap identified by NICE regarding a lack of good, long-term data on topical corticosteroid safety. For example, we GRADE-assessed the

safety data reported for the main comparisons reported in the summary of findings tables as low or very low certainty.

Key differences with NICE guidance.

- **NICE says use once or twice a day.** This review suggests there is no evidence of additional effectiveness of application of potent topical corticosteroids once a day over twice a day (we GRADE-assessed the evidence as moderate certainty). For mild or moderate topical corticosteroids there is a lack of evidence regarding once- or twice daily application.
- **NICE says there is limited evidence on strategies to prevent flares.** This review provides moderate-certainty evidence for use of weekend (proactive) therapy.
- This review suggests that newer, second-generation topical corticosteroids are probably more effective than older topical corticosteroids; this is not included in NICE guidance. We did not GRADE-assess the evidence within this analysis as it was not one of the main comparisons reported in the summary of findings tables.

We found limited or no evidence to support some of the recommendations in NICE.

- NICE says occlusion strategies should not be used as first-line treatment in children, should only be initiated by a healthcare professional trained in their use, and should only be used for 7 to 14 days without specialist dermatological advice.
- NICE says do not use potent topical corticosteroids in children under 12 months without specialist dermatological supervision.
- NICE says to start treatment of moderate eczema with moderate-potency topical corticosteroid and severe eczema with potent topical corticosteroid. Whilst this review supports the notion that stronger topical corticosteroids probably have increased effectiveness, there was insufficient data in participants with mild to moderate eczema to fully support this stepped approach.
- NICE says, in children over 12 months, to use potent topical corticosteroids for as short a time as possible and in any case for no longer than 14 days.
- NICE says to use mild potency for the face and neck, except for short-term use of moderate-potency topical corticosteroids for severe flares, and to use moderate or potent preparations for short periods only in the axillae and groin.

Scottish Intercollegiate Guidelines Network (SIGN)

Key areas where this review supports SIGN guidance (SIGN 2011):

- **SIGN recommends once daily topical corticosteroid use.** This review clarifies that the evidence base suggests this is most appropriate for potent and very potent topical corticosteroid (GRADE-assessed as moderate-certainty evidence) being used to treat moderate to severe eczema. For mild or moderate topical corticosteroid there is a lack of evidence regarding once or twice daily application.
- **SIGN says there is a lack of evidence on which to base the order of topical corticosteroid and emollient application, maximum duration of continuous use, the frequency with which strategies can be repeated, and recommendations for growth monitoring.** This review confirms this paucity.
- **SIGN says that the short-term use of topical corticosteroid is not associated with observable skin thinning.** The rates of skin thinning were low across this review, though we GRADE-assessed the body of evidence with regards to skin thinning as low or very low certainty.

Key differences with SIGN:

- **SIGN suggests no comprehensive evidence was identified comparing topical corticosteroid with each other in terms of effectiveness.** This review suggests that newer, second-generation topical corticosteroids are probably more effective than older topical corticosteroids, use of stronger-potency topical corticosteroid according to our classification (Table 2) is probably more effective than weaker topical corticosteroid, and confirms the lack of evidence comparing generic versus branded topical corticosteroid. We did not GRADE-assess the evidence within this analysis as it was not one of the main comparisons reported in the summary of findings tables.
- **SIGN says that three RCTs suggest that adding twice-weekly topical corticosteroid application to emollient-based maintenance therapy following stabilisation of eczema reduces relapse rates.** This review updates this evidence, informed by eight trials, GRADE assessed as moderate certainty.

As with NICE, we found limited or no evidence to support some of the recommendations in SIGN, including the choice of topical corticosteroid potency being tailored to the age of the patient, the body region being treated, and the degree to which the skin is inflamed.

Strategy-focused reviews

Daily frequency

This review accords with previous systematic reviews (Green 2004; Green 2005), in concluding that there is probably (evidence GRADE-assessed as moderate certainty) no benefit of topical corticosteroid application more than once daily, building on that initial work with the addition of data from two newer RCTs (Del Rosso 2009; Schlessinger 2006), and several older and foreign language publications (Amerio 1998; Harder 1983; Lebwohl 1999; Nolting 1991; Rafanelli 1993; Rampini 1992a; Ryu 1997). Green and colleagues did include data from an unpublished trial, which could not be obtained for this review (GSK 1995). However, given that the conclusion of this review agrees with Green 2004, it is unlikely to change should GSK 1995 be included in future.

Weekend therapy

The results presented in this review confirm that weekend (proactive) therapy is probably (evidence GRADE-assessed as moderate certainty) of benefit in preventing flares and update the findings of a previous systematic review (Schmitt 2011), with the addition of four further RCTs, two of which we were able to pool.

Wet wrap

Our review included the same six trials of wet wrap therapy as a previous review that also showed there may be little or no benefit of wet wrap (not GRADE-assessed), and cases of skin infection with wet wraps (González-López 2017). However, the effectiveness results in this review are numerically different because of the method used to include within-participant trials and adjust for baseline differences between groups where possible.

Safety-focused reviews

Skin thinning

Issues highlighted by this review regarding certainty of skin thinning data (GRADE-assessed as low or very low certainty) and the need for long-term clinical trials of treatment regimens involving topical corticosteroid have been raised previously (Barnes 2015).

Adrenal suppression

The included trials rarely reported clinically relevant adrenal suppression. In those that reported biochemical markers, the certainty of the evidence was very low, often in a small subset of participants, with poor reporting, and missing numerical data. A systematic review that included nine trials of children, one RCT included in this review (Lucky 1997), and eight observational trials (371 participants), pooled the number of participants with biochemical markers of adrenal suppression. It found that the proportion of cases in those using low- to moderate-potency topical corticosteroid in the short term was 2.7% (95% CI 1.47 to 4.89), however there were no cases showing any clinical signs of adrenal suppression (Davallow Ghajar 2019), which accords with this review. Another meta-analysis by the same authors looking at topical corticosteroids of any potency, therefore also including Schlessinger 2006, reported that risk of adrenal suppression increased with increasing topical corticosteroid potency, but concluded that monitoring was unnecessary even with highest potency unless clinical symptoms were present (Wood Heickman 2018).

Topical corticosteroid withdrawal

None of the RCTs included in this review reported outcome data related to topical corticosteroid withdrawal, therefore this review does not advance the topic from previous systematic reviews of observational data (Hwang 2021; Juhász 2017; Li 2017).

AUTHORS' CONCLUSIONS

Implications for practice

The purpose of this review was not to prioritise one strategy over another, but rather to summarise all the available evidence on the relative safety and effectiveness of different ways of using topical corticosteroids. Most participants had a good response to topical corticosteroids, regardless of the type of topical corticosteroid used and when or how it was applied. This overall effectiveness should be considered alongside the observation that rates of adverse events associated with the use of topical corticosteroids were generally low and associated with potent or very potent topical corticosteroids. Although the trials were usually short term, of just a few weeks' duration, many will have included people with established eczema who may have been using topical corticosteroids for several months or years prior to entry to the trial.

The finding that once daily application of potent topical corticosteroid appears to be probably as effective as applying topical corticosteroids twice or more per day is significant for patients and parents as the application of topical treatments for eczema can be burdensome. Clear advice that only once a day is needed may help with adherence. Applying topical corticosteroid just once a day may also reduce costs to patients and caregivers and the state. There is currently insufficient evidence to confirm if this finding is relevant for mild topical corticosteroid use and for participants with mild- to moderate-severity eczema.

The data in this review supports the concept of reserving very potent topical corticosteroids for those with the most severe eczema, as skin thinning was more frequent with use of very potent topical corticosteroids, and the evidence for superiority over potent preparations was lacking. Additionally, the relatively good safety profile of moderate and potent topical corticosteroids and the finding that they are probably more effective than mild topical corticosteroids for people with moderate to severe disease confirms the use of the more potent topical corticosteroids for these patients. However, further trials are needed in mild eczema, along with trials of how long the topical corticosteroid should be used to treat a flare before any changes to current guidelines can be made. It is possible that a shorter duration of a higher-potency topical corticosteroid is as safe and effective as a lower-potency topical corticosteroid used for longer to control a flare and may be less burdensome to people with eczema; one trial compared a potent topical corticosteroid for three days per week with mild topical corticosteroid for seven days (Thomas 2002).

This review confirmed previous findings that weekend (proactive) therapy, in which topical corticosteroids are applied twice a week on consecutive days, is probably effective in preventing flares, compared to no topical corticosteroid/reactive application. However, in current clinical practice, this strategy is generally recommended by specialists and considered appropriate only for people who experience regular flares. The data here, albeit only from two trials, show that this strategy may also be effective and safe for people with milder disease and may result in wider adoption into primary care. It is also important to note that trials that investigated prevention of flares would typically treat participants with an intense (e.g. once a day for 2 weeks) period of topical corticosteroid to get the eczema under control. It is unclear whether proactive therapy prevents flares without first settling the eczema down, that is, a 'get control and then keep control' approach.

The newer, second-generation topical corticosteroid (mometasone furoate and fluticasone propionate, which are now also available as generic preparations) were more effective than older topical corticosteroids, and the very low rates of skin thinning were similar across the two.

There was a significant emphasis on safety in this review driven by the notion that despite being effective, associated adverse events are one of the key barriers to use of topical corticosteroids. Skin thinning is a key issue for adults with eczema and for parents of children with eczema, both skin thinning and concerns about growth are important. Although the safety data were often poorly reported, making it difficult to comment on the relative safety of different strategies for use of topical corticosteroids, taken together as an overall body of evidence, the risk of developing important adverse events like skin thinning, and affecting adrenal suppression, appears to be low. This may help clinicians in discussing topical corticosteroids as a key treatment for eczema and may help patients overcome concerns regarding their use. The observation that the low rates of skin thinning appeared to be largely associated with potent or very potent topical corticosteroids should also be considered when prescribing topical corticosteroids. Due to a lack of evidence, it is not possible to comment on whether

any adverse events like skin thinning are reversible once the topical corticosteroid treatment is stopped.

The overall data on effectiveness showing that, regardless of which topical corticosteroid is applied or how, it appears to be a very effective treatment suggests that the most important aspect of topical corticosteroid use is simply getting it on the eczematous skin, and that more specific guidance is perhaps less important. Eczema is an inflammatory skin condition that requires anti-inflammatory treatment such as topical corticosteroids. Emollients are used alongside topical corticosteroids for treating the dry skin associated with eczema (see: Van Zuuren 2017), but they are not an anti-inflammatory treatment per se. That said, patients report that the lack of consistent advice on how to use topical corticosteroids is one of the factors that affects adherence to treatment. Some areas of the body, such as the face or genital areas, are more sensitive than others, and may require different treatments from the rest of the body, for example, a mild- or moderate-potency topical corticosteroid on the face and a potent topical corticosteroid for the body. Written action plans may be helpful to provide clearer instructions on what to use, for how long and on which body site (Waldecker 2018).

Implications for research

There is a clear need for good-quality, long-term safety trials. The PETITE trial (Sigurgeirsson 2015), although out of scope for this review, provides reassurance over the safety of topical corticosteroids over five years. However, it is only one trial and more, similar-quality evidence is needed to fully address important questions in eczema research. An overview of systematic reviews (Axon 2021), and a scoping of the literature for a planned review of long-term safety including observational and randomised trials found a lack of observational trials meeting these criteria. Future RCTs should include longer follow-up to increase the body of longer-term safety evidence. A relatively large (750 participants) ongoing parallel-group trial of proactive use of a second-generation topical corticosteroid versus reactive therapy to prevent occurrence and severity of atopic dermatitis leading to development of food allergy is expected to measure effectiveness at 36 months (NCT03742414), however it is unclear what other safety outcomes will be measured. An independent trial to confirm whether second-generation topical corticosteroids are superior to older topical corticosteroids is also needed given the high proportion of industry-funded trials included in this review.

Adverse events also need to be much better measured and reported. How clinically significant skin thinning is measured should be standardised so data across trials can be properly compared. Clinically relevant adverse events relating to hypothalamic pituitary axis suppression, rather than just cortisol levels, should also be measured and reported. Trials need to investigate and report whether adverse events are reversible as this would help understand and manage risks.

Most of the trials included in this review were in outpatient or other hospital settings with people with moderate and severe eczema, yet most people with eczema have mild or very mild disease. For example, whilst this review found that once daily application of potent topical corticosteroids in moderate to severe eczema is probably as effective as twice daily, this finding cannot be generalised to milder topical corticosteroids and milder-severity eczema. There is a need for further research in people with milder disease treated in the community, especially as they are more likely to achieve treatment success with optimal topical corticosteroids and without the need for additional systemic therapies. An ongoing pragmatic randomised controlled open-label trial of second-generation potent topical corticosteroids versus mild topical corticosteroids in children in primary care settings may add useful insight and will measure effectiveness at up to 24 weeks (Van Halewijn 2018; within The Rotterdam Eczema Study). This review has also highlighted the need for further research into the effectiveness and safety of topical corticosteroids when applied to the skin of participants of different age groups and when topical corticosteroid is applied to skin at different anatomical sites. There is also an urgent need to explore if and how the effectiveness and safety of topical corticosteroids differs in participants with darker skin tones. Future trials should aim to include more diverse patient populations and for interventions to be tested in a variety of settings and healthcare systems.

Research is needed to determine how long topical corticosteroids should be used to induce remission when treating a flare as we found no evidence on this important question (one exceptionally small pseudorandomised trial did not meet the inclusion criteria for this review; JPRN-UMIN000010299; 4 participants). This should be combined with assessing the potential for higher-potency topical corticosteroids to be used for a shorter period. Another unanswered question relating to maintenance treatment, such as weekend (proactive) therapy, is when to stop and switch to reactive (as needed) treatment when control has been good for a few months with proactive therapy.

Other comparisons that had minimal evidence for their effectiveness might also be further researched. The third group of strategies, under 'How to use the topical corticosteroid', are particularly important to both patients and healthcare professionals. Some individuals may be liberated by the idea that ‘you can choose’ how to use topical corticosteroid, however others are likely to be disconcerted without evidence to guide their choices of whether to apply emollient or topical corticosteroid first, or how long to leave between application of emollient and topical corticosteroid.

Additional evidence comparing potent topical corticosteroid application under wet wrap to potent topical corticosteroid alone is expected from an ongoing trial (EUCTR2005-003806-27-GB). A within-participant trial comparing two different concentrations of hydrocortisone in addition to a second-generation potent topical corticosteroid is also ongoing (NCT04615962). However, we found no further trials that would address these under-researched comparisons.

Investigator global assessment (IGA) was the most reported effectiveness outcome and most meta-analyses in this review were conducted using IGA data. There is a need for further trials using outcome measures recommended by the Harmonising Outcome Measures for Eczema (HOME) initiative. It is encouraging to see ongoing trials proposing to use outcomes such as the Patient-Oriented Eczema Measure (POEM) and Eczema Area and Severity Index (EASI; NCT03742414; NCT04615962; Van Halewijn 2018). Recap of Atopic Eczema (RECAP) and Atopic Dermatitis Control Test (ADCT) have also recently been included under the core outcome of long-term control.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allenby 1981

Study characteristics

Methods

Trial design

Randomised, double-blind, half-side trial

Trial registration number

Not reported

Setting

Assumed outpatient dermatology departments in the UK from the list of affiliations

Date trial conducted

Not reported

Duration of trial participation

7 days (or as near as possible)

Additional design details

"Methods of assessment and analysis were exactly as described previously (Sparkes and Wilson 1974)." This paper (Sparkes 1974), states that the patient group selected was from a "heterogeneous group ranging from simple contact eczemas". However, as the current paper only states methods of assessment and analysis were as described in the Sparkes paper, we have assumed that patient selection and other details such as the methods of blinding are not necessarily identical.

Inclusion criteria

- Consecutive outpatients
- Eczema (or psoriasis, but analysed separately) requiring treatment in hospital
- Clinically similar bilateral lesions suitable for TCS treatment

Exclusion criteria

Not reported

Notes

Allenby 1981 *(Continued)*

	None
Participants	**Total number randomised** 33 patients with eczema **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** None **Notes** None
Interventions	**Run-in details** NA **Groups** • Clobetasone butyrate 0.05% ointment (proprietary: Eumovate); applied twice daily not under occlusion to either the left or right side. Concurrent treatment: not reported • HC 17-butyrate 0.1% ointment (proprietary: Locoid); applied twice daily not under occlusion to either the left or right side. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** None
Outcomes	• Global assessment (rated healed, improved, static or worse) at 7 days or as near as possible* • Global preference (did one side respond better than the other?) at 7 days or as near as possible *denotes relevance to this review

Allenby 1981 *(Continued)*

Funding source	None stated
Declarations of interest	None declared, however the 2nd author is affiliated to Glaxo Laboratories LTD, Greenford, Middlesex.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The preparations were allocated at random to left or right side." Comment: no information regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no further detail provided about who was blinded and how blinding was done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no further detail provided about who was blinded and how blinding was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: results are provided for all the patients who were included in the trial.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias identified

Amerio 1998

Study characteristics

Methods

Trial design

Parallel, multicentre, single-blind, randomised trial

Trial registration number

Not reported

Setting

13 dermatological centres (University Departments or Hospital Divisions), homogeneously distributed in Italy.

Date trial conducted

Not reported

Duration of trial participation

30 days (15 days' treatment, followed by 15 days' follow-up).

Amerio 1998 *(Continued)*

Additional design details

None

Inclusion criteria

- Patients with AD and allergic contact dermatitis (we have only extracted data for the former).
- Aged 6 months-60 years
- Moderate-severity lesions with respect to erythema, oedema/exudation, and excoriation; at least 1 target region had at least 2 of these signs at moderate severity.
- Skin lesions did not have to extend to > 10% of the skin surface (although some ambiguity in the translation here)

Exclusion criteria

- Patients with hypersensitivity to corticoids
- Patients with signs of skin atrophy
- Pregnant or nursing women
- Patients who were required to use antihistamine therapies

Notes

None

Participants

Total number randomised

97 participants with AD; 50 were randomised to received mometasone furoate, 47 were randomised to receive betamethasone valerate.

Age

Average age 17.8 years (± SE 1.7) in the mometasone group, 21.3 years (± SE 1.9) in the betamethasone valerate group

Sex

22 male and 28 female in the mometasone group, 21 male and 26 female in the betamethasone valerate group

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

The mean global score for baseline signs was 7.3 ± 0.4 (SE) for mometasone and 7.4 ± 0.4 (SE) for betamethasone valerate

Filaggrin mutation status

Not reported

Number of withdrawals

1 AD participant treated with betamethasone valerate no longer returned for examination.

Notes

None

Amerio 1998 *(Continued)*

Interventions	**Run-in details** NA **Groups** • Betamethasone valerate; applied twice daily for 15 consecutive days. Concurrent treatment: none • Mometasone furoate 0.1% cream; applied once daily for 15 consecutive days. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Not reported **Notes** It was reported that there was a mean duration of therapy of 12.7 ± SD 3.7 days in the mometasone furoate group compared to 13.8 ± 2.7 days in the betamethasone valerate group.
Outcomes	• Objective severity score for the target area (erythema, oedema/exudation, scales and/or squamous crusts, scratching and lichenification lesions evaluated on a semi-quantitative 5-point scale: 0 = absent, 1 = mild, 2 = moderate (easily visible sign), 3 = severe (obvious sign), 4 = very serious (very obvious sign)) at baseline, day 3, day 7, between days 8-15, and 15 days after treatment stopped (follow-up) • Patient assessment of the presence of itching and burning (the severity was assessed using a 5-point scale 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe) at baseline, days 3, day 7, between days 8-15, and 15 days after treatment stopped (follow-up)* • Patient acceptability (semi-quantitative 5-point scale: 0 = null, 1 = poor, 2 = discrete, 3 = good, 4 = optimal) at baseline, days 3, day 7, between days 8-15, and 15 days after treatment stopped (follow-up) • IGA of response relative to baseline (the judgment of the dermatologist, semi-quantitative 5-point scale from 1 = healing to 5 = exacerbation) at baseline, days 3, day 7, between days 8-15, and 15 days after treatment stopped (follow-up)* • Indices of cutaneous atrophy (telangiectasias, thinning, translucent skin, striae, loss of elasticity and dermatoglyphics, number of capillaries; evaluated using a 4-point semi-quantitative scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe) at baseline, days 3, day 7, between days 8-15, and 15 days after treatment stopped (follow-up)* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None stated
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: no information provided as to the method of randomisation.
Allocation concealment (selection bias)	Unclear risk	Comment: no information as to the method of allocation concealment.

Amerio 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "single blinded" Comment: no information was provided as to how this was achieved, i.e. were the 2 preparations in a similar base, packaged in a similar way etc?
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "single blind" Comment: no detail provided about who was blinded or how this was done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 participant left the trial so this is unlikely to bias the final results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no further issues identified

Bagatell 1983

Study characteristics

Methods

Trial design

Double-blind, randomised, parallel-group trial

Trial registration number

Not reported

Setting

6 centres in the USA

Date trial conducted

Not reported

Duration of trial participation

3 weeks

Additional design details

None

Inclusion criteria

- Aged ≥ 12 with AD established for ≥ 1 year (moderate-severe)
- Stable or worsening disease within the last week
- TSS ≥ 6 (erythema, induration and pruritus each scored 0 = absent, 1 = slight, 2 = moderate, 3 = severe) and all of the considered signs had to be present on the target lesions (face, neck, trunk and extremities; excluding hands and feet).

Exclusion criteria

- Pregnancy
- Requirement for concomitant topical anti-inflammatory, systemic steroid, or other therapy that might affect the disease (e.g. tar, tranquillisers, antihistamines).

Bagatell 1983 *(Continued)*

- Use of TCS within the past 2 weeks
- Use of systemic corticosteroid within the past 4 weeks

Notes

None

Participants	**Total number randomised** 249; 127 randomised to alclometasone (moderate potency) and 122 with HC (mild potency). Baseline characteristics were presented for the participants analysed; 114 in the alclometasone group and 115 in the HC group. **Age** Of the 229 participants analysed, mean age was 37 in the alclometasone group (range 12-77) and 36 in the HC group (12-72) **Sex** Of the 229 participants analysed there were 43 male and 71 female in the alclometasone group, and 39 male and 76 female in the HC group **Race/ethnicity** Of the 229 participants analysed there were 97 white participants, 13 black participants, and 4 other in the alclometasone group. There were 93 white, 18 black and 4 other in the HC group **Duration of eczema** Mean disease duration was 13 years (range 1-54) in the alclometasone group and 14 (1-48) in the HC group. **Severity of eczema** In the alclometasone group 82 had ≤ 25% percent body involved, 25 had 26%-50%, 6 had 51%-75% and 1 had 76%-100%. In the HC group 79 had ≤ 25%, 29 had 26%-50%, 6 had 51%-75% and 1 had 76%-100%. The trial authors stated that there was a difference. Scores are also available for the 3 individual signs. **Filaggrin mutation status** Not reported **Number of withdrawals** 20 participants were not included; 18 did not meet protocol requirements, 1 experienced an adverse event (alclometasone group stated in the first paragraph of the results, however the safety results state that 3 participants discontinued because of adverse events), 1 experienced exacerbation of the disease (HC). 12 in each group withdrew before the end of the trial because of clearance of their disease. 11 in the alclometasone group and 21 in the HC group withdrew because of treatment failure. In the 3-week data only 82 participants in the alclometasone group and 71 participants in the HC group remained. **Notes** None
Interventions	**Run-in details** NA **Groups** • HC 1% cream (Hytone); applied 3 times daily in a thin layer to the trial lesions without occlusion for 3 weeks. Concurrent treatment: not reported

Bagatell 1983 *(Continued)*

	• Alclometasone dipropionate 0.05% cream (Vaderm); applied 3 times daily in a thin layer to the trial lesions without occlusion for 3 weeks. Concurrent treatment: not reported **Adherence** Unused medication was returned at each trial visit. **Co-interventions** Not reported **Notes** Cream was not applied within 3 h of the trial visits.
Outcomes	• Clinical signs/symptoms (lesions on the face, neck, trunk, and extremities (excluding hands and feet) were evaluated for erythema, induration and pruritus, each of which were scored as follows: 0 = absent, 1 = slight, 2 = moderate, 3 = severe). A total score for all symptoms in addition to a score for each symptom is reported, percentage improvements are calculated at baseline and weeks 1, 2, and 3. • Participants were questioned and examined for evidence of adverse events such as irritation, sensitisation, folliculitis, atrophy, or any systemic effect at weeks 1, 2, and 3.* • IGA (1 = cleared (100% clearance of all signs except for residual discolouration), 2 = marked improvement (between 75% and 100% clearance of signs), 3 = moderate improvement (50%-75% clearance), 4 = slight improvement (clearance of < 50%), 5 = no change, 6 = exacerbation (flare at site) at weeks 1, 2, and 3.* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: no information regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "randomised" Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: both participant groups received treatment, so it is likely that participants were blinded. However no other details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind" Comment: no information regarding whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Because not all patients completed all three weeks of treatment, an "endpoint" analysis was also performed, combining results from the patient's last visit. This made it possible to assess and describe an overall response in all patients." Comment: although an ITT analysis was carried out, this used the last observation carried forward method to complete missing data. As a large proportion of participants were missing by the end of the trial, 32/114 (28%) in the al-

Bagatell 1983 *(Continued)*

		clometasone group (moderate) and 44/115 (38%) in the HC (mild) group, this is likely to influence the results. If participants stopped because they deemed the treatment to be a success or failure then this could change by the end of the trial and so carrying the observation forward may introduce bias.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was identified. All outcomes mentioned in the methods section were reported on.
Other bias	Unclear risk	Comment: JC was concerned that this trial is a 'mini-meta-analysis' and not just a straightforward multicentre trial because of the statement "with the objective of pooling the data". However, there is no detail on randomisation overall or by centre, so it is difficult to determine if there is a risk of bias here.

Beattie 2004

Study characteristics	
Methods	**Trial design** Single-observer, pilot RCT **Trial registration number** Not reported **Setting** A single secondary care centre in Scotland **Date trial conducted** Not reported **Duration of trial participation** 3 weeks **Additional design details** None **Inclusion criteria** • < 5 years of age • AD covering ≥ 30% BSA **Exclusion criteria** • Patients with clinical evidence of infection • Patients requiring TCSs stronger than 1% HC • Use of oral steroids or antibiotics 2 weeks prior to enrolment • Concurrent use of systemic or 'alternative therapies' such as Chinese herbs or homoeopathy **Notes** The abstract states, "using only 1% hydrocortisone prior to the study". The paper includes the statement "We compared the efficacy of WWT [wet wrap treatment]with a standard regime of HC, to control moderate AD in children."
Participants	**Total number randomised**

Beattie 2004 *(Continued)*

19; 10 were randomised to WWT, 9 to the TCS-only group

Age

Mean 1.77 years ± SD 2.74 in the WWT group, 1.44 ± 1.70 years in the TCS-only group. Range for both groups 4 months-3 years

Sex

6 male to 4 female in the WWT group, 4 male and 5 female in the TCS only group

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Mean SASSAD at baseline was 28 in the WWT group and 29.9 in the TCS-only group.

Filaggrin mutation status

Not reported

Number of withdrawals

There were 3 withdrawals from the WWT group: 1 due to an adverse event (folliculitis), 1 to noncompliance and 1 to treatment failure. There was 1 withdrawal from the TCS-only group as the parents were unable to attend due to illness of another family member.

Notes

None

Interventions

Run-in details

NA

Groups

- HC 1%; TCS was applied once daily for 2 weeks. WWT was applied twice daily in the 1st week, then at night in the 2nd week. Concurrent treatment: WWT was demonstrated by a specialist nurse, and parents were shown how to re-apply emollients under wet wraps.
- HC 1%; TCS was applied twice daily for 2 weeks without WWT. Concurrent treatment: none

Adherence

TCS and emollients were weighed at each clinic visit. There was wide variation in the amount of TCS and emollient used, and no significant differences between treatment arms. However, those who used more steroid tended to use more emollient (linear regression coefficient 4.4, 95% CI 0.7–8.0, P = 0.023).

Co-interventions

Both groups were instructed to apply emollient twice daily and as necessary. Emollient was used as required and alone in the 3rd week.

Notes

Application of emollients and HC was discussed with each parent, including recommended quantities of emollients and TCS. To help standardise the amount of HC used by each parent it was recommended that 1 finger-tip unit be spread over 2 hand areas. A 20-min time delay was recommended between the application of steroid and emollient.

Beattie 2004 *(Continued)*

Outcomes	• DFI score at day 0, 14
	• IDQOL specifically the sleep and itch questions;
	  ○ time taken to get off to sleep and total sleep (over the last week approximately how much more time on average has it taken to get your child off to sleep each night? > 2 h = 3, 1-2 h = 2, 15 min-1 h = 1, 0-15 min = 0) (over the last week, what was the total time that your child's sleep was disturbed on average each night? 5 h or more = 3, 3-4 h = 2, 1-2 h = 1, < 1 h = 0)*
	  ○ relating to itch (over the past week how much has your child been itching or scratching, all the time = 3, a lot = 2, a little = 1, none = 0) at day 0, 14*
	• SASSAD severity score (Berth-Jones 1996); head and body score at day 0, 7, 14, 21**
	• Weight of TCS and emollient at day 0, 7, 14, 21
	
	*denotes relevance to this review

Funding source	The project was funded by the Tayside University Hospitals Trust grant scheme.
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized to one of two treatment groups by removing folded, sealed squares of paper from an envelope in the presence of an observer." Comment: the paper does not mention whether pieces of paper were opaque or not. If not this could compromise randomisation.
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomized to one of two treatment groups by removing folded, sealed squares of paper from an envelope in the presence of an observer." Comment: the paper does not mention whether pieces of paper were opaque or not. If not this could compromise randomisation. We also do not know whether the observer knew what was written on the paper.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: the nature of the occlusion intervention requires participant/parent knowledge and there is also no indication that personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: the occlusion intervention may leave visible clues on the skin to an observer, but there is also no mention of the assessor being blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "initial scores of these children were included in the final analysis." Comment: 3 participants dropped out of the WWT group and 1 from the TCS-only group. As there were only 10 participants in the WWT group, this is a large proportion of the participants. These participants were not included in the analysis at the end of treatment it is possible that this could introduce bias (especially as 2 participants dropped out because of noncompliance and treatment failure).
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias detected

Berth-Jones 2003

Study characteristics

Methods	**Trial design** Double-blind, parallel-group, placebo-controlled RCT **Trial registration number** Trial identifier: FLTB4012 **Setting** Dermatology outpatients clinics (6 European countries, 39 centres) **Date trial conducted** January 1998-July 1999 **Duration of trial participation** 20 weeks: stabilisation phase (4 weeks) and maintenance phase (16 weeks) **Additional design details** This trial includes 2 phases - both are relevant to this review. **Inclusion criteria** • Participants with recurrent moderate-severe AD who were experiencing a flare (see outcomes for flare definition). This was assessed from an index lesion (a typical lesion on the patient's neck, hands, or flexural sites of the elbows or knees). • Patients aged 12-65 **Exclusion criteria** • Patients were excluded if they had any medical condition for which TCSs were contraindicated. • Patients with dermatological conditions that may have prevented accurate assessment of AD. • Participants receiving concomitant medications that might affect the trial's outcome. **Notes** None
Participants	**Total number randomised** 376 (of these only 295 participants went into the maintenance phase) **Age** Overall mean 28.8 (SD 12.4); cream once daily 28.4 years (12.2); cream twice daily 28.1 (11.8); ointment once daily 29.6 (13.3); ointment twice daily 28.9 (12.4). **Sex** Overall 171 male (45%), 205 female (55%); cream once daily 44 male, 51 female; cream twice daily 42 male, 49 female; ointment once daily 46 male, 54 female; ointment twice daily 39 male, 51 female **Race/ethnicity** Overall 344 white (91%), 13 black (13%), 19 other (5%); cream once daily 85 white, 7 black, 3 other; cream twice daily 84 white, 2 black, 5 other; ointment once daily 91 white, 4 black, 5 other; ointment twice daily 84 white, 0 black, 6 other

Berth-Jones 2003 *(Continued)*

Duration of eczema

Overall 323 > 5 years (86%), 53 ≤ 5 years (14%); cream once daily 78 > 5 years, 17 ≤ 5 years; cream twice daily 81 > 5 years, 10 ≤ 5 years; ointment once daily 86 > 5 years, 14 ≤ 5 years; ointment twice daily 78 > 5 years, 12 ≤ 5 years. Duration of the current flare: overall 268 > 3 weeks (71%), 108 ≤ 3 weeks (29%); cream once daily 65 > 3 weeks, 30 ≤ 3 weeks; cream twice daily 65 > 3 weeks, 26 ≤ 3 weeks; ointment once daily 74 > 3 weeks, 26 ≤ 3 weeks; ointment twice daily 64 > 3 weeks, 26 ≤ 3 weeks

Severity of eczema

The overall median TIS score for the index lesion was 5.0 (range 4-9); cream once daily 5.0 (4-6); cream twice daily 5.0 (4-9); ointment once daily 5.0 (4-7); ointment twice daily 5.0 (4-7). Data were missing for 1 participant in the cream-once-daily arm. Overall mean (SD) extent of AD (percentage of 13 body areas (front and back of head, front and back of left and right arm, chest, back, front and back of left and right leg, external genitalia): 18.6 (16.5); cream once daily 28.8 (19.0); cream twice daily 17.7 (16.2); ointment once daily 17.5 (14.6); ointment twice daily 18.4 (16.1)

Filaggrin mutation status

Not reported

Number of withdrawals

19 didn't complete the stabilisation phase from cream once daily, 15 from cream twice daily, 23 from ointment once daily, 26 from ointment twice daily. Overall, of those that did not complete the stabilisation phase, 10 were lost to follow-up, 5 withdrew consent, 4 violated the protocol, 9 experienced adverse events and 5 were categorised as "other". 48 participants were categorised as not meeting the criteria to enter the maintenance and all except 2 participants did not proceed to the maintenance phase. During the maintenance phase, 13 participants allocated TCS cream twice-weekly relapsed, as did 54 allocated twice-weekly base cream, 27 allocated twice-weekly TCS ointment and 41 allocated twice-weekly base ointment. Overall 11 were lost to follow-up, 3 withdrew consent, 7 violated the protocol, 4 experienced adverse events and 2 were categorised as "other".

Notes

it is not clear exactly which groups the 'discontinued' participants belonged to for either the stabilisation or the maintenance phases.

Interventions	In the stabilisation phase 376 participants were randomised to receive fluticasone propionate 0.05% cream or fluticasone propionate 0.005% ointment once or twice daily for 4 weeks. Participants who achieved remission (index lesion score of ≤ 1, absent or mild) then entered the maintenance phase (n = 295) using the same formulation as in the stabilisation phase. A number did not fulfil the criteria for entering the maintenance phase (n = 48) though 2 of these participants did enter the maintenance phase). **Groups** **Stabilisation phase** **A**: fluticasone propionate 0.05% cream; once daily for 4 weeks. Concurrent treatment: none **B**: fluticasone propionate 0.05% cream; twice daily for 4 weeks. Concurrent treatment: none **C**: fluticasone propionate 0.005% ointment; once daily for 4 weeks. Concurrent treatment: none **D**: fluticasone propionate 0.005% ointment; twice daily for 4 weeks. Concurrent treatment: none **Maintenance phase** **E**: base cream; participants applied the cream on 2 successive evenings per week for up to 16 weeks. Treatment was applied to all healed sites of potential relapse and newly occurring sites. Concurrent treatment: none

Berth-Jones 2003 *(Continued)*

F: fluticasone propionate 0.05% cream; participants applied the cream on 2 successive evenings per week for up to 16 weeks. Treatment was applied to all healed sites of potential relapse and newly occurring sites. Concurrent treatment: none

G: base ointment; participants applied the ointment on 2 successive evenings per week for up to 16 weeks. Treatment was applied to all healed sites of potential relapse and newly occurring sites. Concurrent treatment: none

H: fluticasone propionate 0.005% ointment; participants applied the ointment on 2 successive evenings per week for up to 16 weeks. Treatment was applied to all healed sites of potential relapse and newly occurring sites. Concurrent treatment: none

Adherence

Treatment adherence was monitored using daily diaries.

Co-interventions

During the maintenance phase, participants in all treatment groups applied emollient (cetomacragol-based cream) twice daily (once on treatment days) and used a bath oil as needed.

Notes

None

Outcomes	• TIS score (the sum of erythema, oedema or papulations, and excoriations, scored between 0 = absent to 3 = severe) at baseline (start of stabilisation phase), week 2, week 4 (end of stabilisation phase, start of maintenance phase), week 6, week 10, week 14 and week 20 (end of maintenance phase)*
	  ○ Time to relapse (relapse (or flare) was defined as a TIS score of ≥ 4). At the start of the trial, for recruitment purposes an index lesion was assessed, but during the maintenance phase a flare occurring at any site could be assessed at relapse (during the maintenance phase from end of week 4 until end of week 16).*
	  ○ Relapse rate (number of participants having a relapse) at relapse (during the maintenance phase from end of week 4 until end of week 16)*
	• Adverse events at baseline (start of stabilisation phase), week 2, week 4 (end of stabilisation phase, start of maintenance phase), week 6, week 10, week 14 and week 20 (end of maintenance phase)*
	• Visual evidence of skin atrophy at baseline (start of stabilisation phase), week 2, week 4 (end of stabilisation phase, start of maintenance phase), week 6, week 10, week 14 and week 20 (end of maintenance phase)*
	
	*denotes relevance to this review

Funding source	Glaxo Wellcome (now GlaxoSmithKline R & D UK)
Declarations of interest	One of the authors was employed full time by GlaxoSmithKline. Additional support was also provided by a number of other employees of GSK (1 employee gave statistical advice, 1 managed the publication process, 3 were involved in the design of the trial and contributed to discussion of the results).
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation code determined the treatment that each patient received through the stabilisation and maintenance phase. Investigators at each centre allocated patients to treatment groups in equal numbers according to a computer generated randomisation code. The block size for the study was eight, and each recruiting centre received 16 treatment allocation numbers."

Berth-Jones 2003 *(Continued)*

		Comment: there were 39 centres responsible for the randomisation. Knowledge of the block size may enable guessing of the sequence and therefore selection bias. There also appeared to be baseline imbalances, e.g. extent of AD was markedly higher in the cream-once-daily group, which might indicate a failure of randomisation.
Allocation concealment (selection bias)	Unclear risk	Comment: potential concerns with allocation concealment (see above)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients who achieved remission (see assessments) then entered a maintenance phase and, using the same formulation as in the stabilisation phase, applied fluticasone propionate or its placebo base on two successive evenings per week for up to 16 weeks." "double blind" study Comment: as participants were receiving a placebo ointment it is likely that they would not be able to tell whether they were receiving active treatment or not, however it is unclear which personnel knew what treatment the participant was receiving.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information as to whether the clinicians assessing the participant were different to those who initially cared for the participant or whether they were likely to know which treatment the participant was receiving.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "We conducted all analyses on an intention to treat basis (all subjects were included in the analysis if they were randomised and applied the study medication at least once)." Comment: although the description of ITT refers to modified ITT, all the participants in the stabilisation phase and maintenance phase received treatment and so should be included in the analysis. There is no information as to how missing data from participants lost to follow-up was handled so it is unclear how any ITT analysis was conducted. 27 participants discontinued and so this could potentially represent a large proportion of a particular group if all participants discontinued in a particular group. The number of discontinuations per group is not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: unable to locate protocol
Other bias	Low risk	Comment: no other source of bias detected

Bleehen 1995

Study characteristics	
Methods	**Trial design** Multicentre, randomised, double-blind, parallel-group comparative trial **Trial registration number** Not reported **Setting** 36 hospitals in the UK **Date trial conducted** Not reported

Bleehen 1995 *(Continued)*

Duration of trial participation

Up to 4 weeks

Additional design details

None

Inclusion criteria

- Male and female patients with atopic eczema who had been referred to the hospital by their general practitioner and have had a diagnosis of atopic eczema confirmed by a dermatologist
- Aged between 1-65 years
- At least moderate severity with a total severity score of ≥ 6 based on erythema, pruritus, and thickening, each graded 0-3 (0 = absent, 3 = severe) at the target area

Exclusion criteria

- Frank infection of eczema
- Eczema so severe it required hospital admission
- Use of any systemic medications for eczema within 3 weeks prior to trial entry (corticosteroid administered by spray or aerosol for asthma or allergic rhinitis was allowed)
- Use of antihistamines or antipruritics within 3 days prior to trial entry
- Any concomitant unstable or serious disease
- A history of adverse response to a topical or systemic corticosteroid

Notes

Participants who had used very potent steroids for 3 weeks or potent steroids for 1 week before trial entry could only enter after a washout period of using only mild or moderate potency topical steroids (Efcortelan or Eumovate cream). Washout period for very potent steroids was 3 weeks, and potent steroids was 1 week.

Participants

Total number randomised

270 participants in total (once daily n = 137; twice daily n = 133)

Age

Once daily group: mean age 17.3 years (range 1-56, SD 14.4); twice daily group: 17.0 (0-62, 13.9)

Sex

Well matched between groups but no data given

Race/ethnicity

Well matched between groups but no data given

Duration of eczema

Well matched between groups but no data given

Severity of eczema

Well matched between groups; the only data given is baseline severity score of median 10.0 for target areas in both once and twice daily groups for the intent to treat population.

Filaggrin mutation status

Not reported

Number of withdrawals

Bleehen 1995 *(Continued)*

	73 participants withdrew. Once daily: 38 participants (45 reasons given including 3 for adverse event, 7 for exacerbation of skin disease, 9 participants failed to return, 2 participants withdrew consent, 12 deviations from protocol, 9 withdrew because of success, and 3 other reasons). Twice daily: 35 participants (42 reasons given including 3 for adverse event, 5 for exacerbation of skin disease, 10 participants failed to return, 1 participant withdrew consent, 14 deviations from protocol, 5 withdrew because of success, and 4 other reasons) **Notes** None
Interventions	**Run-in details** NA **Groups** • Fluticasone propionate 0.05% cream (not stated); applied once daily, with vehicle applied once daily for ≤ 4 weeks if eczema at target area had cleared. Active treatment and vehicle were randomised and labelled A and B. Tubes labelled A were applied in morning and tubes labelled B were applied in evening. A fingertip was used to indicate how much cream to use. Concurrent treatment: once daily application of a vehicle consisting of propylene glycol, mineral oil, cetostearyl alcohol, polyoxyl 20 cetostearyl ether, isopropyl myristate, dibasic sodium phospate, citric acid, purified water and imidurea. • Fluticasone propionate 0.05% cream (not stated); applied twice daily for ≤ 4 weeks if eczema at target area had cleared. Tubes labelled A were applied in morning and tubes labelled B were applied in evening. A fingertip was used to indicate how much cream to use. Concurrent treatment: none **Adherence** Unused medication was returned after each visit and tubes were weighed. There was little difference between groups in the weight of the returned morning tubes containing active treatment or in the weight of returned evening tubes containing active treatment. Total amount of active treatment used in once daily group was approximately half that in the twice daily group. **Co-interventions** No dermatological preparations other than the trial medication or emollients were allowed during the 4-week trial. **Notes** None
Outcomes	• Severity of itch, rash and sleep disturbance (participants completed daily diary cards) at daily for 4 weeks* • Adherence (weighing tubes at each visit) at baseline and week 1, 2, 3, and 4 • Serious laboratory abnormalities at baseline and week 1, 2, 3, and 4* • Adverse events or untoward symptoms (adverse events in terms of digestive system disorders, diseases and symptoms of the nervous system, diseases of the blood, eye, musculoskeletal system, respiratory system, infectious and parasitic diseases, injury and poisoning, kidney and urinary system, mental illness, neoplasms, non-specific symptoms and abnormal findings, or skin disorders) at baseline and week 1, 2, 3, and 4* • Investigator assessment of responses to treatment at a preselected target area (most troublesome site to the participant). Success was defined as target area being cleared, excellent or good compared with baseline (> 50% improvement) at baseline and week 1, 2, 3, and 4* • Severity of six signs and symptoms: investigator assessment of erythema, pruritus, thickening, lichenification, vesiculation and crusting, each scored using a 7-point scale. The sum of scores were calculated and decrease in score from baseline indicated successful treatment at baseline and week 1, 2, 3, and 4.* *denotes relevance to this review

Bleehen 1995 *(Continued)*

Funding source	The trial was sponsored by Glaxo Laboratories Limited who supplied all tubes of cream and who also usually manufacture Fluticasone cream.
Declarations of interest	None stated
Notes	Outcomes are also reported as per the per protocol analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The trial was a multicentre, randomized … study", "Eligible patients were randomly allocated", "This once daily group also had the active and vehicle treatments randomized." Comment: no information as to how the randomisation took place
Allocation concealment (selection bias)	Unclear risk	Comment: no details given on whether allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Eligible patients were randomly allocated to receive either once-daily or twice-daily fluticasone propionate. All patients received 2 x 30 g tubes of cream, labelled A and B, per week, to apply morning (tube A) and evening (tube B) for 4 weeks, or less if eczema at the target area had cleared. For patients in the once-daily group, one of these two tubes contained vehicle" "All tubes of cream (supplied by Glaxo Laboratories Ltd, London, U,K,) were similar in size, and the contents were similar in smell, texture and appearance. The only difference was in coloured labels which distinguished morning (A) and evening (B) treatments" Comment: participants were blinded to whether they received once daily or twice daily by the use of a vehicle in the once daily group. It is not clear if trial personnel were blinded but the trial is referred to as a "double blind" trial, so assume they were.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The trial was a multicentre, randomized, double-blind, parallel group, comparative study involving 36 hospitals in the UK." "Clinical response to treatment was assessed by the same investigator at weekly intervals" Comment: not clear if outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One hundred and ninety-eight of the 270 patients recruited completed the study; 73 patients were withdrawn; one patient who completed the study also withdrew. " Comment: 70% of participants completed the trial. The number of withdrawals (38 in once daily versus 35 in twice daily) and reasons for withdrawal (mainly deviation from protocol or patient failed to return) were fairly similar between groups. The authors also used an ITT analysis taking the last available measurement, and the ITT and per protocol results were similar.
Selective reporting (reporting bias)	Unclear risk	Comment: not clear as no protocol available
Other bias	Unclear risk	Quote: "The two groups were well-matched at baseline for age, sex, ethnic origin, history of eczema and extent, severity and duration of the current exacerbation." Comment: the trial authors say the groups were well matched but no values given to support this (except for age and median severity).

Bleeker 1975

Study characteristics	
Methods	**Trial design** Randomised, double-blind, half-sided trial **Trial registration number** Not reported **Setting** Not reported, however the author is affiliated to a hospital dermatology department in Sweden. **Date trial conducted** Not reported **Duration of trial participation** 2 weeks **Additional design details** None **Inclusion criteria** • Patients with psoriasis or eczema (results presented separately for the patients with AD) • Patients with bilateral lesions which were similar in severity, persistence and aetiology • Patients were selected for the ability to follow instructions for application of the corticosteroid **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised** 27 participants with AD **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** 11 severe, 16 moderate

Bleeker 1975 *(Continued)*

	Filaggrin mutation status Not reported **Number of withdrawals** None of the participants were reported to have withdrawn. **Notes** None
Interventions	**Run-in details** Not reported **Groups** • Halcinonide 0.1% cream (unspecified); applied to the 1 half of the body (according to randomisation) twice daily. Concurrent treatment: none • Clobetasol propionate 0.05% cream (unspecified); applied to the 1 half of the body (according to randomisation) twice daily. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Not reported **Notes** Halcinonide formulation included a specifically designed base with a high content of propylene glycol but sufficient water to maintain proper hydration.
Outcomes	• Side effects were reported at overall (week 2)* • Objective comparative clinical response (erythema, oedema, transudation, lichenification and scaling) at weeks 1, 2, and overall • Subjective criteria (pruritus and pain) at weeks 1, 2, and overall • Overall clinical response (4-point scale: 'excellent', 'good', 'fair', 'poor'); this took into account the objective and subjective criteria as well as rapidity, maximum clearance and maintenance of therapeutic response at overall (week 2)* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The test preparations (halcinonide 0.1% and clobetasol propionate cream 0.05%) were packed identically in 30g tubes and designated for each patient's left or right side in accordance with a table of random assignment" Comment: as researchers used a prespecified table of randomly generated numbers this is likely to have been unbiased.

Bleeker 1975 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: no information is provided as to the method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The test preparations were packed identically in 30g tubes and designated for each patient's left or right side" "Tubes were labelled with the patient's number and the side of the body to which its contents were to be applied" "double blinded" Comment: it is likely that the participants did not know what treatment they were receiving as plain packaging was used, however it is unclear whether the personnel were also blinded. The trial is described as double-blinded however it is unclear as to whether the personnel or outcome assessors were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blinded" Comment: as mentioned in above it is unclear whether personnel or outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were included in the final results table and so this is unlikely to be a source of bias.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available and so this cannot be assessed
Other bias	Low risk	Comment: no other source of bias identified

Bluefarb 1976

Study characteristics

Methods

Trial design

Double-blind, randomised, parallel, multiclinic trial

Trial registration number

Not reported

Setting

Participants were enrolled by 4 dermatologists (multiple clinics in secondary care).

Date trial conducted

Not reported

Duration of trial participation

Up to 3 weeks

Additional design details

None

Inclusion criteria

- Patients with moderately severe or severe, acute or chronic, psoriasis or atopic/neurodermatitis (data presented separately)

Exclusion criteria

Bluefarb 1976 *(Continued)*

- Patients with mild lesions
- Patients who required other local or systemic therapy that may influence the results
- Patients who received local or systemic anti-metabolite therapy within the preceding month
- Women of childbearing potential

Notes

None

Participants	**Total number randomised** Of 210 randomised, 201 were considered evaluable and baseline data were presented for these (9/210 were considered unacceptable because concomitant drug therapy in these participants confounded evaluation of the trial medication). 98 and 103 were randomised to the diflorasone diacetate and fluocinonide groups respectively. **Age** Mean age 43 diflorasone group, 45 in the fluocinonide group **Sex** 50 male and 48 female in the diflorasone diacetate group; there were 53 male and 50 female in the fluocinonide group **Race/ethnicity** Not reported **Duration of eczema** 80% in each group had chronic lesions. **Severity of eczema** 10/98 (10%) in the diflorasone group and 23/103 (22%) in the fluocinonide group had severe lesions ; the difference came from one investigator's group, but when the investigator's data were removed the response pattern did not change, so we pooled all data. **Filaggrin mutation status** Not reported **Number of withdrawals** 9 participants were considered unacceptable because of concomitant drug therapy which confounded evaluation of the trial medication. Week 1, 2 participants missing diflorasone group, 0 from the fluocinonide group. Week 3, 32 missing from the diflorasone group, 14 from the fluocinonide group. End of therapy 25 participants missing diflorasone group, 6 participants missing from the fluocinonide group. The paper states "some patients in both treatment groups could not be evaluated after week 2 for the following reasons: medication error when patients' supplies were replenished, unsatisfactory progress, participants dropped out because lesions cleared, or reasons unknown." It is not clear which reasons applied to which participants. **Notes** None
Interventions	**Run-in details** Not reported **Groups**

Bluefarb 1976 *(Continued)*

- Diflorasone diacetate 0.05% cream; applied twice daily to moderately severe lesions and 3 times daily to severe lesions, without occlusion. Cream was applied in a thin layer and rubbed gently until it disappeared. Duration of the trial was 3 weeks unless participants were judged cleared or deteriorating and requiring further treatment. Concurrent treatment: none
- fluocinonide 0.05% cream; applied twice daily to moderately severe lesions and 3 times daily to severe lesions, without occlusion. Cream was applied in a thin layer and rubbed gently until it disappeared. Duration of the trial was 3 weeks unless participants were judged cleared or deteriorating and requiring further treatment. Concurrent treatment: none

Adherence

Not reported

Co-interventions

Concomitant therapy was not permitted; 9 of the 210 participants initially randomised were subsequently excluded because of this.

Notes

The diflorasone diacetate cream contains 0.05% of the steroid in solution in the propylene glycol-water phase. Propylene glycol constituted 15% of the cream. The lipid phase contained stearic acid. Fluocinonide cream was the marketed product containing 0.05% steroid in FAPG cream.

Outcomes	• Degree of therapeutic response compared to baseline (6-point scale: 76%-100% clinical resolution, 51%-75%, 26%-50%, 1%-25%, no change, or deterioration) at week 1, 2 and 3* • Adverse events (not listed in methods but listed as a result) at up to week 3* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None reported, 1 author works for The UpJohn Company (pharmaceutical manufacturer).
Notes	This trial was performed on institutionalised participants. The trial does state that they were informed of the goals and hazards, and that they gave written consent.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "On the basis of a number code, each patient was assigned randomly to treatment to treatment with diflorasone diacetate cream or fluocinonide cream" Comment: it is unclear where number codes came from (e.g. random number list or a patient code) and so it cannot be judged as to whether the use of this code would introduce bias.
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The patients received identical-appearing 30g tubes and the number on the tube became the patient's medication number". "Double blind" Comment: although it is likely that participants were blinded it is unclear as to whether the personnel or outcome assessors were the other party that was blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: there is no information as to whether outcome assessors were blinded or not.

Bluefarb 1976 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "some patients in both treatment groups could not be evaluated after week 2 for the following reasons: medication error when patients' supplies were replenished, unsatisfactory progress, patients dropped out because lesions cleared, or reasons unknown." Comment: At the endpoint, 25/98 participants were missing from the diflorasone group and 6/103 participants were missing from the fluocinonide group. This is a large proportion of participants in both groups and in particular the diflorasone group. As the reasons that participants dropped out is likely linked to the efficacy of the cream it is likely that the results of the trial are biased.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available and so this cannot be assessed.
Other bias	Low risk	Comment: no other source of bias was identified.

Bryden 2009

Study characteristics	
Methods	**Trial design** 3-arm RCT (only 2 arms are relevant to this review) **Trial registration number** Not reported **Setting** Not stated; author's affiliation is a department of dermatology at a hospital in Scotland, UK **Date trial conducted** Not reported **Duration of trial participation** 3 weeks (2 weeks treatment, 1 week of follow-up) **Additional design details** None **Inclusion criteria** Children < 5 years with mild- moderate atopic eczema **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised**

Bryden 2009 *(Continued)*

	51 (WWT plus TCS n = 24, TCS only n = 27) - the third arm of WWT only (n = 24, no TCS) was not relevant to this review. **Age** 3–54 months across all 3 arms **Sex** 48 male and 27 female across all 3 arms **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** SASSAD was 30 (mean) across all 3 arms **Filaggrin mutation status** Not reported **Number of withdrawals** 3/24 dropped out of the WWT + HC arm compared to 5 of 27 in the HC alone arm **Notes** baseline statistics include all 75 participants from the original 3 arms.
Interventions	**Run-in details** Not reported **Groups** • HC 1% cream; TCS applied twice daily for 2 weeks. Concurrent treatment: none • HC 1% cream; TCS was applied twice daily in the 1st week and once daily for the 2nd week. Concurrent treatment: WWT twice daily for 2 weeks. **Adherence** Not reported **Co-interventions** All groups received Epaderm (Medlock Medical Ltd, Oldham, UK) ointment twice daily, and as required, for 3 weeks. **Notes** None
Outcomes	• IDQOL at baseline and week 1, 2, and 3 • DFI questionnaire at baseline and week 1, 2, and 3 • SASSAD score at baseline and week 1, 2, and 3* *denotes relevance to this review
Funding source	Funded by the British Skin Foundation

Bryden 2009 *(Continued)*

Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "were assigned to three treatment arms using presealed envelopes containing random treatment allocations (computer-generated blocked randomization)". Comment: adequate randomisation
Allocation concealment (selection bias)	Unclear risk	Quote: "were assigned to three treatment arms using presealed envelopes containing random treatment allocations (computer-generated blocked randomization)" Comment: there was no mention of whether the envelopes were opaque or not.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: although blinding of participants is not mentioned, it would be very difficult to blind participants to the treatment that they had received due to the nature of the treatment (i.e. use of WWTs or not).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Assessments were made weekly for 3 weeks by a blinded observer." Comment: outcome assessors was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "When analysed on an intention-to-treat (ITT) basis, carrying forward the last known SASSAD values to replace missing data from the dropouts.." Comment: of the 24 participants in the WWT and HC group, 3 dropped out, whilst 5 out of 27 in the TCS group dropped out. Last observation carried forward was used to estimate the final SASSAD scores for these participants, a method that can lead to bias results. It is unclear how using last observation carried forward would have affected the results as a fairly large proportion of participant data were imputed by this method. Furthermore, no reasons for withdrawals were given.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol found
Other bias	Low risk	Comment: we did not detect any other sources of bias.

Busch-Heidger 1993

Study characteristics

Methods	**Trial design** Randomised double-blind trial **Trial registration number** Not reported **Setting**

Busch-Heidger 1993 *(Continued)*

	4 sites in Germany **Date trial conducted** Not reported **Duration of trial participation** 5 weeks, however, the paper also states: "treatment lasted for a minimum of 3 days and a maximum of 44 days. The median was between 20 and 21 days for both treatment groups." **Additional design details** None **Inclusion criteria** Patients diagnosed with atopic eczema **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised** 75 **Age** An average of 40 years (range 18-82) overall; median 29.5 in the HC buteprate group (range 18-80); 42.0 in the HC 17-butyrate group (18-82) **Sex** 31 male and 44 female overall; 19 male and 18 female in the HC buteprate group; 12 male and 26 female in the HC 17-butyrate group **Race/ethnicity** Not reported **Duration of eczema** 83.8% had eczema since they were ≤ 10, 16.2% had eczema from 11 years upwards (see notes*) **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** 6 people completed the trial prematurely (but all 75 participants were included in the evaluation). Does not state these as withdrawals per se (as applied treatments "until healing" or a max of 5 weeks) **Notes** *not reported in a way can work out duration, only information on onset
Interventions	**Run-in details**

Busch-Heidger 1993 *(Continued)*

The English translation states that "all ongoing treatments had been completed for at least 1 day and with corticosteroids 3 days before baseline"

Groups

- HC buteprate 0.1% fatty cream (proprietary: Pandel CreSa); applied daily to affected areas until healing or up to 5 weeks. Frequency of administration was twice daily at the beginning of treatment, reduced to once in half of the participants in the further course at once daily. In whom the reduction occurred is unclear. Concurrent treatment: not reported
- HC 17-butyrate 0.1% fatty cream (proprietary: Alfson CreSa); applied daily to affected areas until healing or up to 5 weeks. Frequency of administration was twice daily at the beginning of treatment, reduced to once in half of the participants in the further course at once daily. In whom the reduction occurred is unclear. Concurrent treatment: not reported

Adherence

Not reported

Co-interventions

Not reported

Notes

HC buteprate formulation labelled as 'fatty cream'; it is a CreSa oil in water emulsion (30% water content in the outer phase and 70% fat in the inner phase).

Outcomes	• Participant report of side effects at up to 5 weeks* • Tolerability rated by the participant as very good, good, moderate or bad at up to 5 weeks (assumed). • Participant assessment of itching with scores 0 = not available, 1 = mild, 2 = moderate, and 3 = severe. at baseline, week 1, 3 and up to 5 weeks* • Physician assessment of signs and symptoms: erythema, blistering, infiltration, scaling, lichenification, and excoriation as well as itching with scores 0 = not available, 1 = mild, 2 = moderate, and 3 = severe. The sum of scores was the main criterion and 'healing' was defined as blistering, infiltration, excoriation and itching completely disappeared and the parameters erythema, scaling and lichenification reached a maximum score of 1. at baseline, week 1, 3 and up to 5 weeks. • Effectiveness rated by physician as very good, good, moderate or bad at baseline, 1 week, 3 weeks, 5 weeks* • Physician evaluation of tolerability (assumed) at up to 5 weeks (assumed). *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared, however the authors are affiliated to Medical Dept. Basotherm Biberach GmbH.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the assignment to the respective test specimen was randomised". Quoted from English translation Comment: no details provided on sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided

Busch-Heidger 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind study". Quoted from English translation Comment: no detail on how physicians and participants were blinded and how easily they could have been unblinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind study". Quoted from English translation Comment: no detail on how physicians were blinded and how easily they could have been unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "all 75 patients in the clinical comparison were included in the evaluation, 69 people completed the trial on schedule and 6 prematurely". Quoted from English translation Comment: it is not clear what was done with the data from the 6 participants who completed the trial.
Selective reporting (reporting bias)	High risk	Comment: no protocol available. Methods states there were participant-reported data (itch), however these data not presented
Other bias	Low risk	Comment: could not detect any additional sources of bias

Cadmus 2019

Study characteristics

Methods

Trial design

Randomised, half-sided, investigator-blinded, parallel, phase-4

Trial registration number

NCT02680301

Setting

Speciality for Child Dermatology, Dell Children's Medical Center Pediatric and Adolescent Dermatology outpatient clinic in Austin, Texas

Date trial conducted

March 2016-June 2018

Duration of trial participation

3-5 days

Additional design details

None

Inclusion criteria

- Patients aged 3-17 years with symmetrical, bilateral AD (flare) on the upper or lower extremities
- Flares must be over a certain threshold (flare defined as mild to very severe (2-5) on the IGA)
- Only English and Spanish speaking patients were enrolled.

Exclusion criteria

- Patients with systemic infection or bacterial skin infections.
- Patients with eczema herpeticum

Cadmus 2019 *(Continued)*

- Patients with suppression of the hypothalamic-pituitary-adrenal axis

Notes

None

Participants	**Total number randomised** 40; 22 randomised to ointment right/cream left, 18 to ointment left/cream right **Age** Of 39 participants that completed the trial mean age was 7.77 (SD 3.61); in ointment right/cream left mean was 8.14 (3.88); in ointment left/cream right mean was 7.29 (3.27) 16 participants were aged 4-7 years, 13 participants 8-10 years, 10 participants 11+ **Sex** Of 39 participants who completed the trial 14 were male and 25 were female; in ointment right/cream left there were 10 male and 12 female; in ointment left/cream right there were 4 male and 13 female **Race/ethnicity** Of 39 participants who completed the trial 20 were Hispanic/Latino and 19 were not (8 African American, 5 Asian, 4 white (non-Hispanic), 1 Pacific Islander and 1 multiracial); in ointment right/cream left 11 were Hispanic/Latino and 11 were not; in ointment left/cream right 9 were Hispanic/Latino and 8 were not. of 39 participants who completed the trial 24 were white, 8 were black/African American, 1 was Native Hawaiian/other Pacific Islander, 5 were Asian and 1 was > 1 race. In ointment right/cream left 13 were white, 2 were black/African American, 1 was Native Hawaiian/other Pacific Islander, 5 were Asian and 1 was > 1 race. In ointment left/cream right 11 were white and 6 were black/African American **Duration of eczema** Not reported **Severity of eczema** Baseline IGA cream group 2.59, ointment group 2.56 **Filaggrin mutation status** Not reported **Number of withdrawals** 1 participant did not complete the trial (ointment left/cream right); this participant received treatment but did not attend the follow-up visit. They were not included in the baseline data. **Notes** None
Interventions	**Run-in details** Not reported **Groups** • Triamcinolone 0.1% cream (unspecified); applied twice daily to the designated extremity, using the wet wrap technique. Concurrent treatment: none • Triamcinolone 0.1% ointment (unspecified); applied twice daily to the designated extremity, using the wet wrap technique. Concurrent treatment: none

Cadmus 2019 *(Continued)*

Adherence

The medications will be weighed before and after each visit and a medication calendar was also used. "Patents were determined to be adhering to the protocol if the number of wet-wraps for each trial arm (cream or ointment) were the same. Because the total number of wraps varied between participants (the protocol required 1-2 wraps per day for 3-5 days), we reviewed medication logs (participants kept medication record sheets where they logged the date and time of wet wrap and steroid application) to determine that each patient completed an equivalent number of ointment and cream wraps." participants reported 100% adherence.

Co-interventions

"an investigator or nursing staff will instruct patients and parents on wet wrap technique (usual practice). A handout about treatment technique will also be provided."

"Wet wraps consisted of any material that was 100% cotton including t-shirts, towels, and pyjamas. Patients were instructed to squeeze a small amount of triamcinolone onto the fingertip and apply a thin layer to the affected areas. Dressings were then soaked in warm water and wrung out to be damp before applying over the treated skin. Patients could use a blanket or dry towel over wet wraps if desired to prevent chills.
Wet wraps were to remain in place for 20-30 min and could be applied 1-2 times a day for the duration of the trial, based on patient tolerance. A technique of 30 min twice a day was recommended, but the trial allowed for as little as 20 min once a day due to concerns of tolerance and patience with small children. Following removal of dressings, a thin coat of moisturiser was applied to all affected areas. Because the aim of the trial was to compare TCS vehicles on symmetric flares on the same patient, they were allowed to use either cream or ointment moisturisers as long as the same product was used on each side in order to maintain consistency within participants."

Notes

None

Outcomes	• Number of participants with local adverse events (reporting description not specified) at 3-5 days* • Photographs of the affected areas at 3-5 days (assumed) • "(POEM) and/or a Children's' Dermatology Life Quality Index (CDLQI) index will also be provided to determine the patient's-point of view regarding their management using validated tools" at baseline and 3-5 days (see risk of bias assessment) • IGA (change in AD): 0 = clear; 1 = almost clear; 2 = mild disease; 3 = moderate disease; 4 = severe disease; 5- very severe disease. Lower scores represent a better outcome at baseline and after 3-5 days.* The raters consisted of a medical student and a clinical research nurse who were both supervised by board-certified paediatric dermatologists. • Participant report of which topical steroid formulation was more effective at 3-5 days* • Participant preference and ease of application at 3-5 days *denotes relevance to this review
Funding source	Seton Healthcare
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information about sequence

Cadmus 2019 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "Patients will also be given a sealed and coded envelope containing instructions to apply one steroid formulation to the right extremity and the other to the left." Comment: probably done, although it is not specified if the envelope was opaque.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single (Investigator)" masked. Comment: participants were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Single (Investigator)" masked. Comment: it is not clear what was done to ensure blinding of outcome assessment, and as participants are young children they may also compromise blinding even if requested not to
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1 participant did not complete the trial; no information is given about why, however it is only 1 participant in a split-body trial of 40, so unlikely to contribute significant bias
Selective reporting (reporting bias)	High risk	Quote: "Patient Oriented Eczema Measure (POEM) and/or a Quality of Life (QoL) index will also be provided before and after treatment in order to determine the patient's-point of view regarding their management using validated tools." - protocol Comment: POEM was not recorded in this trial.
Other bias	Low risk	None

Cahn 1961

Study characteristics	
Methods	**Trial design** Within-participant, double-blinded controlled trial **Trial registration number** Not reported **Setting** Not reported **Date trial conducted** Not reported **Duration of trial participation** 1 week **Additional design details** The paper includes 2 trials of fluocinolone vs HC. 1 which is 0.01% (moderate) and 1 which is 0.025% (potent). The moderate vs potent trial is not included within the review, as there is no mention of randomisation having taken place **Inclusion criteria**

Cahn 1961 *(Continued)*

None reported

Exclusion criteria

None reported

Notes

The original trial included 53 participants with inflammatory dermatoses of whom 20 had AD.

Participants	**Total number randomised** 40 sides (20 on each participant) **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** None **Notes** None
Interventions	**Run-in details** Not reported **Groups** • Fluocinolone acetonide 0.025% cream (Synalar); treatment was applied to each of the paired sites 3 times daily for 1 week. Concurrent treatment: none • HC 1% cream (unspecified); treatment was applied to each of the paired sites 3 times daily for 1 week. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Not reported **Notes**

Cahn 1961 *(Continued)*

	Fluocinolone acetonide was formulated in an aqueous, water-washable base. The base itself contained stearic acid, propylene glycol, sorbitan monostearate and mono-oleate, polyoxyethylene sorbitan monostearate, with methyl and propylparaben as preservatives.
Outcomes	• Number of participants in whom fluocinolone was deemed better, HC deemed better or both deemed equal at assumed week 1* • Instances of primary irritation or allergic reactivity at assumed week 1* *denotes relevance to this review.
Funding source	Synalar Cream and the other materials used in this paper were supplied by Syntex laboratories (manufacturers of Synalar).
Declarations of interest	None reported
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized fashion" Comment: no information as to how participants were randomised
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized fashion" Comment: no information regarding the method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind" Comment: no information as to how this was done and whether it was participants, personnel or outcome assessors.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind" Comment: no information as to how this was done and whether it was participants, personnel or outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were accounted for in the effectiveness data.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no additional sources of bias detected

Craps 1973

Study characteristics

Methods	**Trial design** Double-blind, randomised, half sided **Trial registration number**

Craps 1973 *(Continued)*

	Not reported **Setting** None stated, however, trial authors are affiliated to Sandoz Ltd, Switzerland **Date trial conducted** Not reported **Duration of trial participation** 14 days **Additional design details** None **Inclusion criteria** Patients with bilateral eczema*; we assume this has been diagnosed by a medical doctor **Exclusion criteria** Not reported **Notes** *making some level of assumption that all are eczema patients (as does mention psoriasis in the introduction too, but then methods seems to suggest eczema patients included)
Participants	**Total number randomised** 50 **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported **Notes** None

Craps 1973 *(Continued)*

Interventions	**Run-in details** Not reported **Groups** • Clocortolone pivalate 0.1% cream (proprietary: Purantix, Sandoz Ltd.); unspecified frequency, applied to the designated side for 14 days. Concurrent treatment: not reported • Fluocinolone acetonide 0.025% cream (proprietary: Synalar, Syntex.); unspecified frequency, applied to the designated side for 14 days. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** None
Outcomes	• Degree of severity of signs reported by the clinician (assumed): a 4-point scale from 0 = absent to 3 = very severe; based on erythema, exudation, vesiculation, desquamation, pruritus, lichenisation at baseline, 14 days* • Side effects "systematically investigated and registered" at up to week 2* *denotes relevance to this review
Funding source	None stated, however trial authors are affiliated to Sandoz Ltd, Switzerland.
Declarations of interest	None stated, however trial authors are affiliated to Sandoz Ltd, Switzerland.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised allocation of the preparations" Comment: no information about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "it is essential one observer should be responsible for examining the patient. The use of a double-blind procedure avoids any subjective element that might result from employing dissimilar products". Comment: no details of how this is achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "it is essential one observer should be responsible for examining the patient. The use of a double-blind procedure avoids any subjective element that might result from employing dissimilar products". Comment: no details of how this is achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: data appear complete with respect to the included participants.

Craps 1973 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no protocol available. Side effects were stated to be systematically looked for, yet the results have not been reported.
Other bias	Low risk	Comment: no additional sources of bias detected.

Cullen 1971

Study characteristics	
Methods	**Trial design** Randomised, double-blind, half-sided trial reported alongside 2 other trials; 1 where a TCS was compared to placebo and 1 in patients that did not have AD, hence they have not been extracted here. **Trial registration number** Not reported **Setting** Private dermatology practice, USA **Date trial conducted** Not reported **Duration of trial participation** At least 14 days **Additional design details** None **Inclusion criteria** Patients with AD (also psoriasis, but those results have not been extracted). The paper states "simultaneous symmetrically-paired comparison method" from which it can be inferred that patients were judged to have bilateral lesions. AD was categorised as severe and moderate in the results, however it was not clear whom they had intended to recruit in terms of severity. **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised** 12 (it is assumed that no more were randomised than data were presented for) **Age** Not reported **Sex** Not reported **Race/ethnicity**

Cullen 1971 *(Continued)*

	Not reported **Duration of eczema** Not reported **Severity of eczema** 5 participants had severe disease at baseline and 7 had moderate disease. **Filaggrin mutation status** Not reported **Number of withdrawals** None reported **Notes** None
Interventions	**Run-in details** Not reported **Groups** • Flurandrenolone acetonide 0.05% ointment (medications were supplied by Eli Lilly and Co., Indiana); not reported; treatment applied for at least 14 days (assumed). Concurrent treatment: not reported • Tralonide 0.025% ointment (medications were supplied by Eli Lilly and Co., Indiana); not reported; treatment applied for at least 14 days (assumed). Concurrent treatment: not reported **Adherence** "Medications were supplied in coded packages designed to minimize any tendency to patient application error." **Co-interventions** Not reported **Notes** None
Outcomes	• Adverse reactions e.g. uncomfortable burning, changes in pigmentation, folliculitis, skin atrophy, or increased capillary fragility at up to day 14* • Evaluation of effectiveness through observation by looking at objective (erythema, scaling, vesiculation, oozing, crusting, pustulation, fissuring, lichenification, thickening, and induration) and subjective parameters (pruritus, burning, and pain), judged as 1 of 5 categories: excellent, good, partial improvement, no improvement, or worse at baseline days 4, 7, and 14 "as far as was practical"* • Comparative effectiveness at day 14 (assumed as not stated) *denotes relevance to this review
Funding source	None stated, however medications were supplied by Eli Lilly and Co., Indiana
Declarations of interest	None declared, however medications were supplied by Eli Lilly and Co., Indiana
Notes	None
Risk of bias	

Cullen 1971 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Coding was done in a random distribution fashion and neither patient nor physician knew the identity of the compounds used." Comment: no information provided about how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "Coding was done in a random distribution fashion and neither patient nor physician knew the identity of the compounds used." Comment: coded packages were provided by A. F. Crumley at Eli Lilly and Co., an independent organisation, however no details were provided on the method of concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Coding was done in a random distribution fashion and neither patient nor physician knew the identity of the compounds used." Comment: coded packages were provided by A. F. Crumley at Eli Lilly and Co., an independent organisation, so it is reasonable to assume that blinding was adequate.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Coding was done in a random distribution fashion and neither patient nor physician knew the identity of the compounds used." Comment: coded packages were provided by A. F. Crumley at Eli Lilly and Co., an independent organisation, so it is reasonable to assume that blinding was adequate.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information provided
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias detected

Del Rosso 2009

Study characteristics	
Methods	**Trial design** Phase-3, double-blind, randomised, parallel-group **Trial registration number** Not reported **Setting** 25 outpatient centres in the USA **Date trial conducted** Not reported **Duration of trial participation** 4 weeks (2 weeks treatment, 2 weeks post-treatment follow-up) **Additional design details**

Del Rosso 2009 *(Continued)*

None

Inclusion criteria

- Otherwise healthy patients aged ≥ 18 years of age
- Clinically diagnosed AD with a treatable area involving at least 2 per cent but not more than 10 percent of BSA determined by the investigator using the "rule of nines".
- Patients who had been clinically stable for at least 1 month.
- Eligible participants had a minimum total symptom score of 7 out of 12 based on the investigator's evaluation (on a scale from 0 = none to 3 = severe) of the severity of (a) erythema, (b) infiltration/papulation, (c) excoriations, and (d) lichenification of all affected treatable areas, at least mild pruritus (score ≥ 1), and a IGA of overall lesion severity of at least 3 (moderate)
- Patients were free of any systemic or dermatological disorder that might interfere with the trial results or increase the risk of adverse events
- A washout period of 4 weeks for any medication known to affect serum cortisol levels or HPA function was required for participants undergoing HPA evaluation.

Exclusion criteria

- Patients who had not undergone a washout period of 2 weeks for TCSs, topical retinoids, or TCIs; 4 weeks for systemic corticosteroids, systemic retinoids, or prolonged sun exposure or ultraviolet light therapy; and 16 weeks for systemic immunomodulating biological agents, such as etanercept
- Patients with unstable AD (spontaneously improving or worsening)
- Patients with any untreated bacterial, mycobacterial, fungal, or viral skin lesion
- Patients with irregular sleep schedules or those who worked night shifts were excluded from HPA evaluation due to the physiological diurnal variation of cortisol levels

Notes

"During the treatment phase, 1 patient in the fluocinonide 0.1% QD [one a day] group continued use of nystatin-triamcinolone. This subject was included in the intent-to-treat (ITT) analysis."

Participants

Total number randomised

313: once daily TCS n = 109; twice daily TCS n = 102; once daily vehicle n = 50; twice daily vehicle n = 52. The latter 2 groups were not extracted as not relevant to this review.

Age

Once daily TCS mean 40.9 ± SD 13.0, range 19–76; twice daily TCS 42.9 ± 15.7, 18–79

Sex

Once daily TCS male n = 40 (40%), female n = 65 (60%); twice daily TCS male n = 52 (51%), female n = 50 (49%)

Race/ethnicity

Once daily TCS white n = 81 (74%), African American n = 17 (16%), Asian n = 0, Hispanic n = 11 (10%), Native American n = 0; twice daily TCS white n = 82 (80%), African American n = 10 (10%), Asian n = 3 (3%), Hispanic n = 6 (6%), Native American n = 1 (1%)

Duration of eczema

Duration of disease (years): once daily TCS mean 17.2 ± SD 14.6, range 0.1–52.0; twice daily TCS 17.8 ± 16.8, range 0.9–64.0. Duration of current episode (months): once daily TCS mean 3.8 ± SD 7.3, range 0.1–40.0; twice daily TCS 4.2 ± 8.3, range 0.1–41.0

Severity of eczema

IGA of overall lesions (0 = cleared, 1 = almost cleared, 2 = mild, 3 = moderate, 4 = severe): once and twice daily TCS mean score 3.15 (approx read from graph). BSA involvement: once daily TCS mean 5.6 ± SD 2.8, range 2–10; twice daily TCS 5.5 ± 2.6, range 2–10

Del Rosso 2009 *(Continued)*

Filaggrin mutation status

Not reported

Number of withdrawals

Number of withdrawals not reported per group (includes participants in the placebo cohorts).

22 participants discontinued the trial for the following reasons: adverse events (n = 5; 1.6%), protocol violation (n = 1; 0.3%), participant's request (n = 5; 1.6%), lost to follow-up (n = 9; 2.9%), and other reasons (n = 2; 0.6%). It is not clear which groups these occurred in, including the placebo groups. Adverse events leading to discontinuation from the trial were worsening of AD (1 participant in each active treatment group and 1 participant in the vehicle twice daily control group), skin fissures, bleeding, peeling, and severe AD in 2 participants in the vehicle once daily control group.

Notes

None

Interventions

Run-in details

NA

Groups

- Fluocinonide 0.1% cream; apply TCS twice daily in the morning and evening for 14 consecutive days. Apply to all affected, treatable areas of the skin. Concurrent treatment: as above
- Fluocinonide 0.1% cream; apply TCS once daily either morning or evening for 14 consecutive days. Apply to all affected, treatable areas of the skin. Concurrent treatment: none

Adherence

Not reported

Co-interventions

Not reported

Notes

"the vehicle characteristic of the cream allows for marked retention of the active ingredient in the stratum corneum, epidermis, and dermis, with a lesser propensity for systemic absorption. Additionally, the cream vehicle is similar to a conventional ointment base in that its water content is very low (<1%).

Outcomes

- Use of concomitant medications (number and percentage of participants) at baseline, week 1, week 2, week 4
- Extent of rebound (comparison of symptom scores and PGA; not presented in the paper) at week 4
- HPA suppression at baseline, week 2 and week 4 (selected sites only, it is unclear why certain sites and participants were selected).*
  - Pre-stimulation blood samples were obtained between 6:30 and 8:30 a.m. prior to intravenous injection of 0.25 mg of cosyntropin and application of trial medication. Samples were collected again 30 min after injection.
  - HPA suppression was defined as a basal serum cortisol level (pre-stimulation) ≤ 5µg/dL, or a 30-min post-stimulation level ≤ 18µg/dL, or a post-stimulation increase over the basal level.
  - Testing occurred at the baseline visit, prior to application of trial medication, and at the end of treatment (week 2). participants with a normal cosyntropin stimulation test at baseline, but abnormal results at week 2, were re-tested at week 4 (2 weeks post-treatment). Those with abnormal results at baseline and the end of treatment could be retested at the investigator's discretion.
- Local and systemic adverse events (number of participants) at baseline, week 1, week 2, week 4*
- BSA (mean ± SD; 'rule of nines' and recorded on a full-body diagram) at baseline, week 1, week 2, week 4

Del Rosso 2009 *(Continued)*

- Skin safety evaluations (number of participants; rating the following 7 signs and symptoms of skin atrophy as present or absent: telangiectasis, skin transparency, loss of elasticity, loss of normal skin markings, skin thinning, striae, and bruising) at baseline, week 1, week 2, week 4*
- Symptom severity ratings (mean without SD; severity of erythema, infiltration/papulation, excoriations, and lichenification of all treatable lesions was scored independent of previous assessments on a 4-point scale where 0 = none to 3 = severe. Overall severity of pruritus was rated as 0 = none (no itching), 1 = mild (slightly bothersome itching), 2 = moderate (bothersome itching, but no loss of sleep), and 3 = severe (constant itching causing intense discomfort and loss of sleep)) at baseline, week 1, week 2, week 4
- IGA of overall lesions (mean without SD, number and percentage 'cleared' or 'almost cleared' judged on a 5-point scale from cleared to severe) at baseline, week 1, week 2, week 4. All treatable lesions designated at the baseline visit were assessed.*

*denotes relevance to this review

Funding source	Not reported
Declarations of interest	Dr. Del Rosso is a consultant, speaker, and/or researcher for Allergan, Coria, Galderma, Graceway, Intendis, Medicis, Onset Therapeutics, Obagi Medical Products, Ortho Dermatology, PharmaDerm, Quinnova, Ranbaxy, SkinMedica, Stiefel, Triax, Unilever, and Warner-Chilcott. Medicis is involved in the marketing of Vanos cream. Although this particular formulation is not specifically mentioned in the method section, the paper refers to the VANOS trial group and references the VANOS Summary of Product Characteristics in the references. Dr. Bhambri reports no relevant conflicts of interest.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "During the baseline visit, subjects were randomized to receive either fluocinonide 0.1% cream or its vehicle. Half of the subjects were randomly selected to apply the cream either QD in the morning or evening, and half were instructed to apply the cream BID, morning and evening, for 14 consecutive days to all affected, treatable areas of the skin." Comment: no description of randomisation method
Allocation concealment (selection bias)	Unclear risk	Quote: as above Comment: unclear if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This Phase 3, double-blind, randomized, parallel-group, vehicle-controlled study was conducted at 25 centers in the United States and was approved by the Institutional Review Board at each participating center." Comment: no description of how the trial was double-blinded. It is highly unlikely participants were blinded as they either applied the TCS cream once daily or twice daily - vehicle was not used in the once daily group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: as above. Comment: described as double-blind but doesn't state who was actually blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Twenty-two subjects discontinued the study for the following reasons: adverse events (n = 5; 1.6%), protocol violation (n = 1; 0.3%), subject's request (n = 5; 1.6%), lost to follow-up (n = 9; 2.9%), and other reasons (n = 2; 0.6%)." Quote: "Demographic data, background characteristics of subjects, and adverse events were summarized for each treatment group using the intent-to-treat population consisting of 313 enrolled subjects"

Del Rosso 2009 *(Continued)*

		Comment: some dropouts but it's not clear which groups they were in and if they were equal across groups. They refer to using an ITT analysis but they don't state the method used to achieve this. It is assumed dropouts were treatment failures and didn't have the adverse event, but it is not clear. Also, it is unclear why certain sites and participants were selected for cortisol measurement and what proportion of sites and participants were selected to measure this outcome.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or clinical trial registry so unable to know if all intended outcomes were reported. There were some missing data (IGA SD and group sizes at follow-up), and 1 outcome that was stated in the methods and not reported.
Other bias	Low risk	Comment: no other biases identified

Dolle 2015

Study characteristics

Methods

Trial design

Randomised, double-blind. Participants were randomised to 3 of 4 possible treatment arms. 3-period incomplete block cross-over design

Trial registration number

NCT01299610, EUCTR2010-022280-35-DE, NCT01381445

Setting

A single centre in Berlin, Germany

Date trial conducted

13 December 2010-14 April 2011

Duration of trial participation

Screening occurred 14 days before the 1st dose, then participants were treated for 21 ± 2 days, then followed up for 7-14 days.

Additional design details

GW870086 is a novel selective corticosteroid, CAS number 827319-43-7.

"Each of the 3 assigned treatments was administered concurrently but on different lesions (the same lesion was used for each treatment throughout the trial period)."

Inclusion criteria

- Modified SCORAD rating of > 25-points
- BSA of > 5% according to the rule of nines
- 3 comparable and representative index lesions (≥ 1 cm^2 in size) with a TIS score of 4-6
- "Patients must be willing to refrain from current active therapy for at least 10 days prior to dosing"
- "Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form"
- "Single QTc, QTcB less than 450 msec; or QTc less than 480 msec in subjects with Bundle Branch Block"
- "AST and ALT < 2xULN; alkaline phosphatase and bilirubin < = 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin less than 35%)"

Dolle 2015 *(Continued)*

- "BMI within the range 19.0 – 29.0 kg/m2 (inclusive)."

"A female subject is eligible to participate if she is of:

- Non-childbearing potential defined as pre-menopausal female with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) greater than 40 MIU/ml and estradiol < 40 pg/ml (< 147 pmol/L) is confirmatory].
- female on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the contraception methods in Section 8.1 if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.
- Male subjects with female partners of child-bearing potential must agree to use one of the contraception methods listed in Section 8.1. This criterion must be followed from the time of the 1st dose of study medication until 90-95 hours post dose."

Exclusion criteria

- Patients with other systemic or active skin disease which might affect the trial results.
- Patients receiving other local treatments within 14 days of the 1st application of trial medication (e.g. tar, retinoids, or TCSs other than 1% HC)
- Patients receiving systemic treatments within 28 days of the 1st application of trial medication
- Patients with disease restricted to the face, feet and/or hands
- "Subjects who present with scars, moles, tattoos, body piercings, sunburn in the test area which could interfere with the assessment of lesions at screening."
- "The subject has a current complication of atopic dermatitis such as erythroderma or overt bacterial or viral infection for which treatment with anti-infectives are indicated"
- "History of recent (less than 6 months) active or presence of current superficial skin infections of viral aetiology such as herpes simplex, or varicella"
- "The subject has been diagnosed as having contact dermatitis in area of target lesions, seborrheic dermatitis and/or occupational eczema at predilection sites of atopic dermatitis"
- "The subject has had topical or transdermal treatments, such as but not limited to retinoids, nicotine or hormone replacement therapies, on or near the intended site of application within 14 days prior to first application of trial medication. Use of other topical preparations such as those containing vitamins, supplements or herbal within 14 days prior to application"
- "The subject has had systemic treatment for atopic dermatitis (including corticosteroids, cyclosporine, tacrolimus, methotrexate, PUVA, or UVB) within 28 days of the first dose of study medication"
- "Foreseeable intensive UV exposure during the study (solar or artificial). Subjects must not be exposed to direct sunlight or skin tanning devices (e.g. sunbed) for the duration of the study"
- "The subject has used topical treatment with tar or any corticosteroid within 14 days of the first dose of study medication except topical 1% HC which may be used twice daily in patients with severe disease who require step-down therapy during the washout period until 3 days prior to study start, after which the hydrocortisone must be discontinued"
- "The subject has used topical treatment with buproprion within 14 days of the first dose of study medication"
- "History of cutaneous photodisorder, such as photoallergic reaction or polymorphic light eruption"
- "History of allergy to steroids or components of test medications, including vaseline, emollient or specific soap and adhesives to be used in the study that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation"
- "History or presence of skin (other than atopic dermatitis), hepatic or renal disease or any other condition known to interfere with absorption, distribution, metabolism or excretion of drugs"
- "Subjects with a history of diaphoresis/excessive sweating not restricted to palms or face"
- "A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening"

Dolle 2015 *(Continued)*

- "Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)"
- "A positive pre-study drug/alcohol screen"
- "A positive test for HIV antibody"
- "History of regular alcohol consumption within 6 months of the study defined as: An average weekly intake of >21 units for male or >14 units for female. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits"
- "The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer)"
- "Exposure to more than four new chemical entities within 12 months prior to the first dosing day"
- "Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety"
- "Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56 day period"
- "Unwillingness or inability to follow the procedures outlined in the protocol"
- "Subject is mentally or legally incapacitated"
- "History of sensitivity to heparin or heparin-induced thrombocytopenia"
- "Consumption of red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study medication"

Notes

None

Participants

Total number randomised

25; 10 into group 1 (GW 0.2%, GW 2%, placebo); 5 into group 2 (placebo, GW 2%, fluticasone propionate 0.05%); 10 into group 3 (GW 0.2%, placebo, fluticasone propionate 0.05%)

Age

Mean 36.2 years (SD 16.68).

Sex

19 male and 6 female

Race/ethnicity

All participants were white

Duration of eczema

Not reported

Severity of eczema

Mean SCORAD overall was 37.2 (SD 7.95)

Filaggrin mutation status

Not reported

Number of withdrawals

There were no withdrawals.

Notes

Dolle 2015 *(Continued)*

	None
Interventions	**Run-in details** Participants were not allowed to receive any other local treatments (e.g. with tar, corticosteroids (except topical 1% HC or retinoids) within 14 days prior to the 1st application of the trial drug. Systemic treatments for AD within 28 days of the 1st dose of trial drug were prohibited. **Groups** • Fluticasone propionate 0.05% cream (proprietary: Flutivate Crème, GlaxoSmithKline); applied once daily to the designated lesion (arms and legs; 1 lesion per limb) for 21 ± 2 days. Concurrent treatment: n = 5 were also receiving placebo or novel steroid 2% on separate lesions, n = 10 were also receiving placebo or novel steroid 0.2% on separate lesions. • GW870086X 2% cream (in development: GlaxoSmithKline (assumed)); applied once daily to the designated lesion (arms and legs; 1 lesion per limb) for 21 ± 2 days. Concurrent treatment: n = 10 were also receiving novel steroid 0.2% or placebo on separate lesions, n = 5 were also receiving fluticasone propionate or placebo on separate lesions. • GW870086X 0.2% cream (in development: GlaxoSmithKline (assumed)); applied once daily to the designated lesion (arms and legs; 1 lesion per limb) for 21 ± 2 days. Concurrent treatment: n = 10 were in a group also receiving novel 2% and placebo on separate lesions, n = 10 were in a group also receiving placebo or FP on separate lesions. **Adherence** Not reported **Co-interventions** "For first three days of the trial, participants applied their randomly assigned treatments at the same time of day during the clinic visits and trial personnel supervised to ensure that the correct application procedures were followed. […] Participants applied their treatments at home on Day 4 to 6, Day 8 to 13 and Day 15 to 20." **Notes** None
Outcomes	• Pharmacokinetic parameters at day 7, 14 and 21 • Skin biopsy pharmacodynamic markers: "A 4 millimeter (mm) punch skin biopsy was taken pre- and post-treatment (Day 1 and Day 21) from each of the 3 index lesions. The results were not analysed for this outcome measure." at day 0 and 21 • TIS: erythema, oedema/papulation, and excoriation scored as 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Reported as an adjusted change from baseline mean, calculated by fitting a mixed effects repeated measures model. A negative response indicates an improvement relative to baseline at days 0, 2, 3, 7, 14 and 22.* • Number of IGA responders: 0 = clear to 5 = very severe. The participant was considered a responder if IGA score reduced by 1 grade and improved from baseline by 2 grades at days 2, 3, 7, 14 and 22. • Safety and tolerability (adverse events, serious adverse events, abnormal haematology, clinical chemistry parameters of potential clinical importance, abnormal electrocardiogram, abnormal vital signs) at up to day 21.* NB more detail available on how these were assessed in clinicaltrials.gov/ct2/show/NCT01299610. *denotes relevance to this review
Funding source	None stated, however 1 of the trial authors is affiliated to GlaxoSmithKline, UK
Declarations of interest	None declared, however 1 of the trial authors is affiliated to GlaxoSmithKline, UK
Notes	None

Dolle 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "double-blind 3-period incomplete block crossover design. The randomisation schedule was generated by Discovery Biometrics (GSK-validated internal software) prior to the start of the study." Comment: probably adequate
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "White to slightly colored opaque cream" for GW870086X and v "White cream" for fluticasone propionate (from trial protocol). "Double-blind" Comment: it is likely that the participants were blinded as the creams were the same, or similar in the case of fluticasone propionate. However, it is not clear which personnel were blinded or how this was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: it is not clear which personnel were blinded or how this was achieved.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no withdrawals and all data appear complete.
Selective reporting (reporting bias)	Low risk	Comment: reported data appear to be consistent with the published protocol.
Other bias	Low risk	Comment: no other source of bias detected

EUCTR2009-012028-98-DE

Study characteristics

Methods

Trial design

Phase 2, placebo-controlled, multicentre, double-blinded, half-sided (each participant received only 1 active treatment, so analysed as a parallel-group trial)

Trial registration number

EUCTR2009-012028-98-DE 2009

Setting

Multiple centres; Germany

Date trial conducted

July-August 2009

Duration of trial participation

21 days

Additional design details

EUCTR2009-012028-98-DE *(Continued)*

None

Inclusion criteria

- Male/female participants with a diagnosis of AD for ≥ 6 months, in active stage (IGA 1-4)
- ≥ 2 comparable areas of stable atopic eczema on bilateral symmetric corresponding sides (not head and genital area; at least 10 cm^2; modified EASI score > 6; ≥ 60% of the test areas afflicted with AD).
- Aged 18-75
- A patient of childbearing potential agreed to contraceptive methods for the duration of the trial: (a) strict abstinence (exception: male partner with vasectomy ≥ 3 months prior), (b) combined oral, implanted or injectable contraceptives on a stable dose ≥ 3 months prior, (c) intrauterine device inserted ≥ 1 month prior
- Patient willing and able to comply with the protocol, e.g. concomitant therapy prohibitions and avoiding intense ultraviolet exposure

Exclusion criteria

- A general medical condition (including underlying dermatological diseases) that in the investigator's opinion may confound the trial assessments
- A medical condition that may put the patient at a general risk and therefore would prevent participation in the clinical trial (including but not limited to: serious infectious diseases, major surgery within the last 4 weeks, coronary artery disease, renal impairment, hepatic impairment, cancer, uncontrolled metabolic diseases, autoimmune diseases)
- Any condition other than AD or treatment that may interfere with the barrier skin function or may lead to dermatitis
- A condition of the skin in the test area that in the investigator's opinion may confound the trial assessments (e.g. extensive body hair, scars, tattoos, piercings) or may put the patient at risk (e.g. localised bacterial or viral infection, suspected Tinea, open wounds)
- The patient has exposed the test areas to excessive UV radiation (or UV therapy) within 1 month prior to baseline or is planning intense UV exposure during the trial
- Very severe AD as measured by the IGA score 5 or, in the judgement of the investigator, an indication for a systemic anti-inflammatory therapy
- An indication for a topical therapy that requires topical treatment anywhere on the body with a corticosteroid more potent than class 2 or > 10 % of the BSA or any non-corticosteroid anti-inflammatory topical treatment during the trial
- Administration of any systemic drug indicated to treat AD (e.g. steroids, immunosuppressives such as ciclosporine, azathioprine, mycophenolat mofetile; leukotriene antagonists) within 1 month prior to trial entry or during the trial
- Systemic administration of antihistamines within 2 weeks prior to trial entry and during the trial
- Administration of any topical treatment (e.g. topical steroids, TCIs) in the region of the designated test areas within 2 weeks prior to trial entry
- Administration of any other topical treatment (including cosmetic products) in the region of the designated test areas during the trial
- Presence or history of a malignant skin disease (other than surgically removed basalioma or sufficiently treated actinic keratosis)
- Presence or history of any malignant disease (other than skin malignancy) in the last 10 years
- Known adverse reactions of any severity or hypersensitivity to any ingredient of the investigational medicinal products (in particular to prednicarbat)
- Presence of cutaneous reactions as a result of vaccination
- Presence of cutaneous manifestation of tuberculosis, of syphilis or of viral infections (e.g. varicella)
- Presence of rosacea
- Presence of perioral dermatitis
- Presence of bacterial or mycotic dermal infections in the test areas
- Immunotherapy (e.g. allergen desensitisation) prior to and during the trial
- Vaccination within 6 days prior to enrolment in the trial and during the trial
- A female patient with a positive urine pregnancy test at baseline (or if retested during the course of the trial), is breast-feeding or is planning to become pregnant or breast-feed a child during the trial

EUCTR2009-012028-98-DE *(Continued)*

- Participation in any other clinical trial within 4 weeks prior or during this trial
- Patient is an adult under guardianship, deprived of freedom or unable to communicate or cooperate with the Investigator due to language or mental problems
- Patient is a suspected substance-abuser or is in the opinion of the investigator unreliable or non-compliant

Notes

None

Participants	**Total number randomised** 50 **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** None **Notes** None
Interventions	**Run-in details** None **Groups** • Prednicarbate 0.25% (o/w) cream (proprietary: prednicarbat); twice-daily cutaneous application (maximum dose 50 g). Concurrent treatment: not reported • Prednicarbate 0.25% ointment (proprietary: prednicarbat); twice-daily cutaneous application (maximum dose 50 g). Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** None reported **Notes**

EUCTR2009-012028-98-DE *(Continued)*

	None
Outcomes	• Physicians' assessment of tolerability (folliculitis, bruise (ecchymosis), whitehead (milia), dermal atrophy, telangiectasia, local infections, local allergic reactions before and after application) at day 0, 7 and 21* • Participants' assessment of tolerability (itching, burning, stinging and tightness of the skin before and after application) at day 0, 7 and 21* • Modified EASI at day 0, 7 and 21* • Adverse events/serious adverse events (severity, nature and frequency) at day 0, 7 and 21 (assumed)* • PGA of tolerability at day 0, 7 and 21 • IGA of tolerability at day 0, 7 and 21 • Abnormal values obtained during physical exam and vital signs at day 7 and 21* *denotes relevance to this review
Funding source	Industry report from Galen pharmaceuticals
Declarations of interest	Industry report from Galen pharmaceuticals
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". Comment: no further information regarding the method used to inform judgement
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blinded" Comment: unclear which parties were blinded and the method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blinded". Comment: unclear which parties were blinded and the method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no dropouts.
Selective reporting (reporting bias)	High risk	Comment: pre-registered protocol available to check. Short-term efficacy data were not presented.
Other bias	Low risk	Comment: no other source of bias detected

Fadrhoncova 1982

Study characteristics

Methods	**Trial design**

Fadrhoncova 1982 *(Continued)*

Randomised, double-blind, half-sided clinical trial

Trial registration number

Not reported

Setting

Hospitalised patients at a dermatology clinic in Prague, assumed from the affiliation of the author

Date trial conducted

Not reported

Duration of trial participation

4 weeks

Additional design details

None

Inclusion criteria

- Patients with bilateral and symmetrical eczema on the limbs and torso (not face)

Exclusion criteria

- Patients with signs of impetiginisation
- Pregnant women
- Patients with malignant disease

Notes

None

Participants

Total number randomised

26 (52 sides)

Age

Range 2-66 years

Sex

10 male and 16 female

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

The paper gives mean scores on various clinical parameters at baseline, but it is very difficult to interpret.

Filaggrin mutation status

Not reported

Number of withdrawals

Fadrhoncova 1982 *(Continued)*

2 participants did not tolerate the treatment and were excluded after week 1. The final column of table 2 (n) suggests that there were no further withdrawals.

Notes

None

Interventions	**Run-in details** Not reported **Groups** • HC 1% cream (unspecified); applied twice daily without occlusion to the designated side for 4 weeks. Concurrent treatment: not reported • HC 17-butyrate 0.1% cream (proprietary: Locoid); applied twice daily without occlusion to the designated side for 4 weeks. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Both participants and nurses were instructed to wash their hands between left and right side applications to prevent contamination. **Notes** None
Outcomes	• Adverse events at up to week 4* • Investigator assessment of 10 clinical signs and symptoms (pruritus, lichenification, infiltration, erythema, exudation, amount of crusts, amount of vesicles, amount of papules, amounts of pustules, and exfoliation), scored from 0 = absent to 4 = very severe, reported separately as group means ± SD and as a combined score. Combined score assumed to be the mean value of each sign/symptom multiplied by the number of participants reporting that sign, summed for all signs/symptoms at baseline and after weeks 1, 2, 3, and 4* • Participant preference for 1 treatment over the other at weeks 1, 2, 3, and 4 • Physician preference for 1 treatment over the other at weeks 1, 2, 3, and 4 *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Tubes marked R (right) and L (left) were assigned to the patients prior to treatment in accordance with the randomized code.' from English translation Comment: no detail given about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information on who allocated side of treatment and how this was done

Fadrhoncova 1982 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind' from English translation Comment: no detail provided on how blinding was done and which investigators were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind' from English translation Comment: no detail provided on how blinding was done and which investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The first two patients did not tolerate experimental treatment and were eliminated from the study after the first week. However, the symptoms of the disease worsened on both sides in the same magnitude' and 'However, no symptoms data from some patients were not taken into account when calculating results', both from the English translation Comment: regarding the 1st quote, although there is insufficient detail about why these 2 participants withdrew, it is unlikely to make a significant contribution of bias, particularly in a half-sided trial.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias detected

Foelster-Holst 2006

Study characteristics

Methods

Trial design

Prospective, half-side RCT

Trial registration number

Not reported

Setting

Germany

Date trial conducted

Not reported

Duration of trial participation

48-72 h of treatment with a follow-up period of 14 days

Additional design details

Due to randomisation, the right side (arm or leg) of 13 participants was treated with TCS plus WWT dressing, the left side with corticosteroid only. The treatment of the remaining 11 participants was done vice versa.

Inclusion criteria

- Patients with an acute episode of AD
- Similar disease severity on both sides: local SCORAD ≥ 10
- All patients needed to be treated with TCS

Foelster-Holst 2006 *(Continued)*

Exclusion criteria

- No systemic treatment with corticosteroids/antibiotics was allowed for 7 days, or TCSs for 2 days, prior to the trial.

Notes

None

Participants	**Total number randomised** 24 participants; 13 randomised to WWT on the right, 11 on the left **Age** 20 adults aged 18–63 years and 4 children aged 6–16 years; average age 30.5 years **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Duration of AD was 21 years (range: 8 months-42 years); the acute episode averaged 2.4 months (range: 4 days-1 year) **Severity of eczema** Local objective local SCORAD average 12.0 ± SD 1.04 **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported **Notes** "According to statements of patients previous phases of exacerbated AD had been treated as follows: most patients had been treated with topical medications (n = 23) containing corticosteroids or other preparations. Five patients had been treated with oral drugs (e.g. corticosteroids) and the usage of concomitant measures (such as UV therapies) was mentioned by 7 participants. Another three patients used dietary therapy. Two patients already had experience with wet-wrap dressings."
Interventions	**Run-in details** Not reported **Groups** • Prednicarbate ointment (proprietary: Dermatop, Aventis Pharma, Frankfurt am Main, Germany); TCS applied to 1 arm or leg alone that had been rubbed with emollient, then covered with the wet-wrap dressing that had been soaked in warm water. Dry dressings were then wrapped over the wet ones. Concurrent treatment: none • Prednicarbate ointment (proprietary: Dermatop, Aventis Pharma, Frankfurt am Main, Germany); TCS applied to 1 arm or leg alone. Emollient used as required. Concurrent treatment: none **Adherence** Not reported

Foelster-Holst 2006 *(Continued)*

	Co-interventions Emollient as required: Alfason Basis CreSa **Notes** None
Outcomes	• Objective Local SCORAD (six parameters erythema, papulation, lichenification, exudation, excoriation and dryness were judged by the physician (on a scale of 0–3; 0 = absent, 1 = mild, 2 = moderate, 3 = severe) at baseline and day 2-3* • Side effects at up to day 16-17* • Withdrawal effects at up to day 16-17 *denotes relevance to this review
Funding source	Grant from Paul Hartmann AG, Heidenheim, Germany, who manufacture the tubular bandage Coverflex, used as the dressings in the WWT in this trial.
Declarations of interest	Not declared, however 2 authors are affiliated to Paul Hartmann AG.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "one arm or one leg was randomly treated [with TCS and WWT]", "randomized" Comment: no information about how this was done
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: it would be very difficult for participants not to know which treatment they were receiving as they would be applying WWT dressings to 1 arm or leg
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: there is no mention of whether the outcome assessor was blinded. It is also possible to see markings from the WWT in some instances, so the observer would know what treatment the participant had received and therefore this may influence their assessment introducing bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there is no information about whether all participants completed the trial, however given the length of the treatment period, it seems unlikely that follow-up will have been problematic.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol found
Other bias	High risk	Comment: participants in the WWT group were routinely applying emollient as part of the WWT, whereas in the TCS alone arm, emollient was applied as required. Emollient use potentially could have accounted for any difference in results.

Fukuie 2012

Study characteristics

Methods

Trial design

RCT

Trial registration number

Not reported

Setting

Japan; assumed by the affiliations of the authors

Date trial conducted

Not reported

Duration of trial participation

6 months; cortisol measurements were taken at 0, 3 and 6 months so treatment may have continued until this point, however steroid treatment may have finished before this point.

Additional design details

None

Inclusion criteria

- Children
- Moderate-severe AD

Exclusion criteria

Not reported

Notes

None

Participants

Total number randomised

11

Age

Not reported

Sex

Not reported

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Not reported

Filaggrin mutation status

Fukuie 2012 *(Continued)*

	Not reported **Number of withdrawals** Not reported **Notes** None
Interventions	**Run-in details** Not reported **Groups** • HC 1% ointment (unspecified); TCS applied twice daily every 3 days or less to all previously identified affected areas. Concurrent treatment: not reported • No clear information as to whether the comparison group used any medication. The abstract says, "This trial evaluates the morning salivary cortisol levels in children using maintenance treatment with topical corticosteroids with and without proactive approach." This could imply the participants in this comparison group were also applying steroid, though it is unclear how. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** Not reported
Outcomes	• Adrenocorticotrophic hormone stimulation test at month 3* • Salivary samples for cortisol and dehydroepiandrosterone levels collected at home, in the morning, on 3 consecutive days at months 0, 3, and 6* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "prospectively randomized". Comment: no further detail provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: no information

Fukuie 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information
Selective reporting (reporting bias)	Unclear risk	Comment: no information
Other bias	Low risk	Comment: no other sources of bias identified

Fukuie 2016

Study characteristics

Methods

Trial design

Randomised, investigator-blinded, parallel-group trial

Trial registration number

JPRN-UMIN000005536

Setting

Single centre in Japan

Date trial conducted

June 2011-April 2013

Duration of trial participation

13 months; 4-week unrandomised acute phase assumed to not be included in the 12-month maintenance phase as described in the methods and not as depicted in Fig. 1.

Additional design details

None

Inclusion criteria

- Diagnosis of AD (Hanifin 1980)
- Patients had moderate-severe AD as defined by SCORAD
- Male and female participants aged 3 months-7 years
- Patients attending the AD educational programme, which consisted of a demonstration and slide presentation on washing and application of topical medication.

Exclusion criteria

- Patients who had received additional systemic therapies e.g. corticosteroids, non-steroidal immunosuppressive agents or biological immunotherapy
- Patients with a history of cardiovascular disease, liver dysfunction or kidney disease
- Other current serious medical problems

Notes

Fukuie 2016 *(Continued)*

Participants were permitted systemic antihistamines, leukotriene antagonists, antibiotics and inhaled corticosteroids regardless of the dose. There were 73 participants that originally attended the AD education programme. 37 were excluded for the following reasons: 13 long-distance visit (too far for regular visits), 9 repeat participants (already educated about proactive therapy), 6 severe AD with protein losing, 2 mild AD, 1 applied oral corticosteroid, 1 post IV immunoglobulin G for Kawasaki disease and 5 (calculated this number as missing from graph) other reasons e.g. previous history of leukaemia.

Participants	**Total number randomised** 30; 15 into each arm **Age** Median age was 23 months in the proactive group (range 3-90, 0-1 year group n = 8 (53.3%), ≥ 2 years n = 7 (46.7%)) and 24 in the reactive group (3-65, 0-1 year group n = 7 (46.7%), ≥ 2 years n = 8 (53.3%)). **Sex** There were 4 female and 11 male participants in the proactive group and 6 female and 9 male participants in the reactive group. **Race/ethnicity** All participants were categorised as Asian. **Duration of eczema** Not reported **Severity of eczema** Median SCORAD at enrolment was 61.6 (range 30.4-85.6) in the proactive group and 53.4 (28.0-78.7) in the reactive group. 10 participants (66.7%) in the proactive group were considered severe (SCORAD > 50) as were 11 participants (73.3%) in the reactive group. At the end of the active phase, median SCORAD in the proactive group was 7.1 (range 3.5-16.9) and 7.3 (3.7-17.3) in the reactive group. Median total affected BSA was 38.0% (range 13.0-70.0) in the proactive group compared to 27.0% (17.0-71.0). **Filaggrin mutation status** Not reported **Number of withdrawals** 2 participants in each group discontinued at approximately 3 months into the disease control period. The reason for discontinuation in the proactive group was non-compliance due to corticosteroid phobia and the reason for discontinuation in the reactive group was lack of efficacy which led to the application of preventive TCSs at the participant's own discretion. **Notes** For severity, total affected BSA, VAS (states pruritus and insomnia but only gives 1 number) at screening, VAS at the end of the active phase, serum TARC, serum total IgE, HSM-specific IgE given in the baseline treatment table. No significant differences in baseline characteristics were noted.
Interventions	**Run-in details** Following an educational programme (covering washing and topical medication application) at enrolment, all participants/their caretakers applied TCSs twice daily for between 5 days and 2 weeks until remission, then every other day for 2 weeks. The treatment could be applied to all affected body areas. **Groups** • Betamethasone valerate 0.12% ointment proactive (unspecified); applied twice weekly using a fingertip unit (approx 0.5 g) to previously identified affected areas with no exacerbation. When exacerbation occurred, participants applied TCSs twice daily to affected and new areas, then returned to the

Fukuie 2016 *(Continued)*

proactive routine. Concurrent treatment: participants in the proactive group were also provided with a written care plan.

- Betamethasone valerate 0.12% ointment reactive (unspecified); on exacerbation, participants first treated with moisturiser alone for 1 week, then TCSs if there was no improvement. Concurrent treatment: none

Adherence

Participants kept a skincare diary, which was reviewed at each trial visit. The participants were encouraged to use all the prescribed ointments and that all unused ointments would be measured at the end of the trial for the ointment usage calculation (g/m2). Ointment usage was not significantly different between the 2 arms throughout the trial.

Co-interventions

HC butyrate 0.1% could be applied to the face and body trunk. Tacrolimus 0.03% ointment could also be applied to eczema on the face and neck in participants aged ≥ 2 years. Participants could also take systemic antihistamines, leukotriene antagonists, antibiotics and inhaled corticosteroids as required. All participants were provided with a treatment guide for home management and were educated on washing and correct treatment application, the avoidance of triggers, and on appropriate barrier repair methods.

Notes

We have assumed the TCS was an ointment because the authors refer to "prescribed ointments" elsewhere in the paper from where the TCS was described, and the only other ointment explicitly described is tacrolimus. The trial was performed on an outpatient basis with participants self-administering the ointment at home, except on day 1, when a care plan was designated and the physician applied the ointment in the hospital for each participant. The paper says participants in the trial "mainly" used TCSs for therapy, this possibly implies this isn't universal.

Outcomes	• Serum TARC, serum total IgE and HDM-specific IgE at enrolment (up to week −4), month 12 • Blood eosinophil count, IL-4, IL-5, IL-13, IL-17, IL-33, IFN-gamma in published protocol • Quality of life measured by the CDLQI, DFI, and QPCAD questionnaire at months 0, 3 and 12 • Ointment consumption at months 3, 6, 9 and 12 • HPA function test: a rapid ACTH stimulation test was performed at the 3-month visit (serum cortisol 30 and 60 min after administration) at month 3. Protocol states both serum and salivary cortisol measurements at 6, 12, and 24 months* • Bacterial culture (rubbing rayon-tipped swabs over lesional skin); number participants with MRSA, Number with *Staphylococcus aureus* colonisation, environmental remediations at months 0 and 12* • VAS calculated from degree of pruritus scored out of 10 added to the degree of insomnia scored out of 10 at enrolment (up to week −4) and baseline, and thereafter recorded daily in participant diaries. Only pruritus mentioned in published protocol. • SCORAD at enrolment (up to week −4), baseline (week 0), month 3, month 6, month 9, and month 12. Published protocol states "Proportion of patients with SCORAD Local adverse events, such as signs of cutaneous atrophy, striae, telangiectasia and infection at each trial visit up to month 12. Published protocol states up to 24 months* *denotes relevance to this review
Funding source	Japan Society for the Promotion of Science Grant in Aid for Young Scientists B (no. 23791165)
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement

Fukuie 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was 1:1 stratified by age (<2 or ≥2 years) with a random permuted block method. The random number table and the sealed envelopes were equipped by the study center in the Division of Allergy, Department of Medical Subspecialties at the National Center for Child Health and Development." Comment: randomisation appears adequate
Allocation concealment (selection bias)	Low risk	Quote: "The random number table and the sealed envelopes were equipped by the study center in the Division of Allergy, Department of Medical Subspecialties at the National Center for Child Health and Development." The study protocol states that concealment would be achieved by "central registration" Comment: the report does not mention whether the envelopes were opaque, however the trial protocol mentions that randomisation was completely centrally. If this is this was the case randomisation is likely to be adequate.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial is described as "open label". Comment: there was no control used in this trial and so participants would have been aware that they were not using active treatment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "During the 12-month disease control period, the investigator was blinded as to which group the patients were allocated." Comment: the investigator was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "No subject was lost to follow-up during the trial and an intention to treat analysis was performed". Comment: it is unclear whether the 2 or 4 participants that discontinued treatment still continued to contribute data throughout the whole trial. Comment: a minor cause for concern was that ACTH tests were only performed on the "first 12 subjects"; the trial authors were satisfied by this that there was no evidence of adrenal suppression. Cortisol is known to fluctuate according to time of year, but in any case, such a systematic approach to testing may in itself introduce bias.
Selective reporting (reporting bias)	High risk	Quote: the protocol states the primary outcome to be "Proportion of patients with SCORAD < 20 and SCORAD <50 at each study visit [Time Frame: 24 months]" also "Intensity of pruritus at each day as reported in the patient's diary by means of visual analogue scale (VAS)" and "Change of serum and salivary cortisol level at 6, 12 and 24 months [Time Frame: at 6, 12 and 24 months]". Also, protocol is stated to have been modified 9 August 2016. Comment: the median SCORAD was reported, intensity of Itch was not reported and salivary cortisol level are all outcomes relevant to this review that were not reported. Also, the stated final time point for most outcomes was 24 months; the paper only presents data up to 12 months. In addition, #727 - Fukuie 2013 reports different numbers of participants approached.
Other bias	Low risk	Comment: no other sources of bias identified

Gentry 1973

Study characteristics	
Methods	**Trial design** Double-blind, randomised, parallel-group

Gentry 1973 *(Continued)*

Trial registration number

Not reported

Setting

Hospital outpatient dermatology clinics in the USA

Date trial conducted

Not reported

Duration of trial participation

4 weeks

Additional design details

None

Inclusion criteria

- Adults and children of both sexes
- Steroid-responsive dermatoses (results are reported separately for atopic eczema)

Exclusion criteria

Not reported

Notes

None

Participants	**Total number randomised** Of 133, 5 participants had atopic eczema: 2 were randomised to the mild (desonide) group, 3 to potent (fluocinolone) group **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported **Notes**

Gentry 1973 *(Continued)*

	"Comparison of the distribution of age, sex, and diagnoses of patients receiving each preparation indicated adequacy of randomisation. The duration of the diseases and the clinical activity of the disease processes at the time the study was initiated was similar in both groups." This comment refers to all the participants in the trial, not just those with AD.
Interventions	**Run-in details** NA **Groups** • Desonide 0.05% cream (Tridesilon); apply sparingly twice daily. Concurrent treatment: not reported • Fluocinolone acetonide 0.025% cream; apply sparingly twice daily. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** None
Outcomes	• Adverse effects were noted at end of treatment (assumed as not stated)* • Laboratory tests: complete blood cell count with differential cell count, liver function tests e.g. serum glutamic oxaloacetic transaminase and alkaline phophatase, renal function tests e.g. blood urea nitrogen, and total urinalysis at pre- and post-treatment • IGA of disease response (6-point scale rated as cleared, excellent, good,fair, poor, no effect and exacerbation) at weeks 1, 2, 3, and 4* • Physician assessment of signs and symptoms: notation of the degree of erythema, induration, pruritus and scaling scored 0-3 at weeks 1, 2, 3, and 4 *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The material was dispensed in numerical order from consecutively numbered units; the distribution of the two agents in these units had been randomised formally." Comment: no mention of how the randomisation sequence was generated and so risk of bias cannot be assessed.
Allocation concealment (selection bias)	Low risk	Quote: "The material was dispensed in numerical order from consecutively numbered units; the distribution of the two agents in these units had been randomised formally.""Each formulation was packaged in identical, coded tubes so that neither patient nor investigator knew which preparation was being used."

Gentry 1973 *(Continued)*

		Comment: as the investigator had no way of identifying what medication was in the package it would be unlikely that they would be able to influence which treatment a participant was going to receive.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each formulation was packaged in identical, coded tubes so that neither patient nor investigator knew which preparation was being used." Comment: both participant and investigator appear to have been adequately blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Evaluation of the results of treatment was made in each case while the identity of the agent remained unknown" Comment: outcome assessors appear to have been adequately blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The variability of patient numbers at weekly intervals is explained by the fact that patients cleared after each week of treatment were not required to be monitored subsequently, although a few patients' responses continued to be evaluated." Comment: only 1 participant in the atopic eczema group was deemed to be cleared and therefore possibly not evaluated at the end of the trial. As there were only 5 participants in this group, this may have introduced bias to the results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available and so this cannot be assessed comprehensively.
Other bias	Low risk	Comment: no other bias detected

Giannetti 1981

Study characteristics	
Methods	**Trial design** Double-blind, half-sided, RCT **Trial registration number** Not reported **Setting** Outpatients, assumed Universita di Pavia lstituto di Clinica Dermatologica from the affiliation of the authors **Date trial conducted** Not reported **Duration of trial participation** 3 weeks **Additional design details** University of Pavia Institute of Dermatological Clinic **Inclusion criteria** Patients with AD of mild to medium severity. The trial also states that lesions were to be symmetrical and not complicated by microbial or fungal infections. Patients stopped all therapy for ≥ 15 days.

Giannetti 1981 *(Continued)*

Exclusion criteria

Not reported

Notes

20 participants, selected from outpatients for reasons of compatibility with the period of treatment foreseen in the research protocol - no access to this to extract this

Participants	**Total number randomised** 20 **Age** Range 7 months-14 years **Sex** 10 male and 10 female **Race/ethnicity** Not reported **Duration of eczema** Average 5 years and 4 months (range 5 months-13 years) **Severity of eczema** Average scores (± SD, based on 0 = symptom absent to 3 = severe) for each symptom and sign were as follows: erythema 1.6 ± 0.8 in the potent (HC 17-butyrate) group and 1.7 ± 0.8 in the mild (HC acetate) group; vesiculation 1.3 ± 0.5 in the potent (HC 17-butyrate) group and 1.1 ± 0.6 in the mild (HC acetate) group; exudation 1.0 ± 0.7 in the potent (HC 17-butyrate) group and 0.8 ± 0.4 in the mild (HC acetate) group; desquamation 1.3 ± 0.5 in both groups; excoriation 1.4 ± 0.7 in the potent (HC 17-butyrate) group and 1.4 ± 0.9 in the mild (HC acetate) group; lichenification 1.6 ± 0.6 in the potent (HC 17-butyrate) group and 1.7 ± 0.7 in the mild (HC acetate) group; and pruritus 1.8 ± 0.5 in the potent (HC 17-butyrate) group and 1.7 ± 0.6 in the mild (HC acetate) group **Filaggrin mutation status** Not reported **Number of withdrawals** None, assumed by table 2 **Notes** None
Interventions	**Run-in details** Participants stopped all therapy for ≥ 15 days. **Groups** • HC acetate1% ointment (unspecified); applied twice daily (morning and evening) under occlusion with a simple bandage for 3 weeks. Concurrent treatment: not reported • HC 17-butyrate 0.1% ointment (proprietary: Locoidon, Brocades); applied twice daily (morning and evening) under occlusion with a simple bandage for 3 weeks. Concurrent treatment: not reported **Adherence** Not reported

Giannetti 1981 *(Continued)*

	Co-interventions Not reported **Notes** It was stated in the methods that treatment would be suspended in the event of any side effects.
Outcomes	• Side effects including cutaneous atrophy at weeks 1, 2, and 3* • Assessment of signs and symptoms: erythema, vesiculation, exudation, desquamation, excoriation, lichenification and pruritus, each scored 0 = symptom absent to 3 = severe at baseline and weeks 1, 2, and 3 • IGA (assumed) of improvement relative to baseline: number of sides where complete healing or partial symptom regression occurred were reported. It is assumed that is the signs and symptoms assessment combined (erythema, vesiculation, exudation, desquamation, excoriation, lichenification and pruritus, each scored 0 = symptom absent to 3 = severe) at baseline and weeks 1, 2, and 3* • Where possible, itching scores should also be noted (it has been assumed this is participant assessed because of nature of the symptom and says "where possible", but not clear in report) at baseline, week 1, week 2, week 3 *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	Translated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "according to a double-blind randomised code' (translated from Italian) Comment: no information given about sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "Upon admission of patients to the study two ointment tubes, labelled with the parents of the children (who had accepted the therapeutic protocol), were delivered with the abbreviations D (right) and S (left), according to a double-blind randomized code." Comment: not clear who recruited participants to the trial and who allocated the code to each participant. Insufficient information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind'; 'upon admission of patients to the study two ointment tubes, labelled with the parents of the children (who had accepted the therapeutic protocol), were delivered with the abbreviations D (right) and S (left), according to a double-blind randomised code' (both translated from Italian) Comment: whilst there is minimal detail on the blinding procedures, the labelling of the tubes suggests they were identical to prevent participants and clinicians guessing which tube contains which treatment. However, statement of "double blind" is not clear who this refers to out of trial team
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind"; 'upon admission of patients to the study two ointment tubes, labelled with the parents of the children (who had accepted the therapeutic protocol), were delivered with the abbreviations D (right) and S (left), according to a double-blind randomized code."

Giannetti 1981 *(Continued)*

		Comment: lack of information about if the person assessing the outcomes is included in the "double blind" statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no withdrawals reported
Selective reporting (reporting bias)	High risk	Comment: no protocol available, and the methods states adverse events were looked for yet there was no mention of these in the results section.
Other bias	High risk	Quote: "twenty patients, selected from outpatients for reasons of compatibility with the period of treatment foreseen in the research protocol" (translated from Italian) Comment: concerned that the trial authors may have selected an unrepresentative population, which may lead to bias

Glazenburg 2009

Study characteristics

Methods

Trial design

Randomised, double-blind, multicentre trial

Trial registration number

Not reported

Setting

12 clinical centres in the Netherlands and 1 in Belgium

Date trial conducted

Not reported

Duration of trial participation

20 weeks (consisting of a 4-week acute phase (see 'run-in details' below) and 16-week randomised maintenance phase)

Additional design details

None

Inclusion criteria

- Children with AD as defined by Hanifin and Rajka(Hanifin 1980) and modified by Williams and colleagues (Williams 1994).
- ≥ 4 of the following features: history of/visual flexural dermatitis, presence of an itchy rash, onset representative index lesion with a TIS (sum of symptom scores for erythema, oedema/papulations, and excoriation with a maximum of 9) score ≥ 3 and <6
- Those children whose AD was in remission after the acute period (according to stringent defined criteria, index lesion target TIS ≤ 1) were eligible for entry into the maintenance phase.

Exclusion criteria

- Systemic treatment for AD in the preceding month

Notes

Glazenburg 2009 *(Continued)*

	In the last week before the trial started, only restricted medication (emollient, HC acetate 1% and/or antihistamines when needed) was allowed.
Participants	**Total number randomised** 90 children were originally recruited, 75 entered the maintenance phase (n = 36 intermittent placebo, n = 39 intermittent fluticasone) **Age** At enrolment mean 5.7 years ± 2.2 years (n = 90), then 5.9 in the TCS group and 5.8 in the placebo group at the beginning of the maintenance phase **Sex** At enrolment (n = 90); 38 male, 52 female. During maintenance phase: placebo female n = 20 (56%) male n = 16 (44%), fluticasone female n = 26 (67%) male n = 13 (33%) **Race/ethnicity** At the beginning of the maintenance phase, 76% of children in the TCS group and 69% in the placebo group were white **Duration of eczema** At enrolment (n = 90); current episode was > 3 weeks in 83 and 1–3 weeks in 7 children. 39 of the children had been diagnosed with AD for > 5 years, 49 for 1–5 years and 2 for < 1 year. **Severity of eczema** TIS (sum of symptom scores for erythema, oedema/papulations, and excoriation with a maximum of 9) at enrolment: mean 4.6 ± SD 1.1. At the beginning of the maintenance phase this was 0.0 (range 0-1) for both fluticasone and placebo groups. The median objective SCORAD was 7.0 (range 0-24) in the placebo groups and 3.6 (range 0-26) in the fluticasone group. **Filaggrin mutation status** Not reported **Number of withdrawals** 3 children did not complete the acute phase owing to unrelated accidental injury (1), consent withdrawal (1), and the other was lost to follow-up. 12 did not proceed to the maintenance phase because their target TIS was > 1 (9), consent was withdrawn (1), TIS was ≤ 1 at the target lesion but > 1 elsewhere (1) or an AD exacerbation occurred in the 2 days between the acute and maintenance phases (1). The number who dropped out of the randomised phase is not reported. **Notes** 2 different age ranges are quoted in the 2003 abstract (3-11) and the 2009 full paper for the age (4-10).
Interventions	**Run-in details** All children received fluticasone propionate 0.005% ointment to apply twice daily for 4 weeks on original (even if no visible AD) and new lesions. Facial lesions were treated with emollients and/or HC 1%. A standard emollient was provided for use as required. **Groups** • Fluticasone propionate 0.005% ointment (Cutivate, Glaxo Wellcome b.v., the Netherlands and Glaxo Wellcome GmBH & Co, Bad Oldesloe, Germany); in addition to twice-daily emollient, children applied fluticasone twice weekly on 2 consecutive evenings for 16 weeks or until relapse. On days when the trial medication was applied, emollient was applied only in the morning. Concurrent treatment: none

Glazenburg 2009 *(Continued)*

- No TCS; in addition to twice-daily emollient, children applied placebo twice weekly on 2 consecutive evenings for 16 weeks or until relapse. On days when the trial medication was applied, emollient was applied only in the morning. Concurrent treatment: none

Adherence

Compliance was measured (by weighing of tubes) in the acute phase but there is no reference to measurement of compliance in the maintenance phase. Compliance was said to be 'good' in 93% of children in the acute phase.

Co-interventions

Concurrent medications included topical HC acetate 1% for facial eczema, cetirisine for allergic rhinitis and salbutamol for asthma. Bath oil was used as required.

Notes

Trial treatment started on the 3rd day after acute treatment ended.

Outcomes	• Urinary overnight cortisol/creatinine ratio at enrolment (week −4), at the end of the active phase (week 0), and at the end of the trial (week 16)* • Visual assessment of signs of skin atrophy, telangiectasia, striae and hypertrichosis at end of active phase (week 0) and week 2, 4, 8, 12, and 16* • Adverse events (total, related, severe, unspecified) "throughout the study"* • Risk of relapse at up to week 16 of maintenance phase. A relapse was defined as an index lesion with a target TIS score of ≥3. A relapse could occur either at the site of the original index lesion (target lesion) or at any new lesion appearing during the maintenance phase** • Time to relapse at any point • Number and percentage of children experiencing relapse at any point up to week 16 of maintenance phase* • Target TIS (sum of symptom scores for erythema, edema/papulations, and excoriation with a maximum of 9) at enrolment (week −4), week −2, baseline (week 0) and week 16 of maintenance phase or at withdrawal (assumed as not stated) • Objective SCORAD ((0.2 x extent: rule of nines) + (3.5 x intensity: 6 signs scored 0-3) reported as number in each severity band by group and sex) at enrolment (week −4), week −2, baseline (week 0) and week 16 of maintenance phase or at withdrawal. *denotes relevance to this review
Funding source	"This study was conducted with financial support from GlaxoSmithKline, London, UK."
Declarations of interest	The lead author is an employee of GlaxoSmithKline.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was achieved by a computer-generated scheme and performed by the statistician." Comment: probably done. The objSCORAD value was significantly higher in placebo group at the start of the maintenance phase however this was not thought to be of clinical relevance and no evidence of a treatment by baseline interaction was found.

Glazenburg 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: no information provided about how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" "children were randomly allocated to receive FP ointment twice weekly or placebo ointment twice weekly" (in corresponding abstract, Glazenburg 2003) placebo is described as "matching placebo") Comment: as participants were receiving a placebo ointment it is unlikely that they would not be able to tell whether they were receiving active treatment or not. However, it is unclear which personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information is provided as to whether the assessors were blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information regarding whether any participants dropped out due to reasons other than relapse
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was registered.
Other bias	Low risk	Comment: other sources of bias were not detected.

Goh 1999

Study characteristics	
Methods	**Trial design** Open, randomised, third-party-blinded, half-side trial **Trial registration number** Not reported **Setting** National Skin Centre Singapore **Date trial conducted** April 1994-October 1994 **Duration of trial participation** 3 weeks (follow-up on day 22) **Additional design details** None **Inclusion criteria** • Patients with moderate-severe bilateral chronic eczema on the limbs. Chronic eczema was evidenced with lichenified scaly patches and plaques for at least 6 months. **Exclusion criteria** • Pregnancy • Known hypersensitivity to corticosteroids

Goh 1999 *(Continued)*

- Presence of skin atrophy (e.g. telangiectasia and/or striae)
- Those on systemic steroids within 28 days of entering the trial

Notes

Antihistamines must be discontinued 1 day prior to trial day 1. No medication other than the trial medication was to be applied to the trial area.

Participants	**Total number randomised** 120 sides (limbs) randomised (in 60 participants) **Age** Mean age 45.7 years (range 16-85) **Sex** 25 male and 33 female **Race/ethnicity** Not reported **Duration of eczema** Mean duration of eczema was 7.5 years (range 3-30 years) **Severity of eczema** Overall mean signs and symptoms score (including erythema, induration, crusting, scaling, excoriation and pruritus and scored using a severity scale ranging from 0 = none to 3 = severe for each sign/symptom): 8.8 ± SD 3.1 in the mometasone group versus 8.9 ± SD 3.2 in the clobetasol group **Filaggrin mutation status** Not reported **Number of withdrawals** 2 participants withdrew from the trial; no reasons were given. **Notes** The baseline characteristics are only for the 58 participants who completed the trial as the percentages for sex are reported as percentages of the 58 participants.
Interventions	**Run-in details** NA **Groups** • Clobetasol propionate 0.05% cream; TCS applied in a thin layer twice daily to trial sites on 1 limb. Concurrent treatment: none • Mometasone furoate 0.1% cream; TCS applied in a thin layer once daily to the trial sites on the other limb. Concurrent treatment: none **Adherence** Cream tubes were dispensed at the beginning of each week of the trial; participants were asked to return used tubes at the next weekly visit. **Co-interventions** No medication other than the trial medication was to be applied to the trial area.

Goh 1999 *(Continued)*

	Notes None
Outcomes	• Examination for signs of skin atrophy at the target areas at day 1 (baseline), 8, 15 and 22* • Cosmetic acceptability at the target areas at day 1 (baseline), 8, 15 and 22 • Participants' assessment of response to treatment (excellent, good, fair, or poor) at day 1 (baseline), 8, 15 and 22* • Dermatologists' assessment of response to treatment (cleared = 100% improvement; marked = > 75% improvement; moderate = 50%-75% improvement; slight = signs/symptoms of chronic eczema (including erythema, induration, crusting, scaling, excoriation and pruritus) were scored upon entry into the trial using severity scale which ranges from 0 = none to 3 = severe). Overall total scores were also calculated at day 1 (baseline), 8, 15 and 22. • Side effects (not specifically mentioned apart from skin atrophy, but mentioned in the results/discussion) at day 1 (baseline), 8, 15 and 22.* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The side to be treated with mometasone furoate cream was chosen randomly." Comment: no further information given
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "third-party blind" Comment: the use of this term possibly implies that the medication was prepared by a third party and so participants and personnel would have been blinded (though there is no standard definition for this phrase), however there is no detail as to how this was carried out (i.e. was the medication labelled in such a way that the participant did not know what they were receiving). There is no mention of a placebo cream being used and so it would have known they were applying a cream more often to 1 site.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The side to be treated with mometasone furoate cream was chosen randomly and the assessor was blinded to this" Comment: the trial authors took steps to ensure that the assessor did not know what treatment the participants received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 withdrew from the trial; no reasons were given, however this is a small proportion of the total trial population, so unlikely to influence the outcomes markedly, and it is a half-side comparison anyway.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol found
Other bias	Low risk	Comment: no other sources of bias detected

Guttman-Yassky 2017

Study characteristics

Methods	**Trial design** Randomised, double-blind, half-side comparison (all participants received all treatments*) **Trial registration number** NCT02376049 **Setting** Assumed to be in the USA/Canada from the affiliations of the authors. **Date trial conducted** February-July 2015 **Duration of trial participation** 29 days **Additional design details** A novel intra-individual design where all participants were given all 4 interventions on target lesions comparable in severity and inflammation status (TSS and TAA score), approximately 3 cm in diameter, > 2 cm apart. Only the 2 steroid treatment results have been extracted. **Inclusion criteria** • Mild-moderate AD (IGA of 2 or 3) • Aged ≥ 18 years • 4 comparable TAs (assumed to be an acronym relating to the area), at least 2 cm apart, each with TSS of at least 5, with a difference not greater than 2 between them. • Sign score erythema ≥ 2 between the TAs. **Exclusion criteria** • Patients with a Fitzpatrick Skin Type > 5 • Patients who received systemic immunosuppressants in the last 4 weeks • Patients who received topical steroids/immunomodulators in the last 2 weeks • Patients who used moisturisers within the 3 days prior to treatment • Patients who had participated in other interventional trials within 4 weeks prior to randomisation • Investigator's opinion (stated in protocol) • Phototherapy within prohibited timeframe (stated in protocol) **Notes** None
Participants	**Total number randomised** 30 **Age** Mean 24 years (range 18-71) stated in the methods; 33.9 (SD 14.9) stated in the paper, 29.3 stated in the narrative results **Sex**

Guttman-Yassky 2017 *(Continued)*

16 male and 14 female

Race/ethnicity

There were 25 white participants, 4 African American participants and 1 Asian participant. All were non-Hispanic.

Duration of eczema

For 29 participants it was stated that the mean duration was 29.3 years (SD 16.3)

Severity of eczema

Baseline severity not reported; all outcome data are presented relative to baseline

Filaggrin mutation status

Not reported

Number of withdrawals

1 participant that had used prohibited medications was withdrawn after the 1st week.

Notes

None

Interventions	**Run-in details** Not reported **Groups** • Betamethasone dipropionate 0.05% cream (proprietary: Diprosone); applied once daily for 2 weeks to target lesion (~3 cm diameter and > 2 cm apart), excluding face and scalp; approximately 1.5-2.0 mg/cm^2, without occlusion. Concurrent treatment: 3 other lesions treated with Glaxal Base (vehicle), pimecrolimus 1% (Elidel), and clobetasol propionate 0.05% (Dermovate) • Clobetasol propionate 0.05% cream (proprietary: Dermovate); applied once daily for 2 weeks to target lesion (~3 cm diameter and > 2 cm apart), excluding face and scalp; approximately 1.5-2.0 mg/cm^2, without occlusion. Concurrent treatment: 3 other lesions treated with Glaxal Base (vehicle), pimecrolimus 1% (Elidel), and betamethasone dipropionate 0.05% (Diprosone) **Adherence** Not reported **Co-interventions** Participants were excluded if they used prohibited topical or systemic medications. 4 lesions on body being treated with 4 different treatments. **Notes** "Each application area and surrounding landmarks were drawn on a transparency at baseline. Circular application areas were drawn on the skin with a marker and redrawn at subsequent visits when faded. No adhesives were used to identify the target application areas."
Outcomes	• Adverse events at day 15* • Punch biopsies for biomarker assessment at day 15 • Transepidermal water loss at baseline, week 1 and week 2 • TAA (6-point scale from 0 = clear to 5 = very severe) at baseline, week 1 and week 2* • TSS: 6 signs (erythema, oedema/papulation, oozing/crusting, excoriation, lichenification, and dryness) scored on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), therefore a total range of 0-18 at baseline, week 1 and week 2

Guttman-Yassky 2017 *(Continued)*

*denotes relevance to this review

Funding source	Research grant from LEO Pharma A/S
Declarations of interest	"E. Guttman-Yassky receives grant support from LEO Pharma A/S; serves on the advisory board for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Celsus, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, and Leo Pharma; serves as a consultant for Regeneron, Sanofi, MedImmune, Celgene, Stiefel/GlaxoSmithKline, Celsus, BMS, Amgen, Drais, AbbVie, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, LEO Pharma, Novartis, Pfizer, Vitae, Mitsubishi Tanabe, and Eli Lilly; and has received research support from Janssen, Regeneron, Celgene, BMS, Novartis, Merck, LEO Pharma, and Dermira. D. Todd and T. Labuda are employees of LEO Pharma A/S. M. Suarez-Farinas has received research support from Pfizer and Quorum Consulting. R. Bissonnette receives grant support from LEO Pharma A/S; receives consulting fees from LEO Pharma, AbbVie, Amgen, Celgene, Eli Lilly and Company, Galderma, Incyte, Janssen, Merck, and Novartis; and receives speakers' fees from AbbVie, Amgen, Galderma, Janssen, and Merck. The rest of the authors declare that they have no relevant conflicts of interest."
Notes	There were 2 additional treatments in this trial, pimecrolimus and placebo; we did not extract data for these.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatments were randomly assigned to target lesional areas by using Latin square randomization". Comment: reports a blocking procedure that suggests a random component has been used in the sequence generation process.
Allocation concealment (selection bias)	Low risk	Quote: "Each row represents 1 specific treatment group determining the allocation of treatments to target AD lesions. Each subject was randomly assigned to a treatment group by taking the next (ascending) randomization code number available at the trial center". "The randomization list was kept in a secure area by the designee (who was identified by the site investigator, remained unblinded, and prepared products for administration)." Comment: ascending suggests no room to bias allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "All medicinal products were sourced by the investigational sites (4 in total). All products were blinded to all study staff performing study assessments. Consequently, all site staff performing assessments remained unaware of individual treatment assignment during the conduct of the trial. The randomization list was kept in a secure area by the designee (who was identified by the site investigator, remained unblinded, and prepared products for administration)." Comment: no detail provided on how blinding was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "All medicinal products were sourced by the investigational sites (4 in total). All products were blinded to all study staff performing study assessments. Consequently, all site staff performing assessments remained unaware of individual treatment assignment during the conduct of the trial. The randomization list was kept in a secure area by the designee (who was identified by the site investigator, remained unblinded, and prepared products for administration)." Comment: no detail provided on how blinding was achieved
Incomplete outcome data (attrition bias)	Low risk	Quote: "One patient was withdrawn after 1 week because of use of prohibited medications."

Guttman-Yassky 2017 *(Continued)*

All outcomes		Comment: it is not clear what was done with the data that had already been collected on this participant, however, given that it is 1/30 and in a trial where all participants received all treatments, it is unlikely that the risk of bias here is significant.
Selective reporting (reporting bias)	Unclear risk	Comment: primary outcome remains the same as clinical trial registry, however the registry does not report all outcomes measured, therefore could still be open to selective reporting bias.
Other bias	Low risk	Comment: no other sources of bias were detected.

Handa 1985

Study characteristics	
Methods	**Trial design** Randomised, double-blind, half-sided **Trial registration number** Not reported **Setting** The lead author was affiliated to the Department of Skin and V.D., Government Medical College, Patiala-147 001, India **Date trial conducted** Not reported **Duration of trial participation** 3 weeks **Additional design details** None **Inclusion criteria** • A clinical diagnosis (supported by histopathological evidence where needed), of which AD was 1 of the named conditions with data presented separately. **Exclusion criteria** • Pregnancy • Cases of tuberculosis, syphilis, or viral diseases such as vaccinia, variola, and varicella **Notes** None
Participants	**Total number randomised** 52 cases were said to have completed the trial (unclear if a different number randomised), 7 of which were AD. **Age**

Handa 1985 *(Continued)*

Overall age ranged from 10-75 years, however baseline data were not reported separately for AD participants.

Sex

Overall there were 37 male and 15 female participants, however baseline data were not reported separately for AD participants.

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Not reported

Filaggrin mutation status

Not reported

Number of withdrawals

Not reported

Notes

None

Interventions	**Run-in details** Not reported **Groups** • HC acetate 1% ointment (supplied by Schering A. G. Berlin/Bergkamen); applied 3 times daily for the first 3 days, twice daily for up to 2 weeks, then once daily for the third week. Concurrent treatment: not reported • Diflucortolone valerate 0.1% ointment (supplied by Schering A. G. Berlin/Bergkamen); applied 3 times daily for the first 3 days, twice daily for up to 2 weeks, then once daily for the third week. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** No other corticosteroid was given either locally or systemically. **Notes** None
Outcomes	• IGA (4-point scale: very good/complete healing, good/distinct improvement, poor/slight improvement, failure/no treatment success). There is a comment that special emphasis was laid on the effects on a number of objective (erythema, oedema, exudation, dryness, scaling, lichenification, rhagades) and subjective symptoms (itching, burning, pain), however further data on these is not reported at weeks 1, 2, and 3.* • Systemic effects (not reported in the methods only in the results) at time not reported* • Time to improvement and time to "drying effect" on exuding lesions (h) at when improvement took place

Handa 1985 *(Continued)*

	*denotes relevance to this review
Funding source	The paper states "Medical Scientific Department of Schering A.G. Berlin/Bergkamen (Division of German Remedies Limited) supplied both ointments".
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" Comment: no further information provided
Allocation concealment (selection bias)	Low risk	Quote: "The two ointments in identical looking tubes were labelled with code letters or coloured [b]ands for application on the two sides of the body. […] The code of the ointments was deciphered after analysing the data." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The two ointments in identical looking tubes were labelled with code letters or coloured bands for application on the two sides of the body." "double-blind" "The code of the ointments was deciphered after analysing the data". Comment: as the trial authors took precautions in order to preserve blinding and were also aware of the need for double-blinding (as they described the trial as double-blinded). It is likely that there was a low risk that the participants and their caring clinician knew which treatment they were receiving.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no further information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants appeared to be accounted for.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available; no outcomes are referred to in the paper that are not referred to in the results.
Other bias	Unclear risk	Comment: acute cases were examined more frequently than weekly; no other information is provided about visit frequency deviations.

Haneke 1992

Study characteristics

Methods	**Trial design** 3 double-blind, multicentre, controlled, half-side comparison trials, 1 of which is excluded (methylprednisolone aceponate twice daily v betamethasone valerate twice daily) from our review as it does not include a strategy. **Trial registration number** Not reported

Haneke 1992 *(Continued)*

Setting

Multiple centres in Germany and Austria

Date trial conducted

Not reported

Duration of trial participation

4 weeks

Additional design details

None

Inclusion criteria

- Male and female patients aged ≥ 18 years
- AD with symmetrically distributed lesions

Exclusion criteria

- Pregnant women
- Patients who had recently received corticosteroid treatment: topical or systemic
- Patients with contraindications for corticosteroid treatment, e.g. viral, mycotic, or bacterial skin infection

Notes

None

Participants

Total number randomised

276 evaluable participants (included in all 3 trials, 1 trial did not meet our inclusion criteria) of 291 enrolled whose symmetrical lesions were randomised: 94 participants to methylprednisolone aceponate once and betamethasone valerate twice daily; 88 participants to methylprednisolone aceponate once versus methylprednisolone aceponate twice daily.

Age

Of the included 276, 127 male participants had a median age of 30 years; 149 female participants had a median age of 26 years.

Sex

Of the included 276, 127 were male (46%) and 149 were female (54%)

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

The most common cutaneous baseline symptoms or complaints were erythema, scaling, lichenification or itching occuring in 86%-100% of participants; prurigo (54%) oedema (28%) and pain (28%) were less frequent.

Filaggrin mutation status

Not reported

Haneke 1992 *(Continued)*

Number of withdrawals

Across the 3 trials, 15 enrolled participants were excluded owing to non-adherence to the protocols. Baseline characteristics and treatment allocations were not provided for these participants. Of the 276 included, 14 participants (5%) discontinued: 6 participants (2%) for lack of efficacy; 3 participants (1%) for adverse events (3 in methylprednisolone aceponate, 1 in betamethasone valerate; assuming 1 participant is counted twice here); 5 (2%) for other reasons.

Notes

Unclear at what point participants were excluded. 291 were enrolled, 15 (5%) were excluded due to non-adherence to protocols.

Interventions	**Run-in details** NA **Groups** **A**: methylprednisolone aceponate 0.1% fatty ointment (proprietary: Advantan® (Schering AG, Berlin, Germany)); application of TCS once daily (evening) and steroid-free vehicle in the morning, to 1 side of the body. Concurrent treatment: none **B**: methylprednisolone aceponate 0.1% fatty ointment (proprietary: Advantan® (Schering AG, Berlin, Germany)); twice daily TCS application, morning and evening, to 1 side of the body. Concurrent treatment: none **C**: betamethasone valerate 0.1% fatty ointment; twice daily TCS application, morning and evening, to 1 side of the body. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Treatment was said to be applied with or without a dressing, or under occlusion (an exception). It is not clear how many participants were treated in this way or from which groups. **Notes** Although the trial authors state that the trial participants were randomised into 3 groups they appear to report the results both in terms of the 3 trials but also grouping all the participants that received methylprednisolone aceponate and the participants that received betamethasone valerate regardless.
Outcomes	• "Objective symptoms"; erythema, oedema, weeping, scaling, crust, formation, lichenification, prurigo, papules/vesicles scored as absent, mild or severe (differences between groups are highlighted) at 4 times in the first 10 days, then weeks 2, 3, and 4 • "Subjective complaints"; itching, burning, pain scored as absent, mild or severe at 4 times in the first 10 days, then weeks 2, 3, and 4 • Local and general tolerance, and side effects by severity at 4 times in the 1st 10 days, then weeks 2, 3, and 4 (time points assumed)* • "Therapeutic effect"; IGA (complete healing, marked improvement, moderate therapeutic effect, or treatment failure) at 4 times in the first 10 days, then weeks 2, 3, and 4. (time points assumed)* • "Therapeutic effect"; PGA (complete healing, marked improvement, moderate therapeutic effect, or treatment failure) at 4 times in the first 10 days, then weeks 2, 3, and 4. (time points assumed)* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared

Haneke 1992 *(Continued)*

Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the symmetrically distributed lesions of each patient were randomised' Comment: no information provided about how randomisation was done
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind" Comment: it is unclear who was blinded and how. Participants were given steroid-free vehicle to apply in place of TCS when allocated to once daily treatment, but no other details were provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind" Comment: it is unclear who was blinded and how.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 291 patients were enrolled in these studies, 15 (5%) were excluded due to non-adherence to protocols." Comment: it is unclear whether these participants were excluded before or after randomisation and to which group these participants belonged. Also, examinations were said to be done at multiple time points, however, results were presented at the end of treatment or randomly at day 10 or day 5-6. It was most often the case that aggregate results were presented, and not broken down into the 3 main comparisons. The results are presented as number, percentage or imprecise significance level, but not all together.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias detected

Hanifin 2002

Study characteristics

Methods	**Trial design** Randomised, double-blind parallel-group trial of intermittent TCS versus vehicle maintenance **Setting** 16 centres in the USA and Canada **Trial registration number** FPC40002 **Date trial conducted** Not reported **Duration of trial participation**

Hanifin 2002 *(Continued)*

Unclear; potentially up to 48 weeks for some participants. The trial consisted of several phases: stabilisation phase (up to 4 weeks), maintenance (20 weeks for participants who were successfully stabilised), and follow-up (24 weeks only for participants treated with active cream during the maintenance phase who did not relapse).

Additional design details

Participants who achieved an IGA of ≤ 2 (i.e. cleared, almost cleared or marked clearing), and a score of ≤ 1 (i.e. none or mild) for each of 3 signs/symptoms (erythema, pruritus and papulation/induration/oedema) at any time during this phase were deemed a treatment success and were eligible for the maintenance phase.

Participants who failed to improve at the end of the 4-week stabilisation phase were discontinued from the trial. Participants who entered the 2nd part of the trial were randomised (2:1 within each age stratum) into the double-blind, parallel-group maintenance phase. Participants who relapsed at the beginning of the twice-weekly dosing period were allowed to revert to 4 times/week dosing at the discretion of the investigator. For participants who relapsed at other times during the maintenance phase, the trial code was broken and those on active medication were withdrawn. Participants on vehicle base started the entire trial again at stabilisation phase. Only safety data were collected for these participants. Participants who relapsed a 2nd time were withdrawn from the trial. For those participants who completed the maintenance phase without a relapse the intermittent TCS dosing regimen was extended on an open-label basis for up to 20? 24? (says 2 different things in 2 different places). It is unclear how long the follow-up phase was. 24 participants left the trial during the stabilisation phase, mostly commonly "lost to follow-up" or they were "non responders".

Inclusion criteria

- Moderate-severe AD on the head/neck, trunk, upper/lower limbs as defined by Rajka and Langeland Severity Grading (sum scores > 4)
- Aged 3 months-65 years

There were also criteria for proceeding into the maintenance phase, e.g. IGA ≤ 2 and erythema, pruritus, and papulation/induration/oedema scores ≤ 1, however some participants (11) that did not meet these criteria were still included as they were considered "stabilised" by the trial authors.

Exclusion criteria

- Dermatitis restricted to the face, feet, or hands
- Erythroderma or toxicoderma
- Psoriasis
- Diagnosed contact dermatitis at predilection sites of AD
- Atrophy or telangiectasia
- Having received systemic treatment for AD (including PUVA or UVB) in the month preceding the pre-trial visit
- Having applied topical treatment with tar or corticosteroids in the week preceding the pre-trial visit

Notes

None

Participants

Total number randomised

Of 372 enrolled into the trial, 348 were randomised to the maintenance phase. Of the 348, 229 were randomised to receive fluticasone propionate cream and 119 vehicle.

Age

Of the 348 participants, 231 were in the paediatric population and 117 were in the adult population. Of 372 enrolled the mean age was 16.8 years ± SD 15.6 (range 0.2-63). 55 (15%) were 3 months-2 years, 65 (17%) were 2-5 years, 127 (34%) were 5-16 years, and 125 (34%) were 16-65 years.

Sex

Hanifin 2002 *(Continued)*

Of 372 enrolled 156 (42%) were male and 216 (58%) were female. 108 (44%) of the paediatric participants were male compared to 48 (38%) of the adults

Race/ethnicity

Of 372 enrolled 242 (65%) were white, 62 (17%) were black, 50 (13%) were Asian, and 18 (5%) were 'other'. Of the paediatric participants, 159 (64%) were white, 39 (16%) were black, 35 (14%) were Asian, and 14 (6%) were 'other'. Of the adult participants, 83 (66%) were white, 23 (18%) were black, 15 (12%) were Asian, and 4 (4%) were 'other'.

Duration of eczema

Not reported

Severity of eczema

Of 372 enrolled the mean Rajka and Langeland severity score was 7.0 (7.2 for children, 6.7 for adults), with 236 (63%) having a 'moderate' score of 5-7 and 136 (37%) having a 'severe' score of 8-9. 66 (18%) had < 9% of skin involvement, 169 (45%) had > 9% and < 36% of skin involved, and 118 (32%) had > 36% of skin involved. 32 (9%) had > 3 months' remission each year, 64 (17%) had < 3 months' remission, and 276 (74%) had a continuous course.

149 paediatric cases (60%) were 'moderate', 98 (40%) were 'severe'. 39 (16%) had < 9% of skin involvement, 102 (41%) had > 9% and < 36% of skin involved, and 87 (35%) had > 36% of skin involved. 17 (7%) had > 3 months' remission each year, 34 (14%) had < 3 months remission, and 196 (79%) had a continuous course.

87 adult cases (70%) were 'moderate', 38 (30%) were 'severe'. 27 (22%) had < 9% of skin involvement, 67 (54%) had > 9% and < 36% of skin involved, and 31 (25%) had > 36% of skin involved. 15 (12%) had > 3 months' remission each year, 30 (24%) had < 3 months' remission, and 80 (64%) had a continuous course.

Filaggrin mutation status

Not reported

Number of withdrawals

24 participants withdrew after the stabilisation phase, most common reasons being "lost to follow-up" and "non-responder". Of the 348 eligible for the randomised maintenance phase, 44 were lost to follow-up (32 TCS, 12 emollient vehicle). 3 of the 32 TCS participants withdrew after the maintenance period. 170 completed the 20-week trial in the intermittent TCS group and entered the follow-up phase; 5 completed the 20-week trial in the vehicle group and entered the follow-up phase. 27 participants in the TCS group relapsed and were withdrawn, 36 relapsed as per the protocol but continued at the discretion of the investigator, and 83 participants in the vehicle group relapsed. Of those, 2 withdrew and 81 began an open-label repeat to collect further safety data.

Notes

None

Interventions

Run-in details

An up to 4-week, open-label, stabilisation phase preceded the RCT during which all participants applied fluticasone propionate 0.05% cream twice daily to existing and new sites. Participants also applied an emollient cream at least once daily. Participants were assessed at weekly clinic visits (via recording of IGA and 3 signs/symptoms).

Groups

- Fluticasone propionate 0.05% cream; applied once daily on Sunday, Tuesday, Thursday and Saturday, for the first 4 weeks of the maintenance phase, then once daily only on Sunday and Thursday. Concurrent treatment: none

Hanifin 2002 *(Continued)*

- No TCS; vehicle base applied once daily on Sunday, Tuesday, Thursday and Saturday, for the first 4 weeks of the maintenance phase, then once daily only on Sunday and Thursday. Concurrent treatment: none

Adherence

Used and unused drugs were brought to each trial visit where they were inspected by the investigator. The amount of cream remaining was recorded in the participant's clinical record form. Any participant found to be non-compliant (i.e. missing ≥ 25% doses in stabilisation phase and ≥ 10% doses in maintenance phase) was withdrawn from the trial.

Co-interventions

Regular daily emollient cream

Notes

Participants who relapsed at the beginning of the twice-weekly dosing period were allowed to revert to 4 times/week dosing at the discretion of the investigator.

Outcomes	• Cosyntropin stimulation test (CST) at last trial visit (only 3 sites)* • Adverse event monitoring, including assessment for concurrent antibiotic use and visual inspection for signs of skin atrophy and abnormal pigmentation changes at weeks −4, −3, −2, −1, 0, 2, 4, and then 4-weekly until the end of the trial, including during the follow-up phase* • Risk of relapse in the maintenance phase up to week 20.* AD relapse was defined as an IGA score of ≥ 3 (modest clearing) and a score of 2-3 for any 2 of the 3 signs or symptoms (erythema, pruritus and papulation/induration/oedema).* • Time to relapse and number of relapses, where relapse was defined by IGA ≥ 3 and a score of 2–3 for any 2 of the following: erythema, pruritus and papulation/induration/oedema up to week 20* • PGA (excellent, good, fair or poor). Reported as number of participants categorised as 'excellent' or 'good' at not reported* • Percentage BSA used in efficacy assessment at weeks −4, −3, −2, −1, 0, 2, 4, 8, 12, 16, 20 • Monitoring of lichenification, scaling and erosion/oozing/crusting at weeks −4, −3, −2, −1, 0, 2, 4, 8, 12, 16, 20 (assumed as not stated) • Antibiotic use at weeks −4, −3, −2, −1, 0, 2, 4, 8, 12, 16, 20 • Adherence/compliance at weeks −4, −3, −2, −1, 0, 2, 4, 8, 12, 16, 20 • 3 signs/symptoms (erythema, pruritus and papulation/induration/oedema) scored 0 = absent; 1 = mild; 2 = moderate; 3 = severe at weeks −4, −3, −2, −1, 0, 2, 4, 8, 12, 16, 20* • IGA: healing assessed using the following 6-point scale: 0 = cleared; 1 = almost cleared; 2 = marked clearing; 3 = modest clearing; 4 = no change; 5 = exacerbation or worsening at weeks −4, −3, −2, −1, 0, 2, 4, 8, 12, 16, 20* *denotes relevance to this review
Funding source	Conducted with a grant from Glaxo Wellcome Inc., Research Triangle Park, NC, USA
Declarations of interest	1 author is affiliated to Glaxo Wellcome Inc.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". Comment: no details provided on how this was done
Allocation concealment (selection bias)	Unclear risk	Comment: no details provided whether/how allocation was concealed

Hanifin 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: trial described in the methods as "double blind" Comment: although vehicle base was used as a comparator there was no information regarding what measures were taken to ensure participants and personnel did not know which treatment was being used (for example presentation of medication, directions for application etc.)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ."Efficacy assessments of all treated and affected areas were made by the investigator, blinded to all treatments" Comment: it is likely that the investigator did not know which treatments participants were receiving.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: ."The analysis and results presented here related to all subjects randomised to treatment in the Maintenance Phase (i.e. the intent to treat population". Comment: the proportion of participants who withdrew was small in both groups (14% TCS group vs 10% in vehicle group) however this could have introduced bias to the results. Measurements were taken at multiple time points, and were not all presented, but were used in the overall rate of relapse and adverse event analyses. It was often difficult to establish clear time points.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available for us to look at, although the linked abstract states FPC40002. All key outcomes reported in the methods appear to have been mentioned in the results.
Other bias	High risk	Quote: "Overall, 173 subjects on intermittent FP [fluticasone propionate 0.05% cream] therapy completed the 20-week maintenance phase, 36 of whom had experienced a protocol defined relapse but continued in the study at the discretion of the investigator." Comment: the trial protocol was violated and there is no clear reason provided as to the reason for this. If this did not occur in the vehicle group it is possible this may have led to bias.

Harder 1983

Study characteristics	
Methods	**Trial design** Single-blind, randomised trial **Trial registration number** Not reported **Setting** A single dermatology clinic in Switzerland; Dermatologic Polyclinic of Kantonsspitals Basel **Date trial conducted** Not reported **Duration of trial participation** 3 weeks **Additional design details**

Harder 1983 *(Continued)*

The trial states that if premature termination was due to clearance of disease, symptoms were rated as "missing" after 3 weeks. If discontinuation was due to the lack of efficacy, symptoms were fixed at the last reported severity. The same procedure was followed for the evaluation of the overall impression of the improvement.

Inclusion criteria

Patients with eczema (acute, subacute and chronic)

Exclusion criteria

Not reported

Notes

None

Participants	**Total number randomised** 98 (though it is not clear if this was the number randomised as the paper states "98 patients were included in the study") **Age** Median 31.4 years for female and 30.5 for male participants **Sex** 35 male (36%) 63 female (64%) **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Of 98 participants included in the trial, 26 were excluded; 7 did not come for 2nd consultation, 8 did not provide important information, 4 did not use the drug given and the prescribed mode of administration, and 7 used additional medications potentially affecting the result. The trial authors stated that the 26 participants who were excluded did not show a different distribution of baseline characteristics. **Notes** None
Interventions	**Run-in details** NA **Groups** • Betamethasone 17-valerate 0.1% ointment (proprietary: Betnovate); applied 3 times daily. Concurrent treatment: none

Harder 1983 *(Continued)*

	• Diflorasone diacetate 0.05% ointment (proprietary: Florone); applied once daily in the morning. Concurrent treatment: none **Adherence** Therapy discontinuation, additional treatments required, and the amount of medication (number of tubes) consumed were evaluated **Co-interventions** None **Notes** None
Outcomes	• Side effects (not stated as an outcome in the methods, but noted in the results) at unclear* • Overall impression of the improvement (−1 = deterioration, 0 = no change, 1 = 1%-25% improved, 2 = 26%-50% improved, 3 = 51%-75% improved, 4 = 76%-100% improved) at week 1 (5-9 days), week 2 (12-16 days), and week 3 (19-23 days)* • Presence and severity of the following signs/symptoms (erythema, oedema, lichenification, induration, scaling, excoriation, pruritus and ulceration 1 = no change, 2 = light, 3 = medium, 4 = serious changes) (not extracted as overall impression of improvement has been extracted) at week 1 (5-9 days), week 2 (12-16 days), and week 3 (19-23 days) *denotes relevance to this review
Funding source	None stated
Declarations of interest	None stated
Notes	Translated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised' Comment: no other information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "single-blind" Comment: no information regarding who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "single blinded" Comment: no information regarding who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 98 patients included in the study, 72 could be evaluated. Seven did not only come for second consultation, eight did not provide important information, four did not use the drug given and the prescribed mode of administration, seven used additional medications potentially affecting the result. All 26 patients had to be excluded from the study." [English translation] Comment: high proportion of dropouts who were not accounted for in the analysis

Harder 1983 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias detected

Haribhakti 1982

Study characteristics	
Methods	**Trial design** Double-blind, half-sided RCT **Trial registration number** Not reported **Setting** Secondary care, the author is a consultant at hospital in Ahmedabad. **Date trial conducted** Not reported **Duration of trial participation** Up to 3 weeks **Additional design details** Each of the participants were followed at weekly intervals for 2 weeks and if necessary 3 weeks. **Inclusion criteria** • Children with bilateral eczema **Exclusion criteria** • Children with tuberculosis, viral and fungal skin disease • Children requiring treatment with antihistamines, systemic drugs or other drugs that might interfere with the trial medications **Notes** The methods section states "children with infected lesions were included in the study only after treatment with appropriate antibiotics."
Participants	**Total number randomised** The trial was completed in 21 children (however the male to female ratio implies that 25 participants started the trial) **Age** Average age 2.96 years ± standard error 0.665 **Sex** 18 male and 7 female **Race/ethnicity**

Haribhakti 1982 *(Continued)*

	Not reported **Duration of eczema** Average duration was 6.7 months **Severity of eczema** Average BSA involved was 12.5% ± SE 1.43 **Filaggrin mutation status** Not reported **Number of withdrawals** No withdrawals are mentioned however possibly 4 more participants started the trial (if the male to female ratio is correct). **Notes** None
Interventions	**Run-in details** NA **Groups** • HC cream; parents/caregivers were instructed to apply the creams twice daily without occlusion for 2 weeks; 3 if necessary. The outpatient card also advised on quantity to be applied. Concurrent treatment: none • Clobetasone butyrate cream (proprietary: Eumovate); parents/caregivers were instructed to apply the creams twice daily without occlusion for 2 weeks; 3 if necessary. The outpatient card also advised on quantity to be applied. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Not reported **Notes** Standard strengths have been assumed to enable potency classification.
Outcomes	• Participant preference for 1 of the creams at weeks 1, 2, and if necessary, 3 • Investigator preference for treatment at weeks 1, 2, and if necessary, 3 • Clinical examination (this looked for local changes suggestive of skin atrophy) at baseline and weeks 1, 2, and if necessary, 3* • Objective parameters (erythema, oedema, papules, vesicles, exudation, crusting, scaling, lichenification/hyperkeratosis, excoriation and others) were graded 0/absent, 1/mild, 2/moderate or 3/severe at baseline and weeks 1, 2, and if necessary, 3* • Subjective parameters (pruritus and pain) were graded 0/absent, 1/mild, 2/moderate or 3/severe at baseline and weeks 1, 2, and if necessary, 3* • Average absolute and percentage reduction in total scores (assumed to be the sum of the objective and subjective parameters) at baseline and weeks 1, 2, and if necessary, 3* *denotes relevance to this review

Haribhakti 1982 *(Continued)*

Funding source	None stated, however the following is stated in the acknowledgments: "I also thank M/s Glaxo Laboratories, Bombay for supplying drugs and for their help in conducting the trial."
Declarations of interest	none declared; see 'Funding source'
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised'. Comment: no further information about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information about how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The guardian accompanying the patient was then given two identical looking tubes bearing the patient's serial number, week of treatment for which they were to be used and letters R marked in red ink and L marked in green ink for right and left sides respectively." "double blind." Comment: whilst the participants and caregivers were blinded there is no information about who, or how, investigators were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: there is no further information about who, or how, investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: scores are not presented for individual signs and symptoms, withdrawals are not mentioned, and it is unclear how many participants were included in the week 3 observations.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available and so this cannot be assessed.
Other bias	Low risk	Comment: no other source of bias was identified.

Henrijean 1983

Study characteristics

Methods	**Trial design** Double-blind, randomised, half-sided **Trial registration number** Not reported **Setting** Assumed to be a hospital dermatology department in Belgium from the author's affiliation **Date trial conducted** Not reported

Henrijean 1983 *(Continued)*

Duration of trial participation

4 weeks or until "complete bleaching" of symptoms; we assume this means complete healing of symptoms. However, the maximum length of time for the 3 participants we can use data from (with AD in which potencies were compared) was 2 weeks.

Additional design details

"In cases of extended lesions, a second and third tube was supplied upon patient's request."

Inclusion criteria

Ambulatory patients with paired, non-infected AD (trial included patients with other dermatoses presented separately whom we have not extracted).

Exclusion criteria

Not reported

Notes

None

Participants	**Total number randomised** 2 participants in the desonide v betamethasone valerate group, 1 participant in the desonide v HC butyrate group **Age** Not reported separately for the AD participants **Sex** Not reported separately for the AD participants **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Severity scores for the 3 included participants were 7, 15 and 8 (maximum of 24; see details of clinical evaluation of lesions in list of outcomes) **Filaggrin mutation status** Not reported **Number of withdrawals** Participant 28 (desonide v betamethasone valerate comparison) dropped out and was replaced by a new participant. It is unclear why or when participant 28 dropped out or how the data were dealt with. No data were available for participant 28 after day 14. Participant 5, also from the desonide v betamethasone valerate comparison, also gave no data after day 14. Participant 33 (desonide v HC butyrate comparison) gave no data after day 7. It could be assumed that these participants reached complete clearance as no other reason is given. **Notes** None

Henrijean 1983 *(Continued)*

Interventions	**Run-in details** NA **Groups** • HC 17-butyrate 0.1% cream (proprietary: Locoid); applied twice daily for up to 4 weeks to the assigned side by a 3rd person or the participant themselves, carefully washing their hands between applications of the different medications. Concurrent treatment: none • Desonide 0.1% cream (proprietary: Sterax); applied twice daily for up to 4 weeks to the assigned side by a 3rd person or the participant themselves, carefully washing their hands between applications of the different medications. Concurrent treatment: none • Betamethasone valerate 0.1% cream (proprietary: Betnelan V); applied twice daily for up to 4 weeks to the assigned side by a 3rd person or the participant themselves, carefully washing their hands between applications of the different medications. Concurrent treatment: none **Adherence** Not reported **Co-interventions** None **Notes** None
Outcomes	• Side effects or intolerance (not reported in methods however this is commented on in the results) at week 4 (assumed as time point not stated)* • Participant's opinion - preference (in terms of efficacy, not cosmetic) for a particular treatment at week 4 (assumed as time point not stated). Notes: unfortunately you cannot tell which results related to a particular participant and therefore cannot extract the data for only participants with AD. • Investigator's overall impression - preference for a particular treatment at week 4 (assumed as time point not stated). Notes: unfortunately you cannot tell which results related to a particular participant and therefore cannot extract the data for only participants with AD. • Clinical evaluation of lesions. The following signs/symptoms were assessed: erythema, vesiculae, exudates, itching, excoriations and hyperkeratosis. The score values ranged from 0-4, where 0 means absence of symptoms and 4 means a severe reaction at baseline, 7, 14, 21 and 28 days or until disappearance of symptoms.* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	This paper contains participant data from 40 participants however only 3 participants are relevant to this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "in a randomised order", "Forty randomised, paired samples were allocated for paired left-right comparisons: in a first group 40 Sterax (20 for the left hand side and 20 for the right hand side region) and in a second group 15 Locoid, 15 Betnelan V and 10 Sterac for the opposite side region, in a randomised order"

Henrijean 1983 *(Continued)*

		Comment: no information about sequence generation to rule out if allocation could be guessed
Allocation concealment (selection bias)	Unclear risk	Quote: "at the end of the study and after breaking the sealed code system, we performed a complete analysis of the data." Comment: no details about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind." "Each test sample was composed of 3 identical pairs of 30g cream tubes; creams were dispensed in neutral tubes, labelled with a code number. Codification, number of patient, and side area to be treated were indicated on 40 sealed envelopes." "At the end of the study and after breaking the sealed code system, we performed a complete analysis of the data." Comment: blinding of participants was most likely done, however it is unclear which investigators were blinded or how this was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there is no mention of whether the outcome assessor was blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there were 3 participants with AD within this trial. 2 participants have results at 14 days, 1 participant has results at only 7 days. Participants were followed up until "complete bleaching of symptoms" so it is possible that the condition resolved however it is also possible they were lost to follow-up for some reason.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias detected

Hindley 2006

Study characteristics	
Methods	**Trial design** Randomised, single blinded trial **Trial registration number** Not reported **Setting** Single, secondary care paediatric department at Fairfield General Hospital, Bury in Greater Manchester, UK. Children were referred by general practitioners, health visitors, and paediatric colleagues. **Date trial conducted** July 2000-July 2003 **Duration of trial participation** 4 weeks **Additional design details** Recruitment was discontinued early because an interim statistical analysis suggested clinically significant adverse differences between the 2 groups.

Hindley 2006 *(Continued)*

Inclusion criteria

- Age 3 months-5 years
- Diagnosis of atopic eczema according to Hanifin and Rajka criteria (Hanifin 1980) through a medical examination.
- Moderate or severe eczema according to the SCORAD index (score > 15).

Exclusion criteria

- Active skin infection at enrolment
- History of allergic reactions to trial treatments
- Predominantly facial eczema

Notes

None

Participants	**Total number randomised** 50; 28 randomised to WWT intervention, 22 to conventional treatment **Age** Given only for the 45 participants who contributed data to the analysis: age (month): median (IQR), 8 (4 to 27) in the WWT group (n = 23), 14 (7 to 22) in the conventional group (n = 22). **Sex** given only for the 45 participants who contributed data to the analysis:there were 14 male and 9 female in the WWT group and 13 male and 9 female in the conventional treatment group. **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Given only for the 45 participants who contributed data to the analysis SCORAD at baseline: mean (SD) 53 (15) WWT group, 41 (15) in the conventional group **Filaggrin mutation status** Not reported **Number of withdrawals** 5 withdrew from the WWT group owing to non-compliance; none withdrew from the conventional treatment group (18% versus 0%, P = 0.057). Of those who withdrew, 4 children withdrew between the baseline and 96-h visit, and 1 withdrew between the 96-h and week-1 visit. **Notes** Most participants had received some form of treatment for eczema prior to referral e.g. emollients or 1% HC.
Interventions	**Run-in details** NA **Groups**

Hindley 2006 *(Continued)*

- Without WWT: HC 1% ointment applied twice daily (trial authors also state as required). Concurrent treatment: none
- WWT: HC 1% ointment applied twice daily (trial authors also state as required); wet wraps were used over TCS for 24 h daily in the 1st week, then 12 or 24 h daily depending on an assessment by the education nurse. Those using wet wraps for 12 h daily used TCS and emollient as required in the remaining 12 h. Concurrent treatment: none

Adherence

The amount of steroid used was recorded and was available for 24 children in the WWT group and 20 children in the conventional group. Mean difference after 4 weeks was −0.56 g/day (WWT - conventional, 95% CI −1.9 to 0.8 g/day, P = 0.404)

Co-interventions

Regular use of emollients (applied at least 3 times daily and "whenever the skin is dry").

More potent topical steroids were permitted if necessary for both groups; only 1 participant in the WWT group received 1 between 96 h and week 1, and in any case was subsequently withdrawn. A research nurse gave an education session to the children and their carers about atopic eczema and giving advice about administering treatments, application of wet wraps if required, and allergen avoidance. 3 children in both WWT and conventional groups received antihistamines. 5 children in the WWTs group received antibiotics compared to none in the conventional treatment group (difference was 22%, 95% CI 5% to 42%, P = 0.05). The "education nurse" visited regularly during the 4 weeks to troubleshoot and advise.

Notes

None

Outcomes	• Side effects were monitored and noted at 96 h, week 1, 2, and 4 (timing assumed).* • SCORAD including extent, intensity and subjective score (which was reported separately) at baseline, 96 h, week 1, 2, and 4* • Carer assessment of efficacy (scoring on a 5-point scale of "none" to "very good") at week 4 • Scoring nurse assessment of efficacy (scoring on a 5-point scale of "none" to "very good") at week 4 • Carer assessment of tolerability (scoring on a 5-point scale of "very poor" to "very good") at week 4 • Scoring nurse assessment of tolerability (scoring on a 5-point scale of "very poor" to "very good") at week 4 • Carer assessment of ease of application (scoring on a 5-point scale of "very difficult" to "very easy") at week 4 • Scoring nurse assessment of ease of application (scoring on a 5-point scale of "very difficult" to "very easy") at week 4 • Amount of steroid used at up to week 4 • Use of antihistamines at up to week 4 • Use of antibiotics at up to week 4 *denotes relevance to this review
Funding source	The trial was supported by a grant from the NHS Research and Development Fund (North West)
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement

Hindley 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Two equal numbered sets of unmarked envelopes were prepared containing either the word ‘‘wet wrap’’ or the word ‘‘conventional’’. After informed consent was given, an envelope was chosen at random, opened, and the child allocated to the indicated group." Comment: generally randomisation using shuffled envelopes would ensure adequate randomisation but there is no mention of whether these envelopes were shuffled. Also the groups do not appear very balanced and the 4-27 month age range presented in the abstract is the same as the 4-27 month IQR presented for the wet group in the demographics table. (However, the trial authors state that there was no difference in the age distribution of the 2 groups).
Allocation concealment (selection bias)	Unclear risk	Quote: "Two equal numbered sets of unmarked envelopes were prepared containing either the word "wet wrap" or the word "conventional". After informed consent was given, an envelope was chosen at random, opened, and the child allocated to the indicated group." Comment: as there is no information regarding whether the envelopes were sealed or opaque then it is possible that the personnel involved in the randomisation could have been aware of future allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single blinded" "children, parents and the "education nurse" were not blind to allocation". Comment: as the participants/participants carers had to apply dressings every day it would have been extremely difficult to blind this trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The "scoring nurse", who was blind to allocation, assessed the SCORAD, potency, and amount of topical steroid used and noted side effects. Parents were asked to remove any wet wraps and to bathe the child prior to appointments with the ‘‘scoring nurse’’ so that skin marks from wet wraps would fade and not compromise blindness." Comment: steps were taken in order to ensure the blinding of the scoring nurse was maintained.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 50 children were recruited (28 in the wet wraps group and 22 in the conventional group). Outcome data were not available for five children in the wet wraps group, four children withdrew between the baseline and 96 hour visit, and 1 withdrew between the 96 hours and week 1 visit. This meant that intention to treat analyses were not possible." Comment: a large proportion of the participants (5/28) that were in the wet wrap group discontinued (compared to none in the conventional), this was probably because of the nature of the treatment. 39% of the WWT group stated that the treatment was easy or very easy to use as opposed to 73% of the conventional treatment group.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available
Other bias	Low risk	Comment: no further issues identified

Hoybye 1991

Study characteristics	
Methods	**Trial design**

Hoybye 1991 *(Continued)*

Single-blind, randomised, parallel-group, multicentre trial

Trial registration number

Not reported

Setting

3 centres

Date trial conducted

Not reported

Duration of trial participation

6 weeks

Additional design details

3 weeks continuous TCS use followed by 3 weeks intermittent TCS use

Inclusion criteria

- Clinical diagnosis of typical AD
- Stable or slowly progressive disease with a severity score of ≥ 4.5 (where erythema, infiltration, and pruritus were each scored 0-3 where 3 indicated the greatest severity)
- Aged 18-70 years (unclear if they intended to recruit anyone outside of this age range)
- Clinical diagnosis of AD on 2%-50% BSA (unclear if this is baseline severity or inclusion criteria)

Exclusion criteria

- Patients with skin atrophy
- Patients who had used TCSs within the week preceding enrolment
- Patients who had used systemic corticosteroids within the month preceding enrolment

Notes

None

Participants	**Total number randomised** 96 (the trial did not report the number of participants that were randomised to each group) **Age** 18-70 years (median 26 years) **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** 92 out of 96 participants had a disease duration of > 1 year **Severity of eczema** The participants had dermatitis on 2% to 50% of the body surface (unclear if this is inclusion criteria or baseline severity). **Filaggrin mutation status**

Hoybye 1991 *(Continued)*

	Not reported **Number of withdrawals** Not mentioned in text however in results table 1, 49 participants were in the mometasone group after 3 weeks and 48 after 6 weeks. In the HC 17- butyrate group 45 participants were included in the results at 3 weeks and 38 after 6 weeks. **Notes** None
Interventions	**Run-in details** NA **Groups** • HC 17-butyrate 0.1% fatty cream (proprietary: Locoid (Gist- Brocades, NV, Delft, The Netherlands)); applied twice daily for 3 weeks and then twice daily for 3 consecutive days/week for an additional 3 weeks. Concurrent treatment: none • Mometasone furoate 0.1% fatty cream (proprietary: Elocon (Schering plough A/S Denmark, Farum, Denmark.); mometasone was applied once daily for 3 weeks then once a day for 3 consecutive days per week for an additional 3 weeks. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Each participant was given an ample supply of a lubricant cream (trademark: Essex (Schering-Plough A/S, Farum, Denmark) and was instructed to use only this cream in addition to the TCS. **Notes** Mometasone dispensed in a newly formulated fatty cream base that consisted of mometasone furoate, hexylene glycol, propylene glycol stearate, stearyl alcohol and ceteareth-20, titanium dioxide, white wax, white petrolatum, phosphoric acid, and purified water. Strength not given in the paper for the steroids, however we have assumed 0.1% mometasone as this is the standard for Elocon. Similarly we assumed 0.1% HC 17-butyrate as it is the standard for Locoid.
Outcomes	• Morning plasma cortisol levels at week 0, week 3, and week 6 (only reported for 19 participants from the 2 participating centres)* • PGA (participants were asked to evaluate their eczema at baseline on a VAS ranging from no eczema to severe eczema. At week 3 and week 6 they were asked, using a similar scale about change in disease activity; they were asked to choose from the following categories: free of symptoms, improvement, no change or deterioration. The participants also noted whether there had been any change in the degree of eczema during the previous week) at week 0, 3, 6.* • Cosmetic acceptability at week 3, 6 • Side effect monitoring at week 3, 6* • Global evaluation score for atrophy (0 = none to 4 = severe) at week 3, 6* • Severity score (0-3 assigned for erythema, infiltration, and pruritus) at week 0, 3, 6 • Physician global evaluation score for effect of treatment (1 = cleared to 6 = exacerbation) at week 3, 6* *denotes relevance to this review
Funding source	Schering-Plough A/S Denmark assisted in carrying out the trial and provided trial materials.
Declarations of interest	None declared

Hoybye 1991 *(Continued)*

Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: no information as to how the randomisation took place
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single blind" Comment: as outcome assessment is blinded we assumed no other parties were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "These evaluations were made by dermatologists who had no knowledge of which preparation was being used by the individual patient." Comment: it was unlikely the dermatologist knew what the participants were receiving.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the numbers of participants reported in the results paper reduced from week 3 to week 6 and so an ITT analysis was not carried out. It is unclear what happened to the 2 participants who were not included at 3 weeks and another 8 participants were missing at 6 weeks, therefore a significant proportion of participants withdrew from the trial and so this may have influenced results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: none identified

Innocenti 1977

Study characteristics

Methods	**Trial design** Double-blind, randomised, half-sided trial **Trial registration number** Not reported **Setting** Sondrio Civil Hospital dermatology department, Italy, assumed by the authors' affiliation **Date trial conducted** Not reported **Duration of trial participation** 1 week **Additional design details**

Innocenti 1977 *(Continued)*

Not all participants had AD so only some participants were relevant to the review, hence are reported here

Inclusion criteria

Patients with bilateral AD where the lesions were distributed symmetrically were included.

Exclusion criteria

Patients without complete clinical assessment were excluded.

Notes

None

Participants	**Total number randomised** 3 with AD (other conditions were included but results presented separately therefore they haven't been extracted here). **Age** Not reported separately for the AD participants **Sex** Not reported separately for the AD participants **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** 2 participants had moderate severity disease and 1 had high severity. **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported **Notes** None
Interventions	**Run-in details** Not reported **Groups** • Fluocortolone/fluocortolone caproate 0.25% water/oil emulsion (proprietary: Ultralan, Schering Ltd.); applied twice daily to the allocated side. Concurrent treatment: not reported • Diflucortolone valerate 0.1% water/oil emulsion (proprietary: Ultralan, Schering Ltd.); applied twice daily to the allocated side. Concurrent treatment: not reported **Adherence** Not reported

Innocenti 1977 *(Continued)*

	Co-interventions Not reported **Notes** None
Outcomes	• Reporting of adverse events associated with fluoride, systemic absorption, and skin signs "due to increased catabolism secondary to inhibition of fibroblasts" at up to day 7.* • A clinical evaluation of treatment effect judged as either null, small, good, or excellent at days 1, 3, 5, and 7* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	Paper written in Italian

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The two treatments were applied to each patient using double blind random assignment.' Quoted from the English translation Comment: no information given about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blinded' from English translation Comment: no other information about how blinding was achieved or exactly which personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blinded' from English translation Comment: no other information about how blinding was achieved or exactly which personnel were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no withdrawals reported in the AD participants and data appear complete with respect to the stated outcomes
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias detected

Jorizzo 1995

Study characteristics

Methods	**Trial design** Multicentre, randomised, investigator-masked, parallel-group trial

Jorizzo 1995 *(Continued)*

Trial registration number

Not reported

Setting

5 centres (authors are all from the USA)

Date trial conducted

Not reported

Duration of trial participation

5 weeks for the majority of participants; extended to 6 months for a subgroup of 36/113 participants.

Additional design details

None

Inclusion criteria

- Children with mild-moderate AD up to and including those who were 12 years of age
- Participants were required to have a sum of scores* of ≥ 5 to qualify for entry into the trial. (*erythema, lichenification, excoriations, oozing and crusting, induration and papules were assessed by the physician. The participants, guardians or parents subjectively assessed pruritus. Each safety and efficacy feature was ranked on a scale of 0-3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Exclusion criteria

Not reported

Notes

None

Participants

Total number randomised

113; 57 randomised to moderate (desonide) and 56 to mild (HC)

Age

Overall mean age was 4.8 years (range 10 months-12 years). In the moderate (desonide) group 47.4% of participants were ≤ 3 years, 21.1% were 4-6, 15.8% were 7-9 and 15.8% were 10-12. In the mild (HC) group, 39.3% were ≤ 3 years, 30.4% were 4-6, 19.6% were 7-9 and 10.7% were 10-12. The ages of the subgroup of 36 participants that continued until 20 weeks were distributed as follows: in the moderate (desonide) group 43.8% were ≤ 3 years, 25% were 4-6, 6.3% were 7-9, and 25% were 10-12; in the mild (HC) group 25% were ≤ 3 years, 30% were 4-6, 30% were 7-9 and 15% were 10-12.

Sex

Overall 51 participants were male and 62 were female.

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Mean summary score at baseline* (read using WebPlotDigitizer) desonide 8.23, HC 8.40

Jorizzo 1995 *(Continued)*

*based on evaluation of specific lesions. erythema, lichenification, excoriations, oozing and crusting, induration and papules were assessed by the physician. Each safety and efficacy feature was ranked on a scale of 0-3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Filaggrin mutation status

Not reported

Number of withdrawals

Of the 113 participants, 111 were assessable for efficacy (2 participants in the desonide group had no follow-up data). The paper reports that only 90 participants completed 5 weeks of treatment and of those 36 (16 desonide, 20 HC) chose to continue to have an extra 20 weeks of treatment.

Notes

"A baseline comparison of demographics and disease severity revealed no significant differences between treatment groups at the start of the study."

Interventions

Run-in details

"Patients were not to use any interfering topical medication for 14 days, systemic antihistamines for 7 days, or systemic corticosteroids for 30 days before the start of the study but could use emollients during this period. However, the physician could enter a patient into the study before the end of the washout period, if the patient had worsening pruritus that required treatment."

Groups

- HC 1% ointment; applied twice daily to affected areas. Concurrent treatment: none
- Desonide 0.05% ointment; applied twice daily to affected areas. Concurrent treatment: none

Adherence

Compliance was monitored by examination of the returned tubes for approximate use, and all tubes were weighed on return to the sponsor. In addition, participants were provided with a diary to record any missed doses.

Co-interventions

Non-medicated soap (Cetaphil) was provided. Choices of shampoos, sunscreens and emollients were left to the participant.

Notes

Ointments were formulated in a similar base. Each participant applied approximately 4 g of ointment each treatment day.

Outcomes

- IGA of improvement relative to baseline at specific lesions (5-point scale: clear/100% clearance apart from residual discolouration, marked improvement/50%-74% clearance, slight improvement/< 50% clearance, no change, and exacerbation) at weeks 1, 3, 5, and monthly visits at months 2 and 6 for the subgroup that received further treatment.*
- The participants, guardians or parents subjectively assessed pruritus. Each safety and efficacy feature was ranked on a scale of 0-3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) at weeks 1, 3, 5, and monthly visits at months 2 and 6 for the subgroup that received further treatment.*
- Subjective parameters (stinging and burning) ranked 0 = none to 3 = severe at weeks 1, 3, 5, and monthly visits at months 2 and 6 for the subgroup that received further treatment.*
- Signs of atrophy (under an 8x magnifying lamp) ranked 0 = none to 3 = severe at weeks 1, 3, 5, and monthly visits at months 2 and 6 for the subgroup that received further treatment.*
- Evaluation of specific lesions. erythema, lichenification, excoriations, oozing and crusting, induration and papules were assessed by the physician. Each safety and efficacy feature was ranked on a scale of 0-3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) at weeks 1, 3, 5, and monthly visits at months 2 to 6.

Jorizzo 1995 *(Continued)*

*denotes relevance to this review

Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" Comment: no information about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "investigator masked" Comment: implies that the participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "investigator masked" Comment: no information about how the investigator was masked, also if the child participants were not blinded there is a possibility of them compromising the investigator blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 2 participants in the moderate (desonide) group were not assessed for efficacy at all; no reason was given therefore 111/113 participants were included in the "endpoint analysis". Furthermore, only 90/113 participants completed 5 weeks of treatment. Therefore at each time point a significant proportion of participants are lost and we do not know the reasons why these participants decided to stop treatment. It is also clear from the percentage efficacy data given that not all 36 participants that proceeded to the extended phase completed all 20 weeks. Also in the 20-week extension period; groups are not balanced and the participants are generally older.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias was identified

Kaplan 1978

Study characteristics

Methods	**Trial design** Randomised, double-blind, trial **Trial registration number** Not reported **Setting**

Kaplan 1978 *(Continued)*

University dermatology outpatient clinic (authors are from the University of Tennesee and participants as "seen in our clinic").

Date trial conducted

Not reported

Duration of trial participation

3 weeks

Additional design details

None

Inclusion criteria

- Consecutive outpatients presenting with "typical manifestations of chronic AD"
- Patients who had not used topical treatment in the preceding 2 weeks

Exclusion criteria

- Not reported

Notes

None

Participants

Total number randomised

60 in the 2 relevant arms; 30 randomised to HC, 30 to betamethasone valerate

Age

Mean age was 21.2 in the HC group and 19.7 in the betamethasone valerate group.

Sex

Percentage of male participants was 31 in the HC group and 27 in the betamethasone valerate group.

Race/ethnicity

Percentage of black participants was 76 in the HC group and 87 in the betamethasone valerate group.

Duration of eczema

Not reported

Severity of eczema

At the 1st visit, mean global impression of severity was 3.5 in the HC group and 3.4 in the betamethasone valerate group. This was scored using a 6-point rating scale from 0 = none to 5 = severe.

Filaggrin mutation status

Not reported

Number of withdrawals

1 participant in the HC group was lost to follow-up, 1 participant in the HC group (24-year-old black female) discontinued due to adverse events ("immediate burning with subsequent drying of the skin").

Notes

Kaplan 1978 *(Continued)*

	No significant differences were found in the race, age, or sex distributions of the treatment groups. There were no significant differences between treatment groups by analysis of variance on any of the clinical scales at initial evaluation.
Interventions	**Run-in details** None **Groups** • Betamethasone valerate 0.1% cream (proprietary: Valisone); frequency of application was not reported. Treatment was over a 3-week period. Concurrent treatment: not reported • HC 0.5% hydrophilic ointment (unspecified); frequency of application was not reported. Treatment was over a 3-week period. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** The creams were distributed in divided doses, initially and at the 2nd weekly evaluation.
Outcomes	• Pruritus, erythema, scaling, lichenification, oozing, excoriation, and overall global impression were scored on a 6-point rating scale from 0 = none to 5 = severe at baseline and weeks 1, 2, and 3.* • Adverse events were reported for patients who discontinued at up to week 3.* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned" Comment: no information given about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all medications were presented in identically coded containers and each patient was given identical application specifications, which also appeared on each container. Identities of the creams were unknown to both the patients and the physicians." Also "an examination of the product, after the codes were broken […]" Comment: it is likely that participants and personnel did not know what the patient was receiving.

Kaplan 1978 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "identities of the creams were unknown to both the patients and the physicians." Also "an examination of the product, after the codes were broken" Comment: it is likely that personnel did not know what the participant was receiving.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 2 participants in the HC group were not included in the analysis; 1 was lost to follow-up and another experienced an adverse event. As the number of dropouts is so small, there is a low potential for bias to be a problem here.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available and so no assessment can be made as to whether outcomes were selectively reported.
Other bias	Low risk	Comment: no other source of bias was identified.

Kim 2013

Study characteristics

Methods

Trial design

Multicentre, randomised, double-blind, half-sided trial

Trial registration number

Not reported

Setting

Multicentre; it does not specifically mention location however all authors are from South Korea and the trial was approved by Institutional Review Boards at 5 South Korean hospitals.

Date trial conducted

Not reported

Duration of trial participation

15 days

Additional design details

None

Inclusion criteria

- Patients with moderate-severe symmetrical eczematous skin lesions

Exclusion criteria

- Patients < 4 years old
- Patients currently undergoing treatment with systemic glucocorticoids, antibiotics or immunosuppressive agents
- Patients treated with UV radiation
- Patients with other chronic non-eczematous skin diseases, also those with infectious dermatoses
- Patients with a chronic medical illness such as diabetes
- Patients who were pregnant or lactating

Kim 2013 *(Continued)*

- Patients with skin lesions involving the face or genital area
- Patients with other severe dermatoses or scars

Notes

Prior to the start of the trial, participants taking a systemic corticosteroid had a washout period of 4 weeks, and participants who applied a TCS had a washout period of 1 week.

Participants	**Total number randomised** 175 participants (350 sides of the body) **Age** For the 159 participants who were analysed the mean age was 32.32 years (SD 19.86, range 5-79). **Sex** Of 159 participants who contributed data there were 76 male (47.80%) and 83 female (52.20). **Race/ethnicity** Not reported **Duration of eczema** Paper states that 25 (15.72%) participants had "past skin disease history", whilst 134 (84.28%) did not. **Severity of eczema** Baseline IGA of clinical response was 7.46 ± 3.11 in the mometasone furoate group, whilst 7.51 ± 3.18 in the methylprednisolone aceponate group. The index was calculated from assessment of 4 signs/symptoms: erythema, vesiculation, pruritus, and burning/pain where the physician rated each parameter on a 0-3 scale: 0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe. The paper does not describe how this was calculated; possibly it was summed for each participant and a mean calculated. **Filaggrin mutation status** Not reported **Number of withdrawals** 15 participants were excluded due either to violation of protocols or adverse reactions, and 1 participant was excluded due to a screening criteria violation. It is unclear which group they were allocated to. **Notes** None
Interventions	**Run-in details** NA **Groups** • Mometasone furoate cream; applied in a multi-lamellar emulsion cream to 1 side of the body once daily for 2 weeks. Concurrent treatment: none • Methylprednisolone aceponate cream; applied to 1 side of the body once daily for 2 weeks. Concurrent treatment: none **Adherence** Not reported

Kim 2013 *(Continued)*

	Co-interventions The mometasone furoate preparation also contained multi-lamellar emulsions (paper suggests this can aid restoration of the barrier function of the skin) and hexylene glycol (an antimicrobial excipient). **Notes** The concentrations of the 2 TCS preparations were not stated in the paper. Therefore, the methylprednisolone preparation was assumed to be 0.1% and mometasone assumed to be 0.1%. This was because these were the only concentrations identified in the reference sources that we used to identify potency.
Outcomes	• Adverse events (included those deemed treatment-related or not) at up to day 15* • TEWL: measured by Tewameter® to evaluate epidermal permeability barrier function (Courage & Khazaka, Cologne, Germany). The TEWL improvement ratio was calculated as: TEWL improvement ratio (%) = [(TEWLday1-TEWLdayn)/ TEWLday1] × 100 (%) at day 1, 4, 8, and 15. • IGA. The IGA index was calculated from assessment of 4 signs/symptoms: erythema, vesiculation, pruritus, and burning/pain where the physician rated each parameter on a 0-3 scale: 0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe. The IGA improvement ratio was calculated as: IGA improvement ratio (%) = [(IGAday1-IGAdayn)/IGAday1] × 100 (%) at day 1, 4, 8, and 15.* • VAS for pruritus: improvement of pruritus after treatment was scored subjectively, "using 10 visual analogue scales that the patients scored". We assume this means participants marked the severity of the itch on a 10 mm VAS. The VAS improvement ratio was calculated as: VAS improvement ratio (%) = [(VASday1-VASdayn)/VASday1] × 100 (%) at day 1, 4, 8, and 15.* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	The mometasone furoate preparation also contained multi-lamellar emulsions (the paper suggests this can aid restoration of the barrier function of the skin) and hexylene glycol (an antimicrobial excipient).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After informed consent was obtained, the patients were randomly assigned to apply mometasone furorate in MLE [multi-lamellar emulsion] on one side and methylprednisolone aceponate on the other side. " Comment: no description of randomisation method
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind" Comment: no information as to which group (participants, personnel or outcome assessors) were blinded or how blinding was achieved (e.g. labelling tubes)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind" Comment: no information as to which group (participants, personnel or outcome assessors) were blinded or how blinding was achieved (e.g. labelling tubes)
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 175 patients were initially enrolled. Fifteen patients were excluded due either to violation of protocols or adverse reactions, and one patient was excluded due to a screening criteria violation. In total, 159 patients were analyzed."

Kim 2013 *(Continued)*

		Comment: a large number of participants were excluded, it was not clear from which group they were excluded. It was also not clear what proportion of participants were excluded due to adverse events and from which group. The authors excluded these participants completely from the efficacy analyses. There were no attempts to include the data already collected for these participants at earlier visits. Also, reasons for exclusion included pruritus.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. Raw data for efficacy outcomes are only given in a graph at day 4 and 8 without dispersion data.
Other bias	Low risk	Comment: no other biases identified

Kirkup 2003a

Study characteristics

Methods

Trial design

Multicentre, randomised, double-blind, parallel-group, comparative trial

Trial registration number

Not reported

Setting

Multicentre, outpatients, 16 centres in 5 countries (in Europe and South Africa according to the acknowledgements)

Date trial conducted

Not reported

Duration of trial participation

Up to 18 weeks (1-2-week run-in phase, 2-4-week acute phase, 3-month maintenance phase, follow-up 2 weeks post-trial)

Additional design details

Participants were randomised once at the end of the run-in period. The randomised part of these trials were also in 2 treatment phases, acute phase (twice daily TCS) and then maintenance (TCS applied at 1st sign of the flare)

Inclusion criteria

- Children aged 2-14 years
- Participants (outpatients) experiencing a flare of moderate-severe AD with a total AD Score of ≥ 6 (see outcomes for definition)

Exclusion criteria

- Participants showing signs of skin infection or the dermatitis was severe enough to warrant hospital admission
- Use of potent or very potent TCS
- Systemic treatment for skin disease during the previous 3 weeks
- Oral or parenteral corticosteroids within the previous 12 months
- History of adverse response to corticosteroids
- Concomitant serious or unstable disease
- Participation in another clinical trial within the previous 4 weeks

Kirkup 2003a *(Continued)*

	Notes None
Participants	**Total number randomised** 137 participants (70 in the fluticasone group, 67 HC group) **Age** Mean age was 8 years (± SD 3, range 4-14) in both arms. **Sex** Fluticasone: female n = 35 (51%), male n = 34 (49%). HC: female n = 38 (57%), male n = 29 (43%) **Race/ethnicity** Not reported **Duration of eczema** Fluticasone: median 5 years, range 0-14 years. HC: median 6 years, range 0-14 years **Severity of eczema** Body areas affected out of a possible 12 areas (i.e. chest, back, hands and wrists, back of arms, front of arms, back of legs, front of legs, feet and ankles, neck and shoulders, buttocks, scalp and face; mean, range): fluticasone 8 (4-12); HC 8 (4-12) **Filaggrin mutation status** Not reported **Number of withdrawals** 31 participants, 18 in fluticasone group and 13 in the HC group withdrew at various times. Reasons for withdrawal (some participants provided > 1 reason) included: treatment failure (2 fluticasone, 8 HC); non-compliance or personal reasons (7 fluticasone, 2 HC); early cure (3 fluticasone, 1 HC); adverse event (1 HC); protocol violation (1 fluticasone, 1 HC). In 8 further cases the reason was not specified (7 fluticasone, 1 HC). In total, 107 (53 fluticasone, 54 HC) completed the 3 month maintenance phase (one participant withdrew at end of the maintenance phase). **Notes** Missing age and gender for 1 participant in the fluticasone group
Interventions	**Run-in details** Initially, all screened participants applied the low-potency HC 1% cream twice daily to affected areas for 1-2 weeks (pre-trial/run-in period) during which time baseline data were established and participants familiarised themselves with trial procedures. **Groups** • Fluticasone propionate 0.05% cream; in the acute treatment phase, participants applied fluticasone to affected areas twice daily for 2-4 weeks until the investigator judged their AD was stabilised. participants then entered a 3-month maintenance phase and applied the trial treatment "as required" (up to twice daily) to affected areas at the 1st sign of a relapse. Investigators were permitted to issue tubes of HC for the face (labelled 'face treatment'). Concurrent treatment: none • HC 1% cream; in the acute treatment phase, participants applied HC to affected areas twice daily for 2-4 weeks until the investigator judged their AD was stabilised. participants then entered a 3-month maintenance phase and applied the trial treatment "as required" (up to twice daily) to affected areas at the 1st sign of a relapse. Investigators were permitted to issue tubes of HC for the face (labelled "face treatment"). Concurrent treatment: none

Kirkup 2003a *(Continued)*

Adherence

Participants/parents were asked to return all used and unused tubes for weighing. Similar amounts of cream were used by each group: 57 g of fluticasone (range 10–259 g) versus 60 g of HC (range 15–252 g)

Co-interventions

Participants were permitted to use emollients as required. Investigators also were permitted to issue HC 1% cream for use on the face. Regular inhaled and intranasal corticosteroids were permitted.

Notes

None

Outcomes	• Physician-reported "overall assessment of treatment success" - grouped 'much improved/improved' or 'same/worse/much worse' at end of acute phase (week 2 or week 4)* • Daytime itch recorded on participant diaries. For the diary card data, mean values over the last 7 days before the end of the acute treatment phase were used in the analysis. For the monthly assessments of symptoms during the maintenance phase, the analysis was based on data from the final clinic visit of the maintenance phase. Data were grouped as improved ('better than ever', 'better than usual') or not improved ('same', 'worse than ever', worse than usual'). A VAS scale was also used with 1 being worse than ever been and 7 better than ever been in the ANCOVA analysis of the acute phase) at daily during acute phase and monthly throughout the maintenance phase.* • Sleep disturbance recorded on participant diaries. For the diary card data, mean values over the last 7 days before the end of the acute treatment phase were used in the analysis. For the monthly assessments of symptoms during the maintenance phase, the analysis was based on data from the final clinic visit of the maintenance phase. Data were grouped as improved ('better than ever', 'better than usual') or not improved ('same', 'worse than ever', worse than usual'). A VAS scale was also used with 1 being worse than ever been and 7 better than ever been in the ANCOVA analysis of the acute phase) at daily during acute phase and monthly throughout the maintenance phase.* • Adverse events at beginning and end of the 1-2 week pre-trial period, after 2-4 weeks of acute treatment phase and then at monthly intervals in the maintenance phase for 12 weeks. Also, follow-up visit 2 weeks post-trial.* • Total AD score: (maximum 21) = number of body areas affected (out of a possible 12 body areas) + sum of scores for target area (maximum 9 as erythema, excoriation and lichenification were each graded 0-3) at beginning and end of the 1-2 week pre-trial period, after 2-4 weeks of acute treatment phase and then at monthly intervals in the maintenance phase for 12 weeks. Also, follow-up visit 2 weeks post-trial • Routine urinalysis, biochemical and haematological screening at enrolment and end of the maintenance phase (up to week 16, - could be earlier than 16 weeks if participant had < 4 weeks acute phase)). • Weight of used and unused trial cream tubes at End of 3-month maintenance phase • Intensity of rash recorded on participant diaries. For the diary card data, mean values over the last 7 days before the end of the acute treatment phase were used in the analysis. For the monthly assessments of symptoms during the maintenance phase, the analysis was based on data from the final clinic visit of the maintenance phase. Data were grouped as improved ('better than ever', 'better than usual') or not improved ('same', 'worse than ever', worse than usual'). A VAS scale was also used with 1 being worse than ever been and 7 better than ever been in the ANCOVA analysis of the acute phase) at daily during acute phase and monthly throughout the maintenance phase. • Usage of antipruritic or sedative drugs at during maintenance phase. • Median time to recurrence of AD. Recurrence defined as an increase of 1.0 in either the number of body areas affected or, in the sum of scores (for erythema, excoriation and lichenification) for the target area. Time to recurrence of AD was calculated from the visit dates for those participants who had a recurrence at during maintenance phase. *denotes relevance to this review
Funding source	A grant from Glaxo Wellcome R & D, U.K (FLT411/412).
Declarations of interest	Not reported

Kirkup 2003a *(Continued)*

Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised'. Comment: no other information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind' Comment: no information about who exactly was blinded or how
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information about who exactly was blinded or how
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All analyses were performed on the Intent to treat population". Comment: although the authors state that they performed an ITT analysis, the numbers of participants reported in the results tables are not the same as the numbers randomised. There is also no information regarding how the missing data were handled in the participants that withdrew. As a large number of participants withdrew from the trial this may have led to bias in the results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol found
Other bias	Low risk	Comment: no other sources of bias detected

Kirkup 2003b

Study characteristics

Methods	**Trial design** Multicentre, randomised, double-blind, parallel-group, comparative trial **Trial registration number** Not reported **Setting** Participants (outpatients) were recruited from 14 centres in 7 countries (in Europe and South Africa according to the acknowledgements) **Date trial conducted** Not reported **Duration of trial participation** Up to 18 weeks (1-2-week run-in phase, 2-4-week acute phase, 3-month maintenance phase, 2-week follow-up post-trial)

Kirkup 2003b *(Continued)*

Additional design details

Participants were randomised once at the end of the run-in period. The randomised part of these trials were also in 2 treatment phases, active (twice daily TCS) and then maintenance (TCS applied at 1st sign of the flare).

Inclusion criteria

- Children aged 2-14 years.
- Participants (outpatients) experiencing a flare of moderate-severe AD with a total AD Score of ≥ 6 (see outcomes for definition)

Exclusion criteria

- Participants showing signs of skin infection or the dermatitis was severe enough to warrant hospital admission
- Use of potent or very potent TCS
- Systemic treatment for skin disease during the previous 3 weeks
- Oral or parenteral corticosteroids within the previous 12 months
- History of adverse response to corticosteroids
- Concomitant serious or unstable disease
- Participation in another clinical trial within the previous 4 weeks

Notes

None

Participants

Total number randomised

128 participants (66 in the fluticasone group, 62 in the HC butyrate group)

Age

Mean age was 8 years (SD 3, range 2-14) in the fluticasone arm and 9 years (SD 3, range 3-14) in the HC butyrate arm

Sex

Fluticasone: female n = 26 (39%), male n = 40(61%). HC butyrate: female n = 33 (53%), male n = 29 (47%)

Race/ethnicity

Not reported

Duration of eczema

Fluticasone: median 4 years (range 0-14). HC butyrate: median 6 years (range 0-14)

Severity of eczema

Body areas affected (out of a possible 12 areas (i.e. chest, back, hands and wrists, back of arms, front of arms, back of legs, front of legs, feet and ankles, neck and shoulders, buttocks, scalp and face)): fluticasone, mean = 8 (range 3-12); HC butyrate: mean = 8 (range 3-12)

Filaggrin mutation status

Not reported

Number of withdrawals

18 participants (7 fluticasone, 11 HC) were officially withdrawn. A further 8 participants did not attend the final trial visit but attended a follow-up visit 2 weeks later. Stated reasons for withdrawal (some participants provided > 1 reason) included treatment failure (5 HC), adverse event (1 fluticasone, 3 HC),

Kirkup 2003b *(Continued)*

protocol violation (2 HC) and non-compliance or personal reasons (2 fluticasone, 3 HC). For 8 participants (4 in each treatment group) reasons for withdrawal were not stated. In total, 102 (57 fluticasone, 45 HC) participants were recorded as completing the 3-month maintenance phase.

Notes

None

Interventions	**Run-in details** Initially, all screened participants applied the low-potency HC 1% cream twice daily to affected areas for 1-2 weeks (pre-trial/run-in period) during which time baseline data were established and participants familiarised themselves with trial procedures. **Groups** • HC 17-butyrate 0.1% cream; in the acute treatment phase, participants applied HC butyrate to affected areas twice daily for 2-4 weeks until the investigator judged their AD was stabilised. Participants then entered a 3-month maintenance phase and applied the trial treatment "as required" (up to twice daily) to affected areas at the 1st sign of a relapse. Investigators were permitted to issue tubes of HC for the face (labelled 'face treatment'). Concurrent treatment: none • Fluticasone propionate 0.05% cream; in the acute treatment phase, participants applied fluticasone to affected areas twice daily for 2-4 weeks until the investigator judged their AD was stabilised. Participants then entered a 3-month maintenance phase and applied the trial treatment "as required" (up to twice daily) to affected areas at the 1st sign of a relapse. Investigators were permitted to issue tubes of HC for the face (labelled 'face treatment'). Concurrent treatment: none **Adherence** Participants returned all used and unused tubes to be weighed. Similar amounts of cream were used by each group: 62 g of FP (range 17-201 g) versus 59 g of HC (range 16-126 g). **Co-interventions** Participants were permitted to use emollients as required. Investigators also were permitted to issue HC 1% cream for use on the face. Regular inhaled and intranasal corticosteroids were permitted. **Notes** None
Outcomes	• Physician reported "overall assessment of treatment success" - grouped 'much improved/improved' or 'same/worse/much worse' at end of acute phase (week 2 or week 4)* • Daytime itch recorded on participant diaries. For the diary card data, mean values over the last 7 days before the end of the acute treatment phase were used in the analysis. For the monthly assessments of symptoms during the maintenance phase, the analysis was based on data from the final clinic visit of the maintenance phase. Data were grouped as improved ('better than ever', 'better than usual') or not improved ('same', 'worse than ever', worse than usual'). A VAS scale was also used with 1 being worse than ever been and 7 better than ever been in the ANCOVA analysis of the acute phase) at daily during acute phase and monthly throughout the maintenance phase.* • Sleep disturbance recorded on participant diaries. For the diary card data, mean values over the last 7 days before the end of the acute treatment phase were used in the analysis. For the monthly assessments of symptoms during the maintenance phase, the analysis was based on data from the final clinic visit of the maintenance phase. Data were grouped as improved ('better than ever', 'better than usual') or not improved ('same', 'worse than ever', worse than usual'). A VAS scale was also used with 1 being worse than ever been and 7 better than ever been in the ANCOVA analysis of the acute phase) at daily during acute phase and monthly throughout the maintenance phase.* • Adverse events at beginning and end of the 1-2 week pre-trial period, after 2-4 weeks of acute treatment phase and then at monthly intervals in the maintenance phase for 12 weeks. Also, follow-up visit 2 weeks post-trial.* • Total AD score: (maximum 21) = number of body areas affected (out of a possible 12 body areas) + sum of scores for target area (maximum 9 as erythema, excoriation and lichenification were each graded

Kirkup 2003b *(Continued)*

0-3) at beginning and end of the 1-2 week pre-trial period, after 2-4 weeks of acute treatment phase and then at monthly intervals in the maintenance phase for 12 weeks. Also, follow-up visit 2 weeks post-trial.

- Routine urinalysis, biochemical and haematological screening at enrolment and end of the maintenance phase (up to week 16, - could be earlier than 16 weeks if participant had < 4 weeks acute phase)).
- Weight of used and unused trial cream tubes at End of 3-month maintenance phase.
- Intensity of rash recorded on patient diaries. For the diary card data, mean values over the last 7 days before the end of the acute treatment phase were used in the analysis. For the monthly assessments of symptoms during the maintenance phase, the analysis was based on data from the final clinic visit of the maintenance phase. Data were grouped as improved ('better than ever', 'better than usual') or not improved ('same', 'worse than ever', worse than usual'). A VAS scale was also used with 1 being worse than ever been and 7 better than ever been in the ANCOVA analysis of the acute phase) at daily during acute phase and monthly throughout the maintenance phase.
- Usage of antipruritic or sedative drugs at during maintenance phase.
- Median time to recurrence of AD. Recurrence defined as an increase of 1.0 in either the number of body areas affected or, in the sum of scores (for erythema, excoriation and lichenification) for the target area. Time to recurrence of AD was calculated from the visit dates for those participants who had a recurrence at during maintenance phase.

*denotes relevance to this review

Funding source	A grant from Glaxo Wellcome R & D, U.K (FLT411/412)
Declarations of interest	Not reported
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised'. Comment: no other information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind' Comment: no information about who exactly was blinded or how
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information about who exactly was blinded or how
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All analyses were performed on the Intent to treat population". Comment: although the authors state that they performed an ITT analysis, the numbers of participants reported in the results tables are not the same as the numbers randomised. There is also no information regarding how the missing data were handled in the participants that withdrew. As a large number of participants withdrew from the trial this may have led to bias in the results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol found
Other bias	Low risk	Comment: no other sources of bias detected

Kohn 2016

Study characteristics

Methods

Trial design

Investigator-blinded, cross-over RCT

Trial registration number

NCT01675232

Setting

Yale Pediatric Dermatology Clinic having been referred by a general paediatrician or community dermatologist

Date trial conducted

July 2012-July 2013

Duration of trial participation

14 days for the majority of participants and a further 14 days for 2 participants who crossed over

Additional design details

3 participants were asked to cross over from the control (dry skin application) arm into the soak and smear arm because of < 75% clearance by EASI score.

Inclusion criteria

- Patients between 2 weeks and 18 years of age
- Patients meeting the clinical criteria for the diagnosis of AD (Eichenfield 2014a)
- Patients with disease affecting ≥ 5% of their total BSA

Exclusion criteria

- Patients with infected AD
- Patients allergic/intolerant of the trial medications
- Lack of follow-up after initial visit or regimen noncompliance
- Patients without access to a bathtub

Notes

None

Participants

Total number randomised

45; 22 to soak and smear and 23 to dry skin application group

Age

Mean 3.2 years ± SD 3.4 in the soak and smear group (range 0.3-11); 3.1 ± 4.0 (0.3-16) in the dry skin application group

Sex

10 female to 12 male in the soak and smear group; 8 female to 15 male in the dry skin application group.

Race/ethnicity

Kohn 2016 *(Continued)*

12 white, 5 black, 2 Asian, 2 Hispanic and 1 other in the soak and smear group; 14 white, 2 black, 5 Asian, 0 Hispanic and 2 other in the dry skin application group.

Duration of eczema

Not reported

Severity of eczema

Initial EASI score was mean 15.8 ± SD 9.1 (range 4.6-34.95) in the soak and smear group; 15.1 ± 6.9 (2.8-29.7) in the dry skin application group.

Filaggrin mutation status

Not reported

Number of withdrawals

All participants were assessed on days 0 and 14. 1 family randomised initially to the control arm crossed over into the soak and smear group, but did not return for the 2nd, day-14 follow-up visit. They reported difficulty in fitting the appointment around work schedules and were frustrated at their lack of AD clearance.

Note

The baseline demographics report, gives n = 24 for the soak and smear group. We assume this is a typographical error as sex and age data can be added up to 22. 3 participants in each group were reported in the summer months.

Interventions

Run-in details

Participants had a washout period of 2 weeks if they had been receiving systemic corticosteroid therapy, and 1 week if they had been receiving TCS or systemic antibiotics (from thesis).

Groups

- Triamcinolone acetonide 0.1% ointment (unspecified); applied twice daily. The following instructions were provided as part of an information leaflet given to this group of participants only: "throughout the treatment period you should apply the medication to the affected areas on dry skin. If applying after a bath or shower, wait at least 15 minutes until the skin is dry before applying the corticosteroid ointment. DO NOT apply the corticosteroid ointment to wet skin." Concurrent treatment: none
- Triamcinolone acetonide 0.1% ointment (unspecified); applied twice daily, once with the following instructions: "soak in a bath (not a shower) in plain, lukewarm water for 10 minutes (use a timer) at night then immediately, without drying the skin, smear on the corticosteroid ointment." Concurrent treatment: none

Adherence

Participants were prescribed a 454 g jar or equivalent and were provided with an estimate of how much TCS should have been applied by the end of the 2-week trial based on age and affected BSA. Participants completed the treatments at home and completed a daily log in which they documented their compliance with the trial medication (answering the question "did you do the treatment regime?". The results of the daily log were as follows: on average, participants randomised to the soak and smear arm missed 0.67 ± 1.09 days of the 14-day intervention. In comparison, participants randomised to the control arm missed on average 0.48 ± 0.59 days of TCS application. There was no statistically significant difference between the compliance rate of the 2 trial arms (P = 0.8). In the thesis, it is discussed that young children may be mobile and active in the bath, and may probably not achieve the same degree of soak as might be expected from an adult, for example.

Co-interventions

HC 2.5% ointment was used in participants < 2 years of age and for application to facial/intertriginous areas. All participants were educated in AD flare treatment and maintenance, and were required to

Kohn 2016 *(Continued)*

	avoid soaps and cleansers. Participants received an educational handout at the start of the trial and a follow-up phone call on day 7. **Notes** The trial authors attribute the good responses in both groups to the fact the participants were given instructions regarding how much steroid to apply and were reassured that the amount they were applying was appropriate. They say that before education "nearly all of our participants presented to our clinic with some level of reluctance towards using adequate amounts of topical corticosteroids".
Outcomes	• Morning serum cortisol in consenting participants at day 14* • EASI at day 0 and 14* • Participant or caregiver daily score for overall quality of sleep (using a scale of 0-3 with 0 indicating participant slept well and 3 indicating that the participant slept poorly) daily (reported to investigators on day 7 and day 14)* • Participant or caregiver daily score for overall quality of life (using a scale of 0-10 with 10 indicating worst quality of life) daily (reported to investigators on day 7 and day 14) • Participant or caregiver daily score for level of pruritus (using a scale of 0-10 with 0 no itch and 10 indicating severe itch) daily (reported to investigators on day 7 and day 14)* • Compliance (answering the question "did you do the treatment regime?") daily (reported to investigators on day 7 and day 14). • Adverse events; combination of participant reporting and observation, specifically commenting on skin atrophy such as wrinkling, thinning or depression, increased venous pattern, striae, or increased skin fragility"), allergic ("contact") dermatitis, acne, rosacea or pigmentation changes and HPA axis suppression at day 14* • Physical examination and photography at day 0 and 14 *denotes relevance to this review
Funding source	Yale University School of Medicine James G. Hirsch, MD, Endowed Medical Student Research Fellowship
Declarations of interest	1 author has been a consultant for Promius, Anacor, Astellas, Ranbaxy, Pierre Fabre, and Hoffman-Laroche Pharmaceuticals.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the thesis: "Patients were randomized in a form of restricted randomization known as random permuted blocks in which patients were randomized in blocks of either length four or six. This allowed for the patients to be randomized maximally while maintaining a relatively equal number of participants in each arm. In addition, because the blocks were of different lengths, and the lengths were randomized, there was less likelihood of the blinded investigator being able to predict the treatment regimen of the last patient in the block in the unlikely event that the blinded investigator was able to determine which patients were assigned to each arm for patients in a block". From the paper: "Participants were randomly assigned to either the control or SS arm with a 1:1 allocation ratio using computer-generated permuted blocks of either 4 or 6 in random order". Comment: It is likely that the randomisation method was adequate.
Allocation concealment (selection bias)	Low risk	Quote: "allocation was revealed only after the patient had been recruited to the study." Comment: It is likely that the allocation method was adequate.

Kohn 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote from the thesis: "Richard Antaya, MD was not blinded and was responsible for demonstrating application of the drug to the patients or parents/guardians." From the paper: " A separate investigator was not blinded and was responsible for demonstrating TCS application technique to the participants." Comment: due to the nature of the intervention, it would have been difficult to blind the participants and personnel regarding which treatment arm the participant belonged to.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from the thesis: "The trial was blinded to Lucinda Liu who was responsible for all patient evaluations. In order to maintain the blind, both the patient and the parent/guardian were instructed not to discuss the prescribed regimen with the blinded investigator." From the paper:"One investigator was blinded and was responsible for evaluating patients." Comment:It is likely that the blinding of the outcome assessor was adequate.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The data were analyzed excluding the crossover group, and again including the crossover group. There was no change in statistical significance between the 2 arms with the inclusion of the crossover group." "Intention-to-treat analysis" Comment: only the 2nd, day-14 assessment was missed by 1 participant, therefore it is unlikely to impact the main conclusions drawn.
Selective reporting (reporting bias)	Unclear risk	Comment: prospectively registered trial protocol available. The primary outcome stated was reported on in the paper, however the protocol states a 3-month follow-up was to be undertaken in order to count adverse events and frequency of flares; the paper does not include anything to suggest this was done.
Other bias	Low risk	Comment: no other sources of bias detected

Koopmans 1995

Study characteristics	
Methods	**Trial design** Multinational, multicentre, randomised, double-blind trial **Trial registration number** Not reported **Setting** Denmark, Norway, Finland and the Netherlands - 1 centre in each country **Date trial conducted** Participants recruited from November 1991-November 1992 **Duration of trial participation** 4 weeks **Additional design details**

Koopmans 1995 *(Continued)*

None

Inclusion criteria

- Patients of either sex if they were over 12 years of age suffering from atopic eczema

Exclusion criteria

- Patients with clear secondary infection of lesions and requiring concomitant use of systemic steroids

Notes

None

Participants

Total number randomised

150 participants were randomised, 75 into each group

Age

The mean age in the once daily group was 28.7 (SD 16.3, range 12-78); the age in the twice daily group was 28.2 (14.6, 12-81).

Sex

There were 27 male and 48 female participants in the once daily group, and 27 male and 47 female participants (1 was unrecorded) in the twice daily group.

Race/ethnicity

Not reported

Duration of eczema

The duration of illness in the once daily group was 17.6 years (SD 13.6, range 0.1-70), and 19.0 (13.0, 0.5-60) in the twice daily group.

Severity of eczema

Signs and symptoms were graded on a 5-point scale from 0 = none to 4 = very severe. For erythema, the score was 2.8 in the once daily group and 2.7 in the twice daily group; induration was 2.3 v 2.1; scaling was 1.7 v 1.6; pruritus was 2.9 v 2.7; excoriation was 1.9 v 1.8; overall was 2.2 v 2.3, with calculated overall scores of 11.5 v 11.0

Filaggrin mutation status

Not reported

Number of withdrawals

3 twice daily participants missed 1 of their visits. 1 participant in once daily group stopped treatment due to folliculitis. In Table II of the publication, 74 participants in once daily and twice daily group are analysed for investigator's opinion. For participant's opinion, 73 in once daily versus 75 in twice daily were analysed. Number of withdrawals is not clear.

Notes

None

Interventions

Run-in details

None

Groups

Koopmans 1995 *(Continued)*

- HC 17-butyrate 0.1% cream (Locoid Lipocream); emollient was applied in the morning and TCS was applied in the evening. Applied until lesions were resolved or up to a maximum of 4 weeks. No occlusive dressings were used. Concurrent treatment: Locobase was used as the emollient.
- HC 17-butyrate 0.1% cream (Locoid Lipocream); TCS was applied twice daily; once in the morning and once in the evening. Applied until lesions were resolved or up to a maximum of 4 weeks. No occlusive dressings were used. Concurrent treatment: none

Adherence

Not reported

Co-interventions

None

Notes

None

Outcomes	• Clinical features scored on a 5-point scale (0 = none to 4 = very severe): erythema, induration, scaling, pruritus, excoriation, and overall severity at baseline, 2 weeks, 4 weeks • Participant's opinion (6-point scale: +4 = clearance to +1 = minimal improvement, 0 = no change and −1 = worse) at 2 weeks, 4 weeks* • Adverse events at up to 4 weeks* • Investigator's opinion (6-point scale: +4 = clearance to +1 = minimal improvement, 0 = no change and −1 = worse) at 2 weeks, 4 weeks* *denotes relevance to this review
Funding source	The trial was sponsored by Yamanouchi Europe BV, Leiderdorp, NL (subsidiary of Astellas Pharma who manufacture Locoid); it is unclear how they were involved in the trial design or its funding.
Declarations of interest	None declared, however the address for correspondence is for an individual not in the authorship list (who were affiliated to hospital dermatology departments except 1 simply at a street address) at Yamanouchi Europe BV.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was a randomized double-blind comparison". Comment: no information about how randomisation was conducted
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided about how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The study was a randomized double-blind comparison of Locoid Lipocream twice daily and an alternating treatment with Locoid Lipocream once daily and Locobase once daily in the treatment of patients with atopic eczema. " Quote: "The patients received two tubes, one to be used in the morning, containing either the vehicle Locobase or Locoid Lipocream fatty cream, and the other to be used in the evening, containing Locoid Lipocream in all cases" Comment: mentions that it was double-blinded and that vehicle was used in the once daily group in the morning. But no details how blinding was maintained and if trial personnel were blinded

Koopmans 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The study was a randomized double-blind comparison of Locoid Lipocream twice daily and an alternating treatment with Locoid Lipocream once daily and Locobase once daily in the treatment of patients with atopic eczema. " Comment: only mentions that it was double-blinded - not sure if outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three patients in the Locoid Lipocream group missed one of their visits to the clinics" Comment: reasons for missing values in table II are not provided, however generally the outcome data appears to be complete
Selective reporting (reporting bias)	Unclear risk	Comment: no clinical trials register entry so unable to make a judgement
Other bias	Unclear risk	Comment: not clear how atopic eczema was diagnosed. Insufficient information to determine other sources of bias.

Kuokkanen 1987

Study characteristics	
Methods	**Trial design** Randomised, double-blind, half-sided trial **Trial registration number** Not reported **Setting** The authors are from Finland **Date trial conducted** Not reported **Duration of trial participation** 3 weeks **Additional design details** None **Inclusion criteria** • White children aged 2-10 years • Diagnosed with eczema (bilateral, symmetrical) and otherwise in general good health. "lesions on the arms, legs, or torso were selected as paired test sites in each participant; lesions of the groin, diaper area, palms, soles, face, or scalp were not chosen. The severity of erythema, induration, and pruritus at test sites was rated on a 4-point scale ranging from 0 (absent) to 3 (severe). To be included in the trial, a child had to have (a) each sign or symptom, (b) the rating of the severity of each had to be equal at paired test sites, (c) the ratings at each test site had to total at least 6, and (d) the condition had to be stable or slowly worsening for more than one week." **Exclusion criteria**

Kuokkanen 1987 *(Continued)*

- Children with evidence of skin atrophy.
- Known hypersensitivity to any component of either trial medication.
- Children to whom steroids had been administered topically or systemically within the 2 weeks preceding enrolment.
- Children requiring > 45gm of medication weekly per test site.
- Children who had received any treatment known to affect eczema within the month preceding the trial.
- Children who required any medication (topical or systemic) that might affect the course of the eczema.

Notes

None

Participants	**Total number randomised** 37, of whom 34 were included in the safety evaluation and 32 in the efficacy evaluation. 34 had their characteristics table reported in the results section; 16 randomised to right-side alclometasone and 18 to right-side HC **Age** Of those randomised to right-side alclometasone mean age was 6.8 (years; median 7.0, range 2.0-10.0). Of those randomised to right-side HC, mean age was 7.6 (years; median 7.0, range 3.0-10.0). **Sex** There were 10 male and 6 female participants randomised to right-side alclometasone and 9 male and 9 female randomised to right-side HC **Race/ethnicity** White **Duration of eczema** Mean duration of disease was 4.5 years in the group randomised to right-side alclometasone (median 5.0, range 0.3-8.0). In those randomised to right-side HC the mean duration of disease was 6.2 years (median 6.5, range 1.0-10.0). **Severity of eczema** In the right-side alclometasone group 5 were stable, 10 slowly worsening, and 1 rapidly worsening. In the right-side HC group 6 were stable, 10 slowly worsening, and 2 rapidly worsening. Pretherapy eczema was moderately severe in 22/34 participants and severe in 12/34 participants. The severity of erythema, induration, and pruritus was equal at each pair of test sites in all 34 children. **Filaggrin mutation status** Not reported **Number of withdrawals** 3 of 37 did not return after the initial visit and were not included. 2 received antibiotics during the trial and were evaluated for safety but not comparative efficacy. 8 children did not return for follow-up visits "at the weekly interval" but were still included. **Notes** 12 of 34, 6 per group, had been treated with ≥ 1 treatments previously; 11 had received HC lotions or liniments, 3 with emollient creams or ointments. 1 participant also received antihistamine for urticaria for 4 days in the 1st week of treatment.
Interventions	**Run-in details**

Kuokkanen 1987 *(Continued)*

NA

Groups

- HC 1% ointment (unspecified); applied at 12 h intervals (i.e. twice daily). Participants were told to apply enough to cover the test site and to gently massage in the medications. They were also instructed to wash their hands carefully between applications. Nothing other than trial treatments could be applied to the test sites. Treatment continued for 3 weeks. Concurrent treatment: none
- Alclometasone dipropionate 0.05% ointment (unspecified); applied at 12 h intervals (i.e. twice daily). Participants were told to apply enough to cover the test site and to gently massage in the medications. They were also instructed to wash their hands carefully between applications. Nothing other than trial treatments could be applied to the test sites. Treatment continued for 3 weeks. Concurrent treatment: none

Adherence

The 1st application was supervised. The 2 tubes of medication dispensed each week were returned after the week of treatment (by the caregiver of the participant), at which time the parents or guardians were questioned to determine whether medications were applied as directed.

Co-interventions

Ointments could be applied to sites other than the test sites but applications to the left and right sides was to be maintained. Medications were to be applied at least 3 h before the trial visits. Treatment with systemic or other topical steroids, medicated shampoos, tar baths, UV light, or grenz rays was prohibited. Concomitant therapy for conditions other than eczema was acceptable, provided that it remained constant throughout the trial. Baths and showers were permitted only before or at least 8 h after application and the children's exposure to sun was to be minimised.

Notes

"When lesions cleared in less than three weeks, application of the trial medication was to continue but in an area of only 3 cm^2 within each test site."

Outcomes	• Severity of erythema, induration, and pruritus at paired test sites was rated on the 4-point scale (0 absent - 3 severe) and summed at baseline and weeks 1, 2, and 3.* • Adverse events were looked for by careful examination and questioning of caregivers at assumed at each visit (week 1, 2 and 3).* • Visual assessment of test site for signs of cutaneous atrophy; skin thinning, shininess, striae, bruising, telangiectasia, loss of hair, elasticity and normal skin markings and wasting of muscle and subcutaneous fat. Skin thinning, shininess, and striae was graded on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). The presence or absence of remaining signs were simply noted. Repeated measurements were taken by the same physician at baseline and weeks 1, 2, and 3.* • Telangiectasia evaluated at a 3 cm^2 area within each test site using a 2 x magnifying lens. Visible blood vessels were counted at baseline and weeks 1, 2, and 3.* • Comparative efficacy (equivalent, alclometasone results better or HC results better) at weeks 1, 2, and 3 • IGA (cleared, with 100% clearance of monitored signs and symptoms except for residual discolouration; markedly improved, with 75% to < 100% clearance of monitored signs and symptoms; moderately improved, with 50% to < 75% clearance of monitored signs and symptoms; slightly improved, with < 50% clearance of monitored signs and symptoms; unchanged; or exacerbated). These evaluations were performed by the same physician throughout the trial (only a narrative comment was reported in the paper).* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared

Kuokkanen 1987 *(Continued)*

Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised", "specified by a randomisation code" Comment: no information regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized" "Each child enrolled was sequentially assigned a number corresponding to the number on the boxes of the study medications." Comment: it was unclear whether the personnel allocating the medication knew what was in the boxes and so they could have potentially influenced who received what treatment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" "Each box contained one 45-gm tube of each study medication, the tubes color-coded red and blue and labelled "right side" and "left side" respectively as specified by a randomisation code." Comment: the participants are likely to have been blinded however there is no information as to whether the other party that was blinded was the outcome assessor or the personnel looking after the participant.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: it is not clear which of the personnel were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 37 children enrolled, three did not return after the initial visit and another two received antibiotics during the study. Although eight children did not return for follow-up visits at the designated weekly interval, these children were included in the evaluation of efficacy. Thus 34 and 32 children could be evaluated for the safety and efficacy, respectively, of the two ointments." Comment: all participants seem to be accounted for however, a fairly large proportion of participants were not included in the final results; 5/37 for efficacy and 3/37 for safety. As both participants were applying both creams it is unlikely that a problem or a preference for 1 particular cream would be the reason why a participant dropped out of the trial and so this unlikely to be a source of bias.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available.
Other bias	Low risk	Comment: no other source of bias identified

Lassus 1983

Study characteristics

Methods	**Trial design** Double-blind, randomised, parallel-group trial **Trial registration number** Not reported **Setting**

Lassus 1983 *(Continued)*

Assumed to be secondary care in Finland according to the affiliation of the author

Date trial conducted

Not reported

Duration of trial participation

2 weeks

Additional design details

None

Inclusion criteria

- Patients with an established diagnosis of AD for at least 1 month, stable and worsening over the preceding week
- White children
- Aged 5-11 years
- Each of the following 3 signs present: erythema, induration, pruritus; summed severity score of ≥ 6 when each sign was graded 0 = absent to 3 = severe

Exclusion criteria

Not reported

Notes

None

Participants

Total number randomised

40; 20 randomised to each group

Age

Mean age was 7.5 years in the alclometasone group (median 7.0) and 8.4 in the HC butyrate group (median 8.0)

Sex

There were 7 male and 13 female participants in the alclometasone group, and 10 male and 10 female in the HC butyrate group

Race/ethnicity

All were white.

Duration of eczema

In both groups mean disease duration was 5.5 years; 12 participants in the alclometasone group had been diagnosed 1-5 years, 8 had been diagnosed 6-10 years; 7 participants in the HC butyrate group had been diagnosed 1-5 years, 13 had been diagnosed 6-10 years.

Severity of eczema

Mean TSS pre-treatment in the alclometasone group was 7.70; mean in the HC butyrate group was 8.05.

Filaggrin mutation status

Not reported

Number of withdrawals

There were no withdrawals and all participants were included in the analyses of efficacy and safety.

Lassus 1983 *(Continued)*

	Notes "The two treatment groups did not differ significantly in age, sex, race, duration of disease, or per cent of body involvement."
Interventions	**Run-in details** NA **Groups** • Alclometasone dipropionate 0.05% cream (proprietary: Vaderm, Schering, USA); applied twice daily in a thin layer to areas on the face, neck, trunk, and upper and lower extremities, for 2 weeks. Palms, soles, and scalp were not included. Medication was not to be applied within 3 h of a trial visit. Concurrent treatment: not reported • HC 17-butyrate 0.1% cream (proprietary: Locoid, Brocades UK); applied twice daily in a thin layer to areas on the face, neck, trunk, and upper and lower extremities, for 2 weeks. Palms, soles, and scalp were not included. Medication was not to be applied within 3 h of a trial visit. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** None
Outcomes	• Participant-reported and clinically observed adverse experiences at weeks 1 and 2 (assumed as not stated)* • Disease signs (erythema, induration, pruritus) in pre-selected target areas scored 0 = absent to 3 = severe, reported separately and summed with a percentage improvement also calculated at baseline, week 1 and week 2 • IGA of improvement at treated areas (cleared = 100% clearance of signs and symptoms except for residual discolouration, marked improvement = 76%-100% clearance, moderate improvement = 50%-75% clearance, slight improvement = < 50% clearance, no change, exacerbation) at weeks 1 and 2.* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" Comment: no information provided about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given

Lassus 1983 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no information about how participants and personnel were blinded, or which personnel, and there is only 1 author listed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no information about how personnel were blinded, or which personnel, and there is only 1 author listed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "no patients dropped out of the study and all were included in the efficacy and safety analyses." Comment: all participants were accounted for in the results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias detected

Lasthein Andersen 1988

Study characteristics

Methods

Trial design

Randomised, double-blind, left-right (half-sided), multicentre trial

Trial registration number

Not reported

Setting

Multicentre; 3 dermatological centres in Denmark

Date trial conducted

January 1986-January 1987

Duration of trial participation

4 weeks

Additional design details

None

Inclusion criteria

- Children with dry bilateral symmetrical AD

Exclusion criteria

- Primary bacterial or viral skin lesions such as erysipelas, tuberculosis, syphilis, varicella vaccinia, herpes simplex or herpes zoster
- Obviously secondarily infected lesion(s)
- Concomitant use of systemic steroids
- Malignant disease
- Use of potent corticosteroids within 2 weeks of the trial (this restriction did not apply to HC 1% preparation which could be used up to entry into the trial)

Lasthein Andersen 1988 *(Continued)*

Notes

The flare was undefined.

Participants	**Total number randomised** 96 participants (but treatment randomised to sides of the body) = 192 sides **Age** 2 months-13 years (mean 4.9, SD ± 3.8) **Sex** 44 male and 51 female (and another unspecified) **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Overall severity of lesions (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe) as designed by Fredriksson, Lassus and Salde: baseline severity was mean 1.7 (SD 0.6), Uniderm ointment = 1.7 (0.6) **Filaggrin mutation status** Not reported **Number of withdrawals** 1 participant used Uniderm ointment only during the last 14 days of the trial - therefore, the results after 4 weeks' therapy were disregarded in the analyses. Also, 1 participant stopped treatment after 3 days because of deterioration of the disease, on Uniderm side and then the Mildison side. None of the analyses include all 96 participants but no additional reasons are given as to why. **Notes** None
Interventions	**Run-in details** None **Groups** • HC 1% fatty cream (proprietary: Mildison lipocream); applied to 1 side of the body twice daily until resolution of lesions occurred or for a maximum of 4 weeks. The person applying the medication was instructed to wash their hands between applications to avoid cross-contamination. No occlusive dressings used. Concurrent treatment: none • HC 1% ointment (proprietary: Uniderm); applied to the other side of the body twice daily until resolution of lesions occurred or for a maximum of 4 weeks. The person applying the medication was instructed to wash their hands between applications to avoid cross-contamination. No occlusive dressings used. Concurrent treatment: none **Adherence** Not reported **Co-interventions** None

Lasthein Andersen 1988 *(Continued)*

	Notes None
Outcomes	• Overall severity of symptoms of AD graded on both sides of the body using a 5-point rating scale (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe designed by Fredriksson, Lassus and Salde) at baseline, week 2, week 4 • Side effects/adverse reactions at up to week 4* • Participants' opinion on cosmetic acceptability at week 2, week 4 (or at complete clearance of skin lesions) • Participant's (or parent's/guardian's) preferences with respect to therapeutic efficacy at week 2, week 4 (or at complete clearance of skin lesions)* • Investigator preferences with respect to therapeutic efficacy at week 2, week 4 (or at complete clearance of skin lesions) • Overall improvement of skin lesions on both sides of the body assessed by the investigator using 5 categories (+4 = clearance, +3 = considerable improvement, +2 = definite improvement, +1 = minimal improvement, 0 = no changes, and −1 = worse) at end of treatment (up to week 4)* *denotes relevance to this review
Funding source	Not reported
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "In accordance with a double-blind randomized code, patients were given two sets of five tubes. One set was marked 'LEFT' and the second marked 'RIGHT'." Comment: no details of randomisation method
Allocation concealment (selection bias)	Unclear risk	Comment: no details reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In accordance with a double-blind randomized code, patients were given two sets of five tubes. One set was marked 'LEFT' and the second marked 'RIGHT'. One set of tubes contained Mildison lipocream 30g per tube and the other Uniderm ointment 30 g per tube"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the outcomes were either assessed by the patient (or parent/guardian) or by the trial investigator and both were blinded to trial group.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The total number of patients with data suitable for statistical analysis was 96" Comment: however, none of the outcome data presented includes results for all 96 participants (ranging from 4-8 participants missing) and there is no explanation why.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol so unable to assess
Other bias	Low risk	Comment: no other biases detected

Lebrun-Vignes 2000

Study characteristics	
Methods	**Trial design** Randomised, double-blind, parallel-group trial **Trial registration number** Not reported **Setting** Department of Pediatric Dermatology of the Hôpital de Bordeaux, France **Date trial conducted** October 1989-February 1991 **Duration of trial participation** 30 days (15 days treatment, 15 days follow-up). However, the results state that "in the desonide group 2 participants required 20 days of treatment and 1 required 25 days. 2 participants in the betamethasone dipropionate group required 20 days. However, the mean duration was not different between the 2 groups. "The mean duration of treatment (days) in the Desonide group was 16.43 S.D. 3.06 and in the betamethasone dipropionate group mean 15.21 S.D. 1.48." **Additional design details** None **Inclusion criteria** Children < 8 years admitted to hospital with an episode of severe, non-infected AD **Exclusion criteria** • Unconfirmed diagnosis • Bacterial, viral, or fungal superinfection • History of allergy to desonide or betamethasone dipropionate • Systemic treatment with corticosteroids within the preceding month • Topical treatment with corticosteroids within the preceding 2 weeks **Notes** None
Participants	**Total number randomised** 29 participants; 15 in the desonide (mild) and 14 in the betamethasone dipropionate (potent) group **Age** Mean age in the desonide (mild) group was 13.80 months ± SD 13.81; mean age in the betamethasone dipropionate (potent) group was 14.29 ± 9.24. **Sex** There were 9 male and 6 female participants in the desonide (mild) group. There were 6 male and 8 female participants in the betamethasone dipropionate (potent) group. **Race/ethnicity**

Lebrun-Vignes 2000 *(Continued)*

Not reported

Duration of eczema

Not reported

Severity of eczema

Mean percentage BSA involved in the desonide (mild) group was 44.20 ± SD 20.15; mean percentage BSA in the betamethasone dipropionate (potent) group was 36.86 ± 26.22. Mean lesion score in the desonide (mild) group was 6.87 ± SD 3.14; mean lesion score in the betamethasone dipropionate (potent) group was 7.57 ± 2.28. Assessed for a representative skin area from 0 = absence of improvement to 3 = considerable improvement for erythema, pruritus, discharge, excoriation, and lichenification (max = 15).

Filaggrin mutation status

Not reported

Number of withdrawals

1 participant in the desonide (mild) group was lost to follow-up after the 5th day. The paper also states that "some information was not available," but there is no further information given. 2 participants in the desonide (mild) group required 20 days of treatment and 1 required 25 days; 2 participants in the betamethasone dipropionate (potent) group required 20 days. However, mean duration of treatment did not differ.

Notes

"There were no differences in mean age, gender distribution, weight, height, pre-treatment plasma cortisol levels, IgE level, lesion score or initial BSA involved." 2 participants did not satisfy all inclusion criteria but were still included: 1 received topical HC butyrate until 48 h before, the second was treated with oral betamethasone until 10 days before. These participants (both in the desonide (mild) group) were included because their cortisol had not decreased. The paper states that in 19/29 participants, treatment protocol was maintained; 5 received treatment for longer, 1 participant dropped out, 2 did not meet inclusion criteria but were included anyway. This totals 8 participants, no mention of why the protocol wasn't maintained in the other 2 participants.

Interventions

Run-in details

NA

Groups

- Desonide 0.1% micronised cream (proprietary: Locatop, Laboratoire Pierre Fabre Dermatologie); applied twice daily without occlusion whilst admitted for 5 days, then once daily until day 7, then once on alternate days until day 15 Concurrent treatment: none
- Betamethasone dipropionate 0.05% cream (proprietary: Diprosone, Schering-Plough); applied twice daily without occlusion whilst admitted for 5 days, then once daily until day 7, then once on alternate days until day 15. Concurrent treatment: none

Adherence

Number of tubes used was counted; the mean number of 13 g tubes used over 15 days was 2 and was the same in both groups. Weight in grams used was also reported: the desonide (mild) group used a mean of 30.4 g ± SD 16.4 and the betamethasone dipropionate (potent) group used 26.3 ± SD 10 (P = 0.71 between groups). Compliance was stated to have been good.

Co-interventions

All participants were asked to use mild soap, emollient, and antiseptic foam solution. If necessary, participants could also receive antihistamines, sedatives or antibiotics.

Notes

Lebrun-Vignes 2000 *(Continued)*

	None
Outcomes	• Percentage BSA involved (Wallace's rule of 9s) at baseline and days 5, and 20 • Clinical side effects and local and systemic tolerance assessed by investigator and parents/caregivers at baseline and days 5, 20, and 30* • Plasma cortisol levels (samples taken between 8 am and 9 am, measured by competitive binding assays) at baseline and days 5, 20, and 30* • Number of relapses at day 30* • Lesion score (most representative area) judged by a physician as 0 = absence of improvement, 1 = slight improvement, 2 = moderate improvement, or 3 = considerable improvement for the following signs: erythema, pruritus, discharge, excoriation, and lichenification (max score 15) at baseline and days 5, and 20* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared, however 1 of the authors was affiliated to Laboratoires Pierre Fabre.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: no information given about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind," "the two products were identical in appearance" Comment: the 2nd quote implies the participants were blinded, however it is unclear which personnel were blinded, or how.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: it is unclear which personnel were blinded, or how.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: by day 30, 2 participants are missing from the betamethasone group and 1 participant is missing from the desonide group. The participant in the desonide group is mentioned as being lost to follow-up after day 5, however, there is no explanation why 2 participants were missing from the betamethasone group. Although this is a small number of participants there were only 14 participants originally in this group and so it is unclear whether this could introduce bias to the results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Unclear risk	Quote: "Patients included in the study satisfied all the inclusion criteria with the exception of two patients, one of whom received topical hydrocortisone butyrate (Locoid® cream, 0.1 p. 100) until 48 hours before inclusion, and a second who was treated with oral betamethasone until 10 days before inclusion. These two patients, who were randomized into the desonide group, were included in the analysis because their baseline levels of plasma cortisol had not decreased."

Lebrun-Vignes 2000 *(Continued)*

	Comment: there is general concern about how the investigators adhered to their stated methods. In addition, participants were permitted to take antihistamines, sedatives or antibiotics if necessary, however, there are no data presented on how many required these additional interventions in each group.

Lebwohl 1999

Study characteristics	
Methods	**Trial design** Multicentre, randomised, evaluator-blind, parallel-group trial **Trial registration number** Not reported **Setting** 10 centres in the USA, assumed to be secondary care as the primary author is a dermatologist **Date trial conducted** Not reported **Duration of trial participation** 22 days **Additional design details** None **Inclusion criteria** • Aged 2-12 years • Children had moderate-severe AD • At least 15% total body surface involvement, excluding the face and forehead, with the current exacerbation of AD, with a target area of at least 20 cm^2. • A six-sign/symptom severity score ≥ 8 and ≤ 18 for the target area (erythema, induration/lichenification, scaling/crusting, exudation, excoriation, and pruritus was graded on the following scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe). • A severity score of ≥ 2 required for erythema and for 1 other sign **Exclusion criteria** Not reported **Notes** At enrolment, a target area of dermatitis (not the face or forehead) of at least 20 cm^2 was selected by the investigator for specific evaluation of the effects of treatment on disease signs and symptoms. Areas outside the target area were also treated with the trial medications and evaluated by the investigator in the global response to treatment (see outcomes). No other therapies for AD were permitted.
Participants	**Total number randomised** 109 randomised to mometasone furoate; 110 randomised to HC valerate **Age**

Lebwohl 1999 *(Continued)*

Not reported

Sex

Not reported

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Not reported

Filaggrin mutation status

Not reported

Number of withdrawals

43 discontinued the trial early: clearance of signs and symptoms (18 in the mometasone furoate group, 9 in the HC valerate group); treatment failure (0 in mometasone furoate group, 1 in HC valerate group); non-compliance (3 in mometasone furoate group, 4 in HC valerate group); failed to attend for assessment (2 in mometasone furoate group, 5 in HC valerate group); not eligible for enrolment (1 in mometasone furoate group).

Notes

Does not explicitly say that this is the number presented is the number randomised. States 43 participants in the "safety population" discontinued early.

Interventions	**Run-in details** Participants had failed to respond to at least 7 consecutive days of topical HC treatment ending within a week of enrolment of this trial. **Groups** • HC valerate 0.2% cream (unspecified); twice daily. Concurrent treatment: none • Mometasone furoate 0.1% cream (unspecified); once daily. Concurrent treatment: none **Adherence** Not reported **Co-interventions** No other therapies for AD were permitted. **Notes** None
Outcomes	• Severity score of 6 signs and symptoms present in the target area (erythema, induration/lichenification, scaling/crusting, exudation, excoriation, and pruritus graded on the following scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe) at days 4, 8, 15, and 21 • IGA (cleared = 100% improvement; excellent = 75%–99% improvement; good = 50%–74% improvement; fair = 25%–49% improvement; poor < 25% improvement; exacerbation = flare-up at treatment site) at days 4, 8, 15, and 21* • Treatment-related atrophy at up to day 22* • Application site reactions at up to day 22*

Lebwohl 1999 *(Continued)*

- Adverse events at up to day 22 (judged as "probably, possibly or related to treatment")*

*denotes relevance to this review

Funding source	The trial was "supported by a grant from Schering Plough Inc."
Declarations of interest	None declared
Notes	Outcomes also reported at an "endpoint" but it is unclear as to when this endpoint was judged and which participants were included in this analysis, so this was not extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized'. Comment: no information regarding how participants were randomised
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided on how this was done
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "evaluator-blind'. Comment: implies that participants and all other personnel were not blinded. There is also no mention of a placebo treatment being used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "evaluator-blind". Comment: this was probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: results are not reported for all participants and it is unclear as to when participants dropped out. The number of participants at day 4 is 83 in the mometasone group and 81 in the HC group. Given that the initial numbers in the mometasone group were 109 and in the HC group were 110 this is a large drop out.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available and very little information is provided in the methods section.
Other bias	Low risk	Comment: no other sources of bias were found.

Liu 2018

Study characteristics

Methods	**Trial design** Open-label, multi-phase, RCT **Trial registration number** NCT01915914, EudraCT 2017-001574-42 **Setting** 4 outpatient centres in China **Date trial conducted**

Liu 2018 *(Continued)*

Start date for recruitment was 23 December 2013, global end of trial date was 15 February 2015.

Duration of trial participation

The trial was conducted over a period of 37 weeks in 4 phases:

- Phase 1: screening phase which lasted ≤ 7 days
- Phase 2: acute phase, participants received TCS for up to 4 weeks
- Phase 3: maintenance phase, participants received emollient plus steroid or just emollient for up to 20 weeks
- Phase 4: follow-up phase, participants received emollient only twice daily for up to 12 weeks

Additional design details

None

Inclusion criteria

- Aged 1–17 years
- Clinically diagnosed with AD according to The UK working party's diagnostic criteria for AD (Williams 1994).
- Mild-moderate severity of AD on the head/neck, trunk, upper limbs, or lower limbs and PSGA scores of 2-3
- Patients enrolled in the maintenance phase of the trial needed to have achieved treatment success after receiving fluticasone propionate 0.05% cream twice daily up to 4 weeks in the acute phase of the trial.

Exclusion criteria

- Having dermatitis of only the face, feet or hands.
- Having AD which affected > 10% of the total BSA.
- Diagnosed with contact dermatitis at predilection sites of AD.
- The presence of atrophy, telangiectasia, and/or extensive scarring lesions in the area or areas to be treated.
- Received topical therapies including but not limited to TCIs (topical tacrolimus or topical pimecrolimus), corticosteroids, or antihistamines within 14 days prior to screening.
- Received nonsteroidal immunosuppressants, ultraviolet light treatments, or systemic corticosteroids within 4 weeks prior to screening.
- Being pregnant or breast-feeding.
- History of immunocompromised disease or malignancy.
- Presence of open skin infections.
- Patients were excluded from the maintenance phase if they had accepted any other topical therapy other than fluticasone propionate 0.05% cream and emollients during the acute phase and/or if they had developed any active skin infections.

Notes

None

Participants

Total number randomised

107 entered the maintenance phase; 54 were randomised to the TCS arm and 53 were randomised to emollient alone.

Age

Emollient plus TCS: mean (SD) 5.0 (2.8); emollient alone: mean (SD) 4.9 (2.4)

Sex

Liu 2018 *(Continued)*

Emollient plus TCS: 23 female (42.6%) 31 male (57.4%); emollient alone: 30 female (56.6%) 23 male (43.4%)

Race/ethnicity

Emollient plus TCS: Chinese n = 53 (98.1%), other n = 1 (1.9%). Emollient alone: Chinese n = 50 (94.3%), other n = 3 (5.7%)

Duration of eczema

Not reported

Severity of eczema

Participants were included on the basis of mild to moderate severity disease. Baseline mean PSGA scores at beginning of maintenance phase (Mean (SD)): emollient plus TCS 0.3 (0.44), emollient alone 0.4 (0.48).

Filaggrin mutation status

Not reported

Number of withdrawals

In the maintenance phase: emollient plus TCS, 9 participants were excluded (AD relapse n = 3, withdrew consent n = 1, lost to follow-up n = 4, other n = 1). Emollient alone, 32 participants were excluded (AD relapse n = 30, withdrew consent n = 1, lost to follow-up n = 1).

Notes

None

Interventions

Run-in details

In the acute phase, participants continued the treatment up until they achieved treatment success PSGA ≤ 1 with an improvement of ≥ 2, the 6-point scale of PSGA score (range from 0-5 where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) or they had received the treatment for a maximum 4 weeks (those that did not achieve treatment success within the 4 weeks did not enter the next phase). 12 participants did not complete this phase (reasons are provided in EudraCT report). Investigator assessed Eczema Area, AD Severity, Visual Skin Assessment, physical examinations and vital sign measurements were conducted in the acute phase. The efficacy and safety in the acute phase was assessed every 2 weeks up to 4 weeks or until treatment success. 107 of 123 participants achieved treatment success during the acute phase.

Groups

- Emollient was applied twice daily to affected and unaffected areas during the maintenance and follow-up phases. Concurrent treatment: none
- Fluticasone propionate 0.05% cream; applied twice weekly by the participant or their caregiver following the finger-tip unit rule*. The TCS was applied to affected sites (acute phase) and to all healed sites (maintenance phase) and to any newly occurring sites (acute and maintenance phase). Concurrent treatment: emollient was applied twice daily to affected and unaffected areas, before application of fluticasone propionate 0.05% cream if this was also to be applied, during the maintenance and follow-up phases.

*defined as: the amount of ointment dispensed from a tube with a 5 mm nozzle and measuring from the distal skin-crease to the tip of the index finger (approx 0.5 g), which is an adequate amount for application to 2 adult palm areas (approximately 2% of an adult BSA)

Adherence

Mean treatment compliance in the TCS arm was 97.3% (98.4% with the TCS, 97.2% with the emollient lotion) and for emollient alone was 96.8%. No details provided on how this was measured.

Liu 2018 *(Continued)*

Co-interventions

None

Notes

The emollient lotion that was used was Physiogel lotion (a hypoallergenic, oil-in-water emulsion containing oils, Shea butter, glycerin, squalane, hydrogenated lecithin and ceramide; manufacturer: Stiefel Laboratories Inc., Research Triangle Park, NC, USA).

Outcomes	• PSGA score. The 6-point scale of PSGA score ranges from 0-5, where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe
	• Relapse was defined as exacerbation of AD, which resulted in a ≥ 2-point difference in the PSGA score compared with the PSGA score of a participant's treatment success. There was no information provided about how often participants were monitored for relapse or what participants were instructed to do if they thought they had a relapse. The following information was reported:
	  ○ time to 1st relapse during the maintenance phase calculated using days from start of maintenance phase week 0 to time of relapse (up to 20 weeks)*
	  ○ median time to 1st relapse (days from start of maintenance phase week 0 to end of follow-up, up to 32 weeks)
	  ○ number of participants with recurring relapse (from start of maintenance phase at week 0 up to 20 weeks, and from start of follow-up phase at week 20 to up to week 32)*
	• PGA (5-point rating scale where 0 = clear and 4 = severe): not mentioned in methods or in protocol. At least end of maintenance (up to week 20), end of follow-up phase (up to week 32)*
	• Non-serious adverse events: information on the duration, severity, causality, actions taken, and outcomes of adverse events was collected at from week −4 (beginning of acute phase) up to week 32 (end of follow-up)*
	• Serious adverse events: information on the duration, severity, causality, actions taken, and outcomes of adverse events was collected at from week −4 (beginning of acute phase) up to week 32 (end of follow-up)*
	• Change from baseline in cutaneous atrophy sign score, epidermal thickening/lichenification sign score and abnormal pigmentation score using VAS. The Investigator evaluated and scored the signs of cutaneous atrophy (CA), epidermal thickening/lichenification (ET/L) and abnormal pigmentation (AP) using the VAS (ranging from 0-30, higher values represent a worse outcome) based on their subjective judgment at "throughout the whole study" though its not clear at which exact time points (at least week −4, week 0, end of maintenance week 20 and follow-up week 32)*
	• Clinical laboratory tests, vital signs and physical examinations not reported*
	• Quality of life: using DLQI for participants over 16 years old; CDLQI for children 4-16 years old; and IDQOL for children < 4 years old at baseline (week 0 end of acute phase), end of maintenance (up to week 20), end of follow-up phase (up to week 32)
	• Assessment of preference of skin emollients from those used in the past; a questionnaire to rate the emollients (5-point scale where 5 = "liked the best", to 1 = "liked the least", NA = does not apply to me)) and their qualities at week 32 or at withdrawal.
	• Overall severity assessments for erythema, pruritus and population/induration/oedema at unclear, at least end of maintenance (up to week 20), end of follow-up phase (up to week 32)
	• Total eczema area: not mentioned in methods or in protocol at unclear, at least end of maintenance (up to week 20), end of follow-up phase (up to week 32)
	• Treatment compliance: no information as to how this was measured.
	
	*denotes relevance to this review

Funding source	The trial was funded by GlaxoSmithKline (GSK) manufacturers of fluticasone propionate cream 0.05%.
Declarations of interest	The trial authors are employees of GSK and own stocks/shares in GSK.
Notes	None

Risk of bias

Liu 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized' Comment: no information provided about how this was done
Allocation concealment (selection bias)	Unclear risk	Comment: no information as to how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Not blinded" "open label" Comment: participants and personnel were aware of which treatment they were receiving.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information as to whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The intent-to-treat (ITT) population was defined as all patients that were randomized into the maintenance phase. The ITT population was used for all efficacy analyses. The per-protocol (PP) population comprised all ITT patients who did not violate any major protocol requirements. If the PP population was more than 10% different from the ITT population, it was planned for a sensitivity analysis to be carried out using the PP population to assess efficacy." Comment: ITT analysis was carried out. The number of participants who were lost to follow-up or withdrew consent was low in both groups.
Selective reporting (reporting bias)	Unclear risk	Comment: primary outcomes reported as stated. Some additional secondary outcomes (total eczema area, PGA, overall severity assessments for erythema, pruritus and population/induration/edema) not stated in the protocol are presented in the paper.
Other bias	Low risk	Comment: did not detect any other sources of bias

Lucky 1997

Study characteristics	
Methods	**Trial design** Randomised, parallel, open-label trial **Trial registration number** Not reported **Setting** Assumed to be an outpatient setting in the USA from the affiliations list **Date trial conducted** Not reported **Duration of trial participation** 4 weeks

Lucky 1997 *(Continued)*

Additional design details

None

Inclusion criteria

- Children with a minimum of 20% of their BSA affected by AD.

Exclusion criteria

Not reported

Notes

None

Participants	**Total number randomised** 20; 10 to each group **Age** Mean age was 4.7 in the desonide (moderate group) (range 11 months-11 years, 11 months); mean age was 2.6 years in the mild (HC) group (13 months-8 years, 4 months). There was no statistically significant difference in the mean age of each group (P = 0.14). **Sex** There were 6 male, 4 female participants in the desonide (moderate group) and 7 male, 3 female participants in the mild (HC) group. **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** The average BSA was 38.1% in the desonide (moderate group) (range 20%-70%) and 37.1% in the mild (HC) group (20%-80%). There was no statistically significant difference between the 2 groups (P = 0.92). **Filaggrin mutation status** Not reported **Number of withdrawals** 5 participants did not complete the trial; 3/10 in the desonide (moderate group) and 2/10 in the mild (HC) group. **Notes** None
Interventions	**Run-in details** NA **Groups** • Hydrocortisone 2.5% ointment (unspecified); participants or their caregivers were instructed to apply the ointment twice daily. Patients were asked to use the same amount of ointment for each application. Concurrent treatment: none

Lucky 1997 *(Continued)*

	• Desonide 0.05% ointment (proprietary: DesOwen, Galderma Laboratories, Inc.); participants or their caregivers were instructed to apply the ointment twice daily. Patients were asked to use the same amount of ointment for each application. Concurrent treatment: none **Adherence** Mean quantity of treatment applied was 3 g/day **Co-interventions** Not reported **Notes** None
Outcomes	• Serum cortisol values 30 and 60 min after stimulation with IV ACTH (Cortrosyn) at baseline and day 28* • Baseline morning serum cortisol samples (obtained before 9 am) at baseline and days 14 and 28.* Notes: the normal range for baseline morning cortisol in this group was 2-25 µg/100 mL. • Adverse reactions (e.g. irritation, contact dermatitis, general malaise) at days 14 and 28 (assumed not stated, but this is when blood samples were taken)* *denotes relevance to this review
Funding source	None stated, although it was stated that all laboratory trials were performed by SmithKline Beecham, Clinical Laboratories.
Declarations of interest	None declared, however several trial authors are affiliated to Galderma Laboratories, Inc, Fort Worth, Texas, who produce the desonide ointment used.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" Comment: no information given about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label study" Comment: participants and personnel are likely to be aware of the treatment received by participants
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label study" Comment: personnel are likely to be aware of the treatment received by participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Fifteen of the twenty subjects, seven of the desonide and eight of the hydrocortisone group, completed the entire 4-week study with baseline and day 28 cortisol stimulation." Comment: 25% of participants dropped out with no reasons given and it is not clear how missing data were dealt with. They do not appear to have contributed any data to the final analysis.
Selective reporting (reporting bias)	High risk	Comment: no protocol is available and even though adverse events were said to have been collected they are not reported within the paper.

Lucky 1997 *(Continued)*

Other bias	Low risk	Comment: no other sources of bias detected

Mahrle 1989

Study characteristics

Methods

Trial design

Randomised, multicentre, double-blind, half-side trial

Trial registration number

Not reported

Setting

Multiple centres in Germany

Date trial conducted

Not reported

Duration of trial participation

21 days

Additional design details

None

Inclusion criteria

- Patients with acute or chronic eczema (duration 1-18 weeks)
- Skin changes had not been treated with glucocorticoids for 1 week prior to therapy

Exclusion criteria

Not reported

Notes

None

Participants

Total number randomised

44

Age

Average 33 years (range 2-78)

Sex

22 male, 22 female

Race/ethnicity

Not reported

Duration of eczema

Participants were included based on duration of 1-18 weeks

Mahrle 1989 *(Continued)*

	Severity of eczema On average moderate-severe disease in all treatment groups. The average severity across all 11 clinical signs was 2.48 ± 1.21 (notated S-bar; assumed to be SD) for the 1-day interval group, 2.74 ± 1.27 for the 2-day interval group, and 2.52 ± 1.37 for the 3-day interval group. **Filaggrin mutation status** Not reported **Number of withdrawals** 2 participants; 1 due to exacerbation of eczema (after 9 days), 1 participant was discharged prematurely from the clinic and did not present for further examination. It was unclear to which comparisons these belonged. **Notes** "Initial clinical findings" are given in table 1 but it is not clear whether this means baseline characteristics or severity after treatment has been initiated (the values look quite low) and table 1 is not referred to in the text, therefore this information was not extracted.
Interventions	**Run-in details** NA **Groups** **A:** (everyday): fluprednidene-21-acetate 0.1% cream (proprietary: Decoderm, Merck); TCS applied twice daily continuously for 3 weeks. Concurrent treatment: none **B**: (1-day interval): fluprednidene-21-acetate 0.1% cream (proprietary: Decoderm and Vobaderm base cream); TCS (assumed applied twice daily) for 3 weeks with 1-day intervals when base cream was applied. Concurrent treatment: none **C:** (2-day interval): fluprednidene-21-acetate 0.1% cream (proprietary: Decoderm and Vobaderm base cream); TCS (assumed applied twice daily) for 3 weeks with 2-day intervals when base cream was applied. Concurrent treatment: none **D:** (3-day interval): fluprednidene-21-acetate 0.1% cream (proprietary: Decoderm and Vobaderm base cream); TCS (assumed applied twice daily) for 3 weeks with 3-day intervals when base cream was applied. Concurrent treatment: none **Adherence** Not reported, although glucocorticoid consumption per half-side was estimated by weighing. **Co-interventions** If participants had other diseases they were not treated with glucocorticoids or UVB therapy. **Notes** Fluprednidene cream referred to in the text as "ambiphilic ointment" and cream.
Outcomes	• Healing of 11 clinical signs and symptoms (erythema, oedema, vesicles, oozing, crusting, papules, scaling, fissures, excoriation, lichenification and itching), scored individually using a 5-valued rating scale (0 = none, 1 = light, 2 = moderate, 3 = pronounced, 4 = severe) and also as a total score. Data were presented as a relative reduction from baseline at day 7, then approximately every 4 days until day 21.* *denotes relevance to this review
Funding source	None stated

Mahrle 1989 *(Continued)*

Declarations of interest	1 of the trial authors is linked to Hermal, Kurt Herrmann, which is a division of Merck.
Notes	Translated from German paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". Comment: no details about how the randomisation was done
Allocation concealment (selection bias)	Unclear risk	Comment: no information about whether allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no information as to how the trial was double-blinded, though participants applied a base cream at the times when they were applying steroid to the other side of the body. It was not clear whether participants were given tubes labelled with the time of application rather than what was contained within the tube.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind". Comment: no details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 participants withdrew; it was unclear whether the data from these participants was included or excluded, however it is unlikely that this would introduce bias as this concerned only a small number of participants.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available and only 1 outcome is mentioned in the methods so it is unclear as to whether any other outcomes were measured. Skin atrophy was measured in healthy volunteers as part of the trial and it is strange that the authors did not mention any information about whether or not skin atrophy was seen in the participants using TCS in the other part of the trial.
Other bias	Low risk	Comment: no further sources of bias identified

Mali 1976

Study characteristics

Methods	**Trial design** Double-blind, randomised **Trial registration number** Not reported **Setting** Private dermatology clinic, assumed to be in Nijmegen, The Netherlands, from the affiliation of the author. **Date trial conducted** Not reported

Mali 1976 *(Continued)*

	Duration of trial participation 3 weeks **Additional design details** None **Inclusion criteria** Patients being treated for the 1st time at a private dermatology clinic for psoriasis and other steroid-responsive dermatoses. **Exclusion criteria** Not reported **Notes** Atopic dermatitis data presented separately
Participants	**Total number randomised** 66 initially randomised, however only 50 were analysed, of whom 16 were AD patients. 7 received betamethasone dipropionate (potent) steroid and 9 received flumethasone (mild) steroid. **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Participants were treated in a private clinic for the 1st time. **Filaggrin mutation status** Not reported **Number of withdrawals** 16 cases were rejected of an initial 66 participants with a mixture of steroid-responsive dermatoses, reasons including concomitant systemic corticosteroid therapy (psoriasis palmarum et plantarum), broken code or insufficient data. This implies that some of the participants that could potentially have had AD were excluded from the trial. **Notes** None
Interventions	**Run-in details** Not reported **Groups**

Mali 1976 *(Continued)*

	• Flumethasone pivalate 0.02% cream (proprietary: Locacorten); applied twice daily for 3 weeks. Concurrent treatment: not reported • Betamethasone dipropionate cream (proprietary: Diprosone); applied twice daily for 3 weeks. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** In the original paper 'flumethasone' is written 'flumethason'; we assumed this is a synonym and have used the spelling that is found in the Korean classification.
Outcomes	• Physician's overall evaluation (5-point scale: judgements were 'much better', 'slightly better', 'no change', 'slightly worse', or 'much worse') at week 3, although assumed as time is not stated. Visits occurred weekly throughout the trial.* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised", "each patient received 3 40-gram tubes of the medication at each visit according to patient number, as set out in a random code". Comment: no information was provided as to how the random code was generated.
Allocation concealment (selection bias)	Unclear risk	Quote: "randomised", "each patient received 3 40-gram tubes of the medication at each visit according to patient number, as set out in a random code". Comment: no information regarding whether allocation was concealed. Also, as participants were rejected because of "broken code", we are concerned at the robustness of any allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind," "both preparations were supplied in identical-appearing 4-gram tubes" Comment: it is likely that participants were blinded, however unclear which personnel were blinded and how
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: it is unclear which personnel were blinded and how.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "16 cases were rejected because of concomitant systemic corticosteroid therapy (psoriasis palmarum et plantarum), broken code or insufficient data." Comment: it is unclear how many of these were AD participants, or which groups they belonged to in order to judge risk of bias.

Mali 1976 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias detected

Marchesi 1994

Study characteristics	
Methods	**Trial design** 3rd-party blind evaluator, randomised, parallel-group trial **Trial registration number** Not reported **Setting** No information, however the trial authors were based at a Dermatology Clinic, University of Milan, Civil Hospital of Bergamo. **Date trial conducted** Not reported **Duration of trial participation** 3 weeks **Additional design details** None **Inclusion criteria** • Patients with at least moderate-severity AD that had been stable or worsening for > 1 week and that were otherwise in good general health. • Patients with all 3 of the following symptoms: erythema, induration and pruritus in a target area. • Total severity score of ≥ 6 based on 0 = none, 1 = slight, 2 = moderate and 3 = severe, presumably for the symptoms listed above • Patients who had not received corticosteroids either topically in the week before the trial or systemically 4 weeks before • Patients who did not show signs of skin atrophy in the target area. • Patients who were not hypersensitive to the drug or the components of its formulation. **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised** 60; 30 into each arm **Age**

Marchesi 1994 *(Continued)*

Mean 37.7 ± SD 17.1 in the mometasone group; 41.9 ± 17.1 in the betamethasone dipropionate group. Range 18-65 for both groups.

Sex

18 male and 12 female participants in the mometasone group; 20 male and 10 female in the betamethasone dipropionate group.

Race/ethnicity

Not reported

Duration of eczema

Mean 28.3 months ± SD 34.2 in the mometasone group; 37.1 ± 48.1 in the betamethasone dipropionate group

Severity of eczema

Disease status at entry: mometasone stable = 6.7% (n = 2); worsening = 93.3% (n = 28). Betamethasone dipropionate stable = 3.4% (n = 1); worsening = 96.6% (n = 29). Percent body involved: mometasone up to 25% = 96.7% (n = 29); 26-50% = 3.3 % (n = 1). Betamethasone dipropionate up to 25% = 86.7% (n = 26); 26-50% = 13.3% (n = 4)

Filaggrin mutation status

Not reported

Number of withdrawals

All participants completed the trial.

Notes

None

Interventions	**Run-in details** NA **Groups** • Betamethasone dipropionate 0.05% ointment; applied twice daily for up to 3 weeks according to instructions. Concurrent treatment: none • Mometasone furoate: mometasone furoate 0.1% ointment; applied once daily for up to 3 weeks according to instructions. Concurrent treatment: none **Adherence** Not reported **Co-interventions** All medications given during the trial were recorded; any that might interfere with the trial drug were prohibited. **Notes** None
Outcomes	• Global evaluation of disease status relative to baseline: physician selected cleared (1 = 100% improvement), marked/good improvement (2 = 75%-100% clearance), moderate improvement (3 = 50%-75% clearance), slight improvement (4 = < 50% clearance), 5 = no changed/unchanged or 6 = exacerbation at days 2, 3, 4, 7, 14, and 21.*

Marchesi 1994 *(Continued)*

- Erythema, induration, and pruritus each scored 0 = none, 1 = slight, 2 = moderate and 3 = severe at baseline and days 2, 3, 4, 7, 14, and 21
- Physician-assessment, via physical examination, of signs of skin atrophy according to scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe at baseline and days 2, 3, 4, 7, 14, and 21*
- Laboratory tests (unspecified) at baseline and end of treatment
- Safety evaluated by examination and questioning of participants at days 2, 3, 4, 7, 14, and 21*

*denotes relevance to this review

Funding source	None stated
Declarations of interest	None declared, however the primary author is affiliated to Schering-Plough S.p.A., Milan.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…the patients were randomly assigned to one of the two treatment groups: mometasone furoate or betamethasone dipropionate. Comment: no description of randomisation method. There also appear to be imbalances in total duration of disease and percent body involved, although the trial authors state that the groups were evenly distributed for all demographic and epidemiological characteristics. However no significant differences were seen in the severity of each of the 3 symptoms.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "third-party blind evaluator" Comment: no indication that participants were blinded, and it is unlikely to be blinded as mometasone was given once daily and betamethasone dipropionate was given twice daily, with no placebo mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "third-party blind evaluator" Comment: the evaluator was blinded and all outcomes were physician-assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients completed the study" Comment: none of the participants withdrew from the trial.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other biases identified

Marten 1980

Study characteristics

Methods	**Trial design** Double-blind RCT **Trial registration number**

Marten 1980 *(Continued)*

Not reported

Setting

Secondary care in England

Date trial conducted

Not reported

Duration of trial participation

4 weeks

Additional design details

"The children were allocated, depending upon the area of skin involvement and thus the amount of ointment required to one of the following groups. Group I: 0.1% HC 17-butyrate ointment, 30 g weekly for 4 weeks. Group II: 1% HC ointment, 30 g weekly for 4 weeks. Group III: 0.1% HC 17-butyrate ointment, 60 g weekly for 4 weeks. Group IV: 1% HC ointment, 60 g weekly for 4 weeks. Those with moderate eczema were allocated to group I or II by double-blind randomisation and those with extensive eczema were allocated similarly to groups III or IV."

Inclusion criteria

- Children with eczema

Exclusion criteria

- Patients receiving systemic corticosteroids
- Patients with infected eczema
- Patients with very limited eczema

Notes

"No other local application was permitted during the period of the trial but if the children were taking an oral antipruritic drug, this was continued at the same dose as before." "All the 20 subjects had been treated with a variety of topical steroids at the time of entering the trial but no one particular preparation seemed responsible [for abnormal pre treatment cortisol levels]."

Participants

Total number randomised

20: 5 moderate cases randomised into each 30 g/week group; 5 severe cases randomised into each 60 g/week group

Age

Ages ranged from 1.5-13 years. Mean ages were 7.0 in the 30 g/week HC 17-butyrate group, 7.7 in the 30 g/week HC group, 11.0 in the 60 g/week HC 17-butyrate group, and 9.3 in the 60 g/week HC group.

Sex

12 male and 8 female participants overall; 3 male and 2 female in the 30 g/week HC 17-butyrate group, 2 male and 3 female in the 30 g/week HC group, 4 male and 1 female in the 60 g/week HC 17-butyrate group, and 3 male and 2 female in the 60g/week HC group.

Race/ethnicity

13 black, 6 white, and 1 Asian participants; 2 black and 3 white participants in the 30 g/week HC 17-butyrate group, 2 black, 2 white and 1 Asian participant in the 30 g/week HC group, 4 black and 1 white participant in the 60 g/week HC 17-butyrate group, and 5 black participants in the 60 g/week HC group.

Duration of eczema

Not reported

Marten 1980 *(Continued)*

Severity of eczema

Initial severity scores (0 = absent, 3 = severe) for the moderate HC 17-butyrate group were 2.0 for itching, 1.6 for excoriation, 1.6 for lichenification, 1.0 for erythema, 0.0 for weeping, 0.6 for crusting, 1.8 for scaling and 1.0 for papules. Scores for the moderate HC group were 1.2 for itching, 1.0 for excoriation, 1.6 for lichenification, 1.0 for erythema, 0.0 for weeping, 0.2 for crusting, 1.4 for scaling and 1.4 for papules. Scores for the severe HC 17-butyrate group were 1.0 for itching, 1.0 for excoriation, 2.8 for lichenification, 0.2 for erythema, 0.0 for weeping, 0.4 for crusting, 0.4 for scaling and 2.8 for papules. Scores for the severe HC group were 2.0 for itching, 1.6 for excoriation, 2.6 for lichenification, 0.8 for erythema, 0.2 for weeping, 1.6 for crusting, 1.4 for scaling and 2.6 for papules.

Filaggrin mutation status

Not reported

Number of withdrawals

It was stated that 3 children were lost to follow-up, but were replaced, and that none were withdrawn for clinical reasons. It is unclear to which group they belonged.

Notes

No significant difference was found between groups with respect to age, sex, height, weight or race.

Interventions

Run-in details

NA. "The use of placebo ointment before entering the trial would have been desirable, but this was not felt to be justified on ethical grounds."

Groups

A: 30 g/week HC: HC 1% ointment (unspecified); applied twice daily without occlusion (polythene or stockinette) for 4 weeks. Concurrent treatment: none reported

B: 30 g/week HC butyrate: HC 17-butyrate 0.1% ointment (unspecified); applied twice daily without occlusion (polythene or stockinette) for 4 weeks. Concurrent treatment: none reported

C: 60 g/week HC: HC 1% ointment (unspecified); applied twice daily without occlusion (polythene or stockinette) for 4 weeks. Concurrent treatment: none reported

D: 60 g/week HC butyrate: HC 17-butyrate 0.1% ointment (unspecified); applied twice daily without occlusion (polythene or stockinette) for 4 weeks. Concurrent treatment: none reported

Adherence

Tubes were weighed at the beginning and end of the trial.

Co-interventions

No other topical medications were permitted, however oral antipruritics were allowed if taken at the same dose as prior to the trial.

Notes

None

Outcomes

- Side effects or "intercurrent disorders" (noted by doctor and participant) at baseline, after 2 weeks for 60 g/week participants, and after 4 weeks for all participants, or if "untoward effects were noticed."*
- Plasma cortisol levels in response to Synacthen test: blood samples were taken prior to injection of 250 µg Synacthen and 30 min later. The tests were performed between 9 am and 10 am. The paper states that cortisol values should be in excess of 140, 200 and 500 nmoL/1 for the baseline sample, the increment and the 30-min sample, respectively at baseline, and after 4 weeks for all participants.*
- Plasma ACTH: individual ACTH at baseline, and after 4 weeks for all participants*

Marten 1980 *(Continued)*

- Clinical signs included itching, excoriation, lichenification, erythema, weeping, crusting, scaling, papules all scored from 0 (absent) to 3 (severe) at baseline, and after 4 weeks for all participants*

*denotes relevance to this review

Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised' Comment: no further information available
Allocation concealment (selection bias)	Unclear risk	Comment: no information available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind' Comment: no further information available on who or how blinding occurred
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind' Comment: no further information available on who or how blinding occurred
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "3 children failed to attend for the final assessment and were replaced.' Comment: no further information provided about why these participants withdrew and how they were replaced. It is also unclear to which group these children belonged. If all were present in the same group and failed to attend for a reason related to the trial medication this may have introduced bias into the evaluation.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. Week 2 visits for the severe cases were not mentioned outside the methods section; it is not clear if data were collected that are not presented.
Other bias	Unclear risk	Quote: "All but 4 of the subjects showed some impairment of adrenal response prior to treatment which may have been the result of earlier therapy with topical steroid preparations". "All 20 subjects had been treated with a variety of topical steroids at the time of entering the study" Comment: all participants had previously received TCS treatment and with such small numbers of participants involved in the analysis, the results may have been due to previous steroid use.

Meenan 1963

Study characteristics

Methods	**Trial design** Randomised, double-blind, half-sided trial

Meenan 1963 *(Continued)*

Trial registration number

Not reported

Setting

The Children's Hospital, Dublin, assumed from the author's affiliation. Both outpatients and inpatients were included.

Date trial conducted

Not reported

Duration of trial participation

Up to 2 weeks.

Additional design details

None

Inclusion criteria

- Patients with infantile (atopic) eczema, said to be in the 'usual pattern'
- Patients with symmetrical and equally severe lesions

Exclusion criteria

Not reported

Notes

The following statement may be of interest: "The cases were of the usual pattern of infantile eczema. The younger children showed weeping and crusted lesions; in the older children, the lesions tended to be erythematous, scaly, and sometimes lichenified."

Participants

Total number randomised

25 treated

Age

Average age was 3 years, 2 months (range 6 months to 12 years).

Sex

Not reported

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Not reported, however it was stated that 22 cases were outpatients and 3 were inpatients. Younger children tended to show "weeping and crusted lesions" and older children tended to be "erythematous, scaly, and sometimes lichenified".

Filaggrin mutation status

Not reported

Number of withdrawals

Meenan 1963 *(Continued)*

5 cases were only treated for 11 days and not 2 weeks, but it is unclear why. Data are presented for 25 treated participants.

Notes

None

Interventions	**Run-in details** The participants did not use TCS in the 3 weeks preceding the trial **Groups** • HC 1% cream (unspecified); applied twice daily for 2 weeks to the designated side. Concurrent treatment: none • Fluocinolone acetonide 0.01% cream (proprietary: Synalar); applied twice daily for 2 weeks to the designated side. Concurrent treatment: none **Adherence** Not reported **Co-interventions** None **Notes** None
Outcomes	• Comparative response assessed by 3 judges: the author, a parent, and an independent judge (medical registrar or nurse). Factors that influenced decision making: diminution of scaling, weeping, redness (and mother able to say if scratched 1 side less). Each could assign a point to the side that had a better response than the other. If there was no difference between sides, no point was awarded. The maximum score possible was 3. For intern participants another nurse replaced the parent at week 2 (or at end of treatment).* *denotes relevance to this review
Funding source	None stated, however Imperial Chemicals Industries, Ltd. provided the creams.
Declarations of interest	None declared, however Imperial Chemicals Industries, Ltd. provided the creams.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "treatment was assigned to the sides according to a random method." Comment: no information about how sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "The creams were dispensed by the pharmacist… The pharmacist was the only person who knew the constituents of each tube until treatment of the twenty-five cases had been concluded." Comment: no details on allocation concealment used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind technique", "mothers were given two tubes of ointment, one marked X and the other marked Y", "the creams were dispensed by the pharmacist […] pharmacist was the only person to know the constituents of each tube until treatment of the 25 cases had been concluded".

Meenan 1963 *(Continued)*

		Comment: although it does not explicitly say tubes were identical, since it was needed to mark them X and Y and both ointments, there is enough detail to suggest that they were.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the creams were dispensed by the pharmacist […] pharmacist was the only person to know the constituents of each tube until treatment of the 25 cases had been concluded". Comment: mother, author and nurse/medical registrar can there fore be assumed to be blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In twenty cases the trial lasted for two weeks, and in five cases eleven days." Comment: although no reason is given for this it is unlikely that this would contribute bias in a half-sided trial.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias detected

Meffert 1999

Study characteristics

Methods

Trial design

5 double-blind, randomised trials (only 1 trial relevant to this review, see notes)

Trial registration number

Not reported

Setting

Multiple centres; locations assumed from the list of ethics committees that permitted the trials: Belgium (N = 5), Germany (N = 37), Holland (N = 2), Poland (N = 6) and Hungary (N = 5). It is not clear which countries trial 5 (the only trial relevant to our review) was conducted in and there is no further information on setting.

Date trial conducted

Not reported

Duration of trial participation

Up to 14 days, as stated in the methods, however, the paper also reports that "depending on the study, the average duration of treatment was between 9 and 16 days" with no further detail provided.

Additional design details

None

Inclusion criteria

- Children between 4 months to 14 years old
- Patients of both sexes with mild to moderately severe acute eczema
- The following types of eczema were included across the 5 trials reported: toxic degenerative, seborrhoeic, nummular (microbial), dyshidrotic allergic contact dermatitis, status eczematicus in varices, eczema vulgare and AD (70% had AD but it's unclear which types the other 30% had).

Meffert 1999 *(Continued)*

Exclusion criteria

Not reported for individual trials

Notes

None

Participants	**Total number randomised** 145; only 70% of these participants had AD: n = 102 **Age** Of all 145 there were 17 children under 1 year, 65 between 1 and 5, and 63 between 6 and 14 years old. However it is unclear how many were AD patients. **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** There were mild-moderate eczema cases, however we do not know how severe the AD patients were. **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported by trial. Across all 5 trials, 31 participants were excluded from the effectiveness analysis. **Notes** None
Interventions	**Run-in details** None **Groups** • HC 17-butyrate: HC 17-butyrate 0.1% lotion (Alfason); applied twice daily for up to 14 days. Concurrent treatment: none • Methylprednisolone aceponate: methylprednisolone aceponate 0.1% lotion (Advantan); applied once daily for up to 14 days. Concurrent treatment: vehicle also used once daily up to 14 days. **Adherence** Not reported **Co-interventions** None **Notes**

Meffert 1999 *(Continued)*

	None
Outcomes	• Laboratory test parameters for safety including complete blood count; biochemistry (liver, kidney, blood glucose, lipid metabolism, electrolytes); serum cortisol levels (at approximately the same time of day after half an hour of rest, with no caffeine-containing drinks or tobacco consumption). Not considered relevant for our review as the data were not reported individually for the 5th trial at baseline (day 0), then between days 9-14 (end of treatment). • Adverse events (unclear how they were assessed, and data were not presented separately for atopic eczema patients) at up to day 14. • Global therapeutic success (investigator-assessed): healing, significant improvement, moderate improvement, no effect or deterioration. participants with complete healing or marked improvement were grouped as "responders" (only narrative data presented separately for atopic eczema patients) at day 9-14.* • Skin condition of the diseased area (investigator-assessed): assessed as very good, good, moderate or poor (data not presented separately for atopic eczema patients) at baseline, day 3-5, day 6-8, day 9-14 • Improvement in selected objective and subjective symptoms (investigator-assessed): erythema, oedema, papules, vesicles, oozing and itching. Each assessed on a scale from 1 (non-existent) to 5 (strong) and summed (6 = all symptoms absent, 30 = all symptoms strongly expressed) (data not presented separately for atopic eczema patients) at baseline, day 3-5, day 6-8, day 9-14. *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared, however 1 of the authors is affiliated to Schering AD, Berlin.
Notes	The paper describes 5 trials. Only trial 5 is relevant as it is methylprednisolone aceponate lotion once daily (potent) versus HC butyrate 0.1% twice daily (potent) - frequency trial. 70% of participants have AD. The other 4 trials are not relevant because: trial 1: methylprednisolone aceponate lotion versus vehicle. Trial 2: methylprednisolone aceponate lotion versus vehicle versus amcinonide (both TCS are potent, and both given twice daily). Trial 3 is methylprednisolone aceponate once daily versus twice daily - it says AD is most prevalent but does not separate the data by condition. Trial 4 - methylprednisolone aceponate once daily versus methylprednisolone aceponate twice daily versus betamethasone valerate 0.1% twice daily (potent) - says mostly in allergic contact dermatitis and data not separated. Translation from German

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized allocation of investigational medication and reference preparations.' (English translation) Comment: no further information about how it was randomised
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quotes (English translation): "The lotions were sufficiently similar in their galenic nature to those of the MPA [methylprednisolone aceponate] milk, so that after refilling into neutral tubes, blinding became possible," "double-blind," 'For patients who only received MPA milk once daily in Study III-V, a second treatment per day with the vehicle was used to perform the studies in a double-blind design" Comment: participants were likely blinded to treatment allocation; however, it's not clear if the trial investigators were blinded to treatment group.
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: it's not clear who made the assessments and if they were blinded to treatment allocation.

Meffert 1999 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: it's not clear how many participants were randomised to each group in trial 5, or followed up. Also, more generally across all 5 trials, 31 participants were excluded from the effectiveness analysis, however there is no indication that the exclusion reasons were prespecified.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Unclear risk	Quote: "The patient population was found to be homogeneous in terms of demographic and anamnestic data across all studies in terms of its distribution among the different treatment groups." (English translation) Comment: however, no data are given in the trial report. Furthermore, there is a lack of data provided solely for the AD participants relevant to this review. Hence, it's not possible to determine if there were any other biases presented.

Mobacken 1986

Study characteristics

Methods

Trial design

Randomised, double-blind, parallel trial

Trial registration number

Not reported

Setting

Not reported

Date trial conducted

Not reported

Duration of trial participation

21 days

Additional design details

None

Inclusion criteria

- Child aged 3-16 years old
- Confirmed diagnosis of eczema of at least 2 months' duration
- The sum of severity scores for signs and symptoms* was to total ≥ 5. At least 2 signs/symptoms* had to be moderate in severity (*The physician chose a test site, excluding palms, soles or scalp, for evaluation in each patient. The physician graded the severity of erythema, induration, pruritus, scaling and excoriation at this site as 0 = absent, 1 = mild, 2 = moderate or 3 = severe).

Exclusion criteria

- Tuberculosis of the skin or viral infections with skin lesions
- Received systemic therapy for eczema within 4 weeks
- Received topical therapy within 2 weeks

Mobacken 1986 *(Continued)*

- Participants who needed additional topical or systemic medication for eczema or any other topical or systemic medication that could affect the disease course
- Participants using occlusive dressings

Notes

None

Participants	**Total number randomised** 60 (although characteristics only reported for the 29 participants in each group included in the efficacy results) **Age** Alclometasone (moderate) mean age 9.1, range (3-16). HC (mild) mean age 10, range (3-16) **Sex** Alclometasone (moderate) 13 male, 16 female. HC (mild) 15 male, 14 female **Race/ethnicity** Not reported **Duration of eczema** Duration of the primary diagnosis (years) alclometasone (moderate)5.5 (0.2-15), HC (mild) 5.9 (0.3-15) **Severity of eczema** Mean sign/symptom scores alclometasone (moderate) 8.28, HC (mild) 8.28. (inclusion criteria was at least moderate rating of 1 sign). **Filaggrin mutation status** Not reported **Number of withdrawals** 1 participant from each group withdrew. 1 girl in the alclometasone (moderate) group did not return for the final visit due to a fever. 1 girl from the HC (mild) group returned early for the final visit because the eczema was "almost unchanged". **Notes** None
Interventions	**Run-in details** None **Groups** • Alclometasone dipropionate 0.05% ointment (unspecified); a thin coat of medication was applied to the test site twice daily, without occlusion. Concurrent treatment: none • HC 1% ointment (unspecified); a thin coat of medication was applied to the test site twice daily, without occlusion. Concurrent treatment: none **Adherence** At the initial visit, medication in 45 g tubes sufficient for 1 week's treatment was provided; at the interim visit, medication was dispensed for the remaining 2 weeks. All tubes of medication (unused, empty or partially used) were returned to the physician.

Mobacken 1986 *(Continued)*

	Co-interventions Medicated shampoos for scalp application were permitted. **Notes** No treatment was applied at least 3 h prior to physician evaluation at interim and final visits. No medication other than the test medication was applied to the test site. Tar baths, UV light or Grenz ray therapy or antipruritic medications were not allowed. Medications that might alter the course of the disease, e.g. antihistamines, tranquillisers or anti-inflammatory agents were not allowed. Concomitant therapy for other conditions was to remain constant and participants were to avoid exposure to the sun or changes to exercise habits or environment.
Outcomes	• Severity of signs/symptoms. The physician chose a test site, excluding palms, soles or scalp, for evaluation in each participant. The physician graded the severity of erythema, induration, pruritus, scaling and excoriation at this site as 0 = absent, 1 = mild, 2 = moderate or 3 = severe at baseline, days 7-10, 19-25. Not extracted as IGA takes priority. • IGA. Defined as (1) cleared: 100% clearance except for residual discolouration (2) marked improvement: between 75% and 100% clearance of signs and symptoms (3) moderate improvement: between 50% and 75% clearance of symptoms (4) slight improvement: < 50% clearance of signs and symptoms (5) no change: no detectable improvement form baseline evaluation and (6) exacerbation: flare at treatment site at days 7-10, 19-25.* • Side effects, volunteered by the participant or determined by the physician at assumed at both visits days 7-10, 19-25. To be recorded as type, severity, duration and relationship to study medication.* • Cosmetic acceptability (regarding staining of skin or clothing, ease of application, skin absorption) at Days 19-25. *denotes relevance to this review
Funding source	Not reported
Declarations of interest	Not reported
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly assigned"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind", no further details as to the method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind", no further details as to the method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 participants did drop out but this was a small proportion and so unlikely to have any effect. Reasons were fully explained

Mobacken 1986 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available.
Other bias	Low risk	Comment: no other source of bias identified

Msika 2008

Study characteristics

Methods

Trial design

Multi-arm (5) RCT

Trial registration number

Not reported

Setting

Multicentre trial conducted by 20 paediatricians

Date trial conducted

March-June 2003

Duration of trial participation

21 days

Additional design details

None

Inclusion criteria

- Mild-moderate AD (inflammatory phase)
- Children whose parents gave informed consent
- TCSs last applied > 8 days prior

Exclusion criteria

Not reported

Notes

None

Participants

Total number randomised

86

Age

Mean age 16 months, range 4-48 months

Sex

41 female participants (47.7%), 45 male participants (52.3%)

Race/ethnicity

Not reported

Msika 2008 *(Continued)*

Duration of eczema

Not reported

Severity of eczema

Mild to moderate AD in the inflammatory phase

Filaggrin mutation status

Not reported

Number of withdrawals

Not reported

Notes

None

Interventions	**Run-in details** No run-in period **Groups** **A**: desonide 0.05% (Tridesonit); applied once daily (morning) for 21 days to lesional skin. Concurrent treatment: none **B**: desonide 0.05% (Tridesonit); applied once daily (morning) for 21 days to lesional skin. Concurrent treatment: emollient containing 2% Sunflower oil oleodistillate (SO) (STELATOPIA MUSTELA DermoPediatrie, Laboratories Expanscience, France) was applied all over the child's body alongside the TCS (not clear if before or after) in the morning and on its own in the evening. **C**: desonide 0.05% (Tridesonit); applied twice daily (morning and evening) for 21 days to lesional skin. Concurrent treatment: none **D**: desonide 0.05% (Tridesonit); applied twice daily (morning and evening) for 21 days to lesional skin. Concurrent treatment: emollient containing 2% Sunflower oil oleodistillate (SO) (STELATOPIA MUSTELA DermoPediatrie, Laboratories Expanscience, France) was applied all over the child's body twice daily, either alongside the TCS (not clear if before or after) every other day or alone in the morning, and every evening. **E**: desonide 0.05% (Tridesonit); applied every other day (morning) for 21 days to lesional skin. Concurrent treatment: emollient containing 2% sunflower oil oleodistillate (SO) (STELATOPIA MUSTELA DermoPediatrie, Laboratories Expanscience, France) was applied all over the child's body twice daily, either alongside the TCS (not clear if before or after) every other day or alone in the morning, and every evening. **Adherence** Not reported **Co-interventions** None **Notes** None
Outcomes	• SCORAD - surface area of atopic lesions, erythema, oedema/papulation, oozing/crusts, excoriation, lichenification, dryness of non-lesional skin, pruritus, loss of sleep at baseline, 7 days, 21 days* • IIGA of overall satisfaction of treatment rated by physician – 5 level scales – completely agree, quite agree, not very agree, not agree, no opinion at baseline, 7 days, 21 days

Msika 2008 *(Continued)*

- IDQOL at baseline, 7 days, 21 days
- DFI Questionnaire at baseline, 7 days, 21 days
- Lichenification item of SCORAD - this was not a prespecified outcome at baseline, 7 days, 21 days
- Tolerance - unsure how this was tested at baseline, 21 days

*denotes relevance to this review

Funding source	Not stated
Declarations of interest	Lead author is employed by Laboratoires Expanscience who make the emollient tested with the trial. No further information given
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The five treatment options studies were successively allocated to patients according to chronological order of entry in the study" Comment: participants were randomised based on chronological order of entry in the trial.
Allocation concealment (selection bias)	High risk	Quote: "The five treatment options studies were successively allocated to patients according to chronological order of entry in the study. Patients were randomized based on chronological order of entry in the study." Comment: trial investigators and potentially participants would be able to guess which treatment allocation is next.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no detail was provided about blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no mention of blinding outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: withdrawals and adverse events were not stated, and it was unclear if adherence was measured. The number of participants was not given alongside each analysis.
Selective reporting (reporting bias)	High risk	Comment: no protocol available so unable to assess if all preplanned outcomes were reported. The publication fails to report raw data for IGA outcome and no dispersion data are available for the other outcomes. No significant differences between groups in SCORAD but the trial authors then present results for lichenification in a graph but only for 2 of the groups, with no dispersion data then claim there is a difference between groups.
Other bias	Unclear risk	Comment: does not present any demographic data at baseline so unable to see how similar the groups were.

Munro 1967

Study characteristics

Munro 1967 *(Continued)*

Methods	**Trial design** Double-blind, randomized, half-sided **Trial registration number** Not reported **Setting** Outpatients from 3 different centres in the UK **Date trial conducted** Not reported **Duration of trial participation** Approximately 1 week; trial states "patients were normally reviewed after 7 days, though some were seen more frequently, and a few at slightly longer intervals." **Additional design details** None **Inclusion criteria** • Individuals were suffering from eczema. • Those having approximately symmetrical involvement of right and left sides were studied. **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised** 66 participants with eczema (43 participants with psoriasis, not extracted) **Age** Not reported separately for eczema-only participants **Sex** Not reported separately for eczema-only participants **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported

Munro 1967 *(Continued)*

Number of withdrawals

2 participants initially included failed to carry out the instructions given and were excluded; it was not clear if these were eczema or psoriasis participants and they were in addition to the 66 reported.

Notes

The 2 groups were divided into those treated with occlusion and those who were not, 37 participants were not treated with occlusion, 29 participants were treated with occlusion. As this was not allocated by randomisation we combined the results.

Interventions	**Run-in details** NA **Groups** • Fluocortolone/fluocortolone caproate 0.25% ointment (Ultralanum Plain); applied twice daily; some under occlusion with polyethylene film where it was felt to be necessary. Concurrent treatment: none • Betamethasone 17-valerate 0.1% ointment (Betnovate); applied twice daily; some under occlusion with polyethylene film where it was felt to be necessary. Concurrent treatment: none **Adherence** 2 participants were removed from the trial for failure to follow instructions, does not state how assessed adherence though **Co-interventions** Mild sedatives or antihistamines were administered if indicated. Betamethasone base was soft paraffin and hydrogenated lanolin, fluocortolone base was soft paraffin aqueous emulsion containing 30% water. **Notes** Each tube contained 30 g of the relevant ointment.
Outcomes	• Participant's assessment of comparison in improvement made by assessing changes in itching or other symptoms. Recorded as healed, improved, static or worse at 1 week (approximately).* • Dermatologist's assessment of comparison in improvement in erythema, scaling, induration, and oedema of the diseased skin. Recorded as healed, improved, static or worse at 1 week (approximately).* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "When the investigation on each patient was concluded, the completed form was returned to a co-ordinating secretary, who decoded the results and plotted them consecutively on previously constructed restricted sequential analysis graphs (Armitage 1960)".

Munro 1967 *(Continued)*

		Comment: the researchers have not prespecified the sample size, therefore may have chosen to stop recruitment when statistical significance was reached.
Allocation concealment (selection bias)	Unclear risk	Quote: "Each paired pack was numbered and the code given to the clinicians in sealed envelopes, which remained closed throughout the trial." "when the investigation on each patient was concluded, the completed form was returned to a co-ordinating secretary, who decoded the results and plotted them consecutively on previously constructed sequential analysis graphs" Comment: it was likely that the participants and the personnel involved did not know what treatment was being used on a particular side, however as the envelopes were not described as opaque it is possible that the personnel involved could have looked at what the participant was receiving.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind trial packs were prepared in pairs marked left and right" "Each paired pack was numbered and the code given to the clinicians in sealed envelopes, which remained closed throughout the trial." "when the investigation on each patient was concluded, the completed form was returned to a co-ordinating secretary, who decoded the results and plotted them consecutively on previously constructed sequential analysis graphs" Comment: it is not clear if the tubes were identical so possible that the participant might not be adequately blinded, also as the envelopes were not described as opaque it is possible that the personnel involved may have known what the participant was receiving.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "when the investigation on each patient was concluded, the completed form was returned to a co-ordinating secretary, who decoded the results and plotted them consecutively on previously constructed sequential analysis graphs" Comment: as the envelopes were not described as opaque, and it is not clear which personnel did what in this trial, it is possible that the outcome assessor and participants knew what they were receiving.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "two patients who were initially included in the trial failed to carry out the instructions given by clinicians and were therefore excluded from the investigation." Comment: these were not included in the initial 66 and probably would not be a relevant source of bias.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	High risk	Quote: as for Random Sequence Generation. Comment: the researchers have not prespecified the sample size, therefore may have chosen to stop recruitment when statistical significance was reached.

Munro 1975

Study characteristics	
Methods	**Trial design** Within-participant, randomised, double-blind trial **Setting**

Munro 1975 *(Continued)*

	Not reported **Date trial conducted** Not reported **Duration of trial participation** Not reported **Additional design details** None **Inclusion criteria** • Not reported **Exclusion criteria** • Not reported **Notes** Participants had bilateral approximately symmetrical lesions.
Participants	**Total number randomised** 409 participants in the results table. **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported **Notes** None
Interventions	**Run-in details** None **Groups**

Munro 1975 *(Continued)*

A: clobetasone butyrate 0.01% cream. The preparations were allocated at random for use on either the right side or the left hand side. Concurrent treatment: none

B: HC 1% cream. The preparations were allocated at random for use on either the right side or the left hand side. Concurrent treatment: none

C: clobetasone butyrate 0.025% cream. The preparations were allocated at random for use on either the right side or the left hand side. Concurrent treatment: none

D: clobetasone butyrate 0.05% cream. The preparations were allocated at random for use on either the right side or the left hand side. Concurrent treatment: none

Adherence

Not reported

Co-interventions

Not reported

Notes

Occlusive dressings were not used. Formulated as a bland cream without the addition of penetrants such as propylene glycol

Outcomes	• Comparison of moderate with mild TCS. Number of participants in which moderate was deemed better, mild better or both deemed equal. Time point detail not reported* • Untoward effects. This was reported in the discussion but it was unclear as to which subsection of participants it related to. Time point detail not reported.* *Denotes relevance to this review
Funding source	Not reported
Declarations of interest	1 of the authors is affiliated with Glaxo Laboratories LTD.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: the researchers have not prespecified the sample size and chose to stop recruitment when statistical significance was reached using a sequential analysis graph.
Allocation concealment (selection bias)	Unclear risk	Comment: tests and control preparations were allocated randomly.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This paper (Munro 1975) references another paper (Williams 1964) for the method of blinding. Quote: Williams 1964 states, "doubled blinded techniques"; "The preparations, allocated at random for use on either right side or left side, and labelled accordingly, were issued in twin-tube individually coded packs. This method- although involving laborious labelling had the distinct advantage that the clinicians could not possibly be aware to which side the betamethasone 17-valerate was applied". Comment: as packs were coded it was likely that participants were blinded to the type of medication received.

Munro 1975 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	This paper (Munro 1975) references another paper (Williams 1964) for the method of blinding. Quote: Williams 1964 states, "doubled blinded techniques"; "The preparations, allocated at random for use on either right side or left side, and labelled accordingly, were issued in twin-tube individually coded packs.This method- although involving laborious labelling had the distinct advantage that the clinicians could not possibly be aware to which side the betamethasone 17-valerate was applied". Comment: it is clearly stated that clinicians were blinded to the type of medication received.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: drop-outs were not reported
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias were identified.

Murphy 2003

Study characteristics	
Methods	**Trial design** Randomised, investigator-blinded 3-arm, parallel-group trial **Trial registration number** Not reported **Setting** UK; participants were recruited from outpatient departments and ward admissions. **Date trial conducted** Not reported **Duration of trial participation** 1 week **Additional design details** None **Inclusion criteria** • Children whose eczema could be objectively categorised as moderately severe or severe • Patients who had failed to respond adequately to standard topical therapy with emollients, weak TCSs and oral anti-histamines **Exclusion criteria** Not reported **Notes**

Murphy 2003 *(Continued)*

	None
Participants	**Total number randomised** 37 (unclear how many were randomised to each group - 1 arm, wet-wraps + emollient not relevant to this review) **Age** Mean 7.2 years, range 3-15 **Sex** 14 male, 23 female **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported **Notes** None
Interventions	**Run-in details** Participants treated with oral or inhaled corticosteroid or systemic antibiotic in the preceding week were required to complete a 1-week run-in period before entry into the trial. **Groups** • Mild steroid applied alone • Mild steroid applied under wet wraps **Adherence** Not reported **Co-interventions** Not reported **Notes** None
Outcomes	• Haematological, biochemical and immunological assays for adverse events at baseline and week 1* • GOS score (no details provided) - response to treatment at baseline and week 1 • SASSAD - response to treatment at baseline and week 1*

Murphy 2003 *(Continued)*

*denotes relevance to this review

Funding source	None
Declarations of interest	None stated
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: no information regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information was provided as to whether participants or personnel were blinded. However, it would be difficult to blind either group due to the nature of the treatment with WWT.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "single blinded investigator" Comment: there is limited information about in the conference abstract about blinding. We do not know if participants were blinded (but it's unlikely given the nature of the intervention) so it is possible that blinding was broken by children informing the investigator of which group they were in.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information was provided as to whether any participants dropped out of the trial.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available.
Other bias	Low risk	Comment: no other sources of bias detected

Ng 2016

Study characteristics

Methods	**Trial design** Prospective, randomised, parallel-group, investigator-blinded trial **Trial registration number** National Medical Research Register NMRR-10-602-5917 **Setting** Not reported, however the trial authors are based in 2 hospital paediatrics departments in Malaysia. **Date trial conducted** Participants were screened between June 2010 and May 2011.

Ng 2016 *(Continued)*

Duration of trial participation

2 weeks

Additional design details

The trial authors stated that 64 participants per group were required to detect a medium effect size with 80% power and a significance level of < 0.05, plus an extra 26 to accommodate an expected 20% dropout rate. Only 46 were randomised, however.

Inclusion criteria

- Children aged 4 months-5 years
- Moderate-severe atopic eczema diagnosed according to the modified Hanifin and Rajka diagnostic criteria (Williams 1994), with severity according to the Rajka and Langeland criteria

Exclusion criteria

- Patients whose parents or caregivers were unable to apply the topical medications
- Patients with other skin disease in the trial area, active skin infections, or other conditions that might interfere with trial evaluation
- Immunocompromised patients or patients with a history of malignant disease
- Patients who had received phototherapy or systemic therapy known or suspected to have an effect on atopic eczema
- Patients with known hypersensitivity to the trial medications

Notes

None

Participants	**Total number randomised** 46 (26 into emollient 1st group, 20 in TCS 1st) **Age** Emollient 1st: mean 26.1 months (SD 17.0), median 22.5 months (range 4.0–56.0). TCS 1st: mean 31.0 months (SD 14.4), median 32.0 months (range 6.0–53.0) **Sex** Emollient 1st: 13 male, 13 female. TCS 1st: 14 male, 6 male **Race/ethnicity** Emollient 1st: 26 Malay. TCS 1st: 16 Malay, 4 Indian **Duration of eczema** • Overall duration, emollient 1st: mean 19.2 months (SD 17.0), median 16.5 (range 2.0–53.0). TCS 1st: mean 23.2 months (SD 13.5), median 24.0 (range 4.0–53.0) • Current episode, emollient 1st: mean 3.1 months (SD 7.6), median 0.5 (range 0.03–36.0). TCS 1st: mean 2.3 months (SD 3.0), median 1 (range 0.1–12.0) **Severity of eczema** Emollient 1st: 16 moderate, 10 severe. TCS 1st: 14 moderate, 6 severe **Filaggrin mutation status** Not reported **Number of withdrawals**

Ng 2016 *(Continued)*

- Emollient 1st: 2 lost to follow-up, 5 discontinued intervention (3 insufficient response, 1 infection and 1 adverse event)
- TCS 1st: 3 lost to follow-up, 5 discontinued intervention (1 insufficient response, 1 infection and 3 adverse events)

Notes

None

Interventions	**Run-in details** NA. **Groups** • Clobetasone butyrate 0.05% cream (Eumovate; GlaxoSmithKline, Petaling Jaya, Selangor, Malaysia); twice daily (~12 h apart), soon after a short bath, parent/caregiver applied emollient (aqueous cream) generously on the whole body followed by a thin layer (fingertip unit) of TCS 15 min later. Concurrent treatment: none • Clobetasone butyrate 0.05% cream (Eumovate; GlaxoSmithKline, Petaling Jaya, Selangor, Malaysia); twice daily (~12 h apart), soon after a short bath, parent/caregiver applied a thin layer of TCS (fingertip unit) followed by emollient (aqueous cream) generously on the whole body 15 min later. Concurrent treatment: none **Adherence** Parents or caregivers were asked to bring the containers of medicine to each visit and to demonstrate which container was used first to determine adherence. Parents and caregivers were also given a diary to record details of medicine application and any adverse effects. **Co-interventions** HC acetate 1% cream (cortisone cream; Dynapharm, Prai, Pulau Pinang, Malaysia) was used for facial eczema. **Notes** Parents or caregivers were told to use the aqueous cream as a soap substitute during the trial. Prohibited medications included ultraviolet therapies, systemic antihistamines, systemic corticosteroids, systemic immunosuppressive medications, traditional medications, and other topical medications. Permitted medications included paracetamol, oral antibiotics, and intranasal/inhaled corticosteroids when restricted to approved indications and doses.
Outcomes	• Overall incidences of all adverse events that the parent, caregiver or investigator observed - parents recorded them in a diary at baseline, week 1, week 2, or at discontinuation.* • Parent or caregiver assessment of itch - no information on scale used at baseline, week 1, week 2, or at discontinuation* • Percentage of BSA affected (estimated from head and neck, upper limbs, trunk including groin, and lower limbs) at baseline, week 1, week 2, or at discontinuation • EASI score at baseline, week 1, week 2, or at discontinuation* • Concomitant medication intake at baseline, week 1, week 2, or at discontinuation • Adherence at baseline, week 1, week 2, or at discontinuation *denotes relevance to this review
Funding source	None stated
Declarations of interest	None stated
Notes	None

Ng 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized to two groups according to a computer generated blinded randomization list." Comment: probably adequate
Allocation concealment (selection bias)	Unclear risk	Quote: "blinded randomisation list" Comment: it is unclear as to how this was done to ensure that the researchers did not know whether the next participant was allocated to either of the 2 groups.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "investigator-blinded" Comment: it is likely that the participants knew which medication they were applying first as they would have needed to know what amount of the preparations to apply to the skin e.g. liberal application of the emollient in comparison to a stated amount of TCS (e.g. fingertip unit).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "investigator blinded". Comment: no further information was provided as to whether this was the investigator who was assessing the participants initially or at the outcome.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 7 participants in the emollient 1st group and eight in the TCS 1st group were lost to follow-up or discontinued the intervention. They were all excluded from the efficacy analysis.
Selective reporting (reporting bias)	Low risk	Comment: primary and secondary outcomes are consistent with the ones reported in the trial register.
Other bias	Low risk	Comment: no other risk of biases identified.

Nolting 1991

Study characteristics

Methods	**Trial design** Randomised, single-blind, parallel-group **Trial registration number** Not reported **Setting** Multiple centres in Germany (assumed from the list of affiliations) **Date trial conducted** Not reported **Duration of trial participation** 3 weeks

Nolting 1991 *(Continued)*

Additional design details

It is stated that results were documented after 1 and 2 weeks of treatment, but also that this was done on the 14th or 21st day

Inclusion criteria

- Children 2-12 years
- Good general condition
- Confirmed diagnosis of atopic eczema, medium-severe grade
- Patients were assessed using the following criteria, erythema, infiltration and itching were used and their expression was determined on the basis of a scale: 0 = not available, 1 = light, 2 = moderate, 3 = severe. If necessary, half values could be used. The maximum output was therefore possible at 9-points. Patients with at least 2 points per symptom, and a total of 6 points when included into the trial.

Exclusion criteria

- Patients with known hypersensitivity to trial medications
- Patients taking local or systemic medications that affect adrenal cortical function or AD, e.g. tar, UV light, antiproliferative medications
- Patients treated with systemic corticosteroids within 4 weeks or TCSs within 7 days of trial enrolment.
- Patients with skin atrophy at baseline

Notes

None

Participants

Total number randomised

67; 33 were randomised to mometasone, 34 to prednicarbate

Age

Mometasone 6.6 + 3.6 years (no information regarding what this statistic is). Prednicarbate 6.4 + 3.1 years (no information regarding what this statistic is).

Sex

There were 17 male and 16 female participants in the mometasone group and 16 male and 18 female in the prednicarbate group.

Race/ethnicity

Not reported

Duration of eczema

Mometasone 3.8 + 3.3 years. prednicarbate 4.1 + 2.7 years (again, it is unclear what these statistics are).

Severity of eczema

The average severity of eczema in the mometasone group was 7.3 years + 1.0; the average severity in the prednicarbate group was 7.2 + 0.8 (unclear what the statistics are). In the mometasone group, 14 participants had 1%-25% BSA involved, 10 had 26%-50% involved, 7 had 51%-75% involved, and 2 had 75%-100% involved. In the prednicarbate group, 16 participants had 1%-25% BSA involved, 9 had 26%-50% involved, 7 had 51-75% involved, and 2 had 75-100% involved.

Filaggrin mutation status

Not reported

Number of withdrawals

Not reported

Nolting 1991 *(Continued)*

	Notes The authors report no differences between groups for age, duration, initial severity, gender, disease severity, localisation and extent of the disease.
Interventions	**Run-in details** Not reported **Groups** • Mometasone furoate 0.1% cream (unspecified); TCS was applied in a thin layer once daily for 3 weeks. Concurrent treatment: none • Prednicarbate 0.25% cream (unspecified); TCS was applied in a thin layer twice daily for 3 weeks. Concurrent treatment: none **Adherence** Not reported **Co-interventions** None **Notes** None
Outcomes	• Laboratory tests such as full blood count (assumed from 'differential blood picture'), haemoglobin, haematocrit, AST, ALT, urea, total bilirubin, alkaline phosphatase, creatinine and urinary status at baseline and day 21* • Side effects were stated as "present" or "absent", especially skin atrophy, shine, striae, telangiectasia, bleeding, hypertrichosis, loss of elasticity and change of the skin relief at days 7, 14, and 21.* • Physician and participant/parent evaluation of efficacy and cosmetic acceptance of the test medication at day 21 • IGA (assumed): 1 = healed (100% healed except for residual post-inflammatory hyperpigmentation of the skin); 2 = marked improvement (75%-99% improvement); 3 = moderate improvement (50%-74% improvement); 4 = slight improvement (< 5% improvement); 5 = no change (no significant change compared to the admission trial); 6 = exacerbation at days 2, 7, 14 and 21* • Severity score (erythema, infiltration and itching each scored 0-3 with 0 = not available to 3 = severe). If necessary, half values could be used. The maximum output was 9 points at baseline and days 2, 7, 14 and 21. *denotes relevance to this review
Funding source	Not stated
Declarations of interest	None declared
Notes	Data extracted from a translation from German.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: the trial states it was randomised, however no details were provided about how this was done.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided on allocation concealment

Nolting 1991 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single blinded" Comment: as outcome assessment is blinded we assume no other parties are blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the assessment was done by the same doctor who did not know which treatment arm the participant was allocated to. It is likely, unless the participant knew and disclosed the nature of the medication they were using, that this was not a source of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information provided as to whether any participants dropped out and how the associated data were dealt with.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias identified

Noren 1989

Study characteristics

Methods

Trial design

Randomised, 4 parallel-group design comparing a mild with a potent steroid, both with and without habit reversal

Trial registration number

Not reported

Setting

Participants were recruited through a private dermatology clinic, assumed to be in Sweden by the authors' affiliations.

Date trial conducted

Not reported

Duration of trial participation

5 weeks: 1 week pretreatment phase, 4 weeks of active treatment

Additional design details

None

Inclusion criteria

- Patients with moderate to severe AD attending a private dermatology clinic
- ≥ 16 years of age

Exclusion criteria

- Patients with serious psychiatric disease
- Patients with infected eczema

Notes

Noren 1989 *(Continued)*

	None
Participants	**Total number randomised** 45 participants (11 participants mild only, 11 participants potent, 13 participants mild + habit reversal, 10 participants potent + habit reversal) **Age** Mean age was 24.8 years (range 16-46) **Sex** There were 16 male and 29 female participants **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Baseline total improvement score was approximately 2.28 (extracted using WebPlotDigitizer). Medical assessment of symptoms: dryness, scaling, erythema and infiltration. Each was graded on a 0-3 scale (0 = nil, 1 = mild, 2 = moderate, 3 = severe). **Filaggrin mutation status** Not reported **Number of withdrawals** 2 participants withdrew; no reason was given and it is not clear to which group they belonged. **Notes** None
Interventions	**Run-in details** Details of the stated pretreatment phase were not reported. **Groups** **A**: HC cream (unspecified); applied twice daily for 4 weeks. Concurrent treatment: none **B**: betamethasone valerate cream (unspecified); steroid was applied twice daily for 4 weeks. Concurrent treatment: participants were stepped down to HC in the last 2 weeks. **C**: HC cream (unspecified); applied twice daily for 4 weeks with habit reversal. Concurrent treatment: habit reversal intervention detailed below **D**: betamethasone valerate cream (unspecified); steroid was applied twice daily for 4 weeks with habit reversal. Concurrent treatment: participants were stepped down to HC in the last 2 weeks. Habit reversal intervention detailed below **Adherence** Participants were asked to note when topical steroids were applied and whenever moisturisers were used. **Co-interventions**

Noren 1989 *(Continued)*

	All participants were instructed on how to apply the medication in the same manner. **Notes** The habit reversal intervention was as follows: when becoming aware of the desire to scratch, participants were asked to clench their fists for 30 seconds. If the itch did not resolve then they were asked to press a finger nail or pinch the itching spot. Participants were also encouraged to practice this at least twice daily. "Awareness was achieved by counting scratching episodes and practising the habit-reversal method several times in the doctor's office."
Outcomes	• Frequency of scratching was reported on the record form by the participant using a hand counter at daily for 5 weeks.* • Investigator assessment of clinical signs: dryness, scaling, erythema, and infiltration, each graded from 0 = nil to 3 = severe at baseline, week 2 and week 4*
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned" Comment: no information regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly assigned" Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "the dermatologist was not aware of which steroid was used during the first two weeks" Comment: the above is the only mention of blinding, therefore we cannot assume it was done for participants and other personnel. In any case, it would not have been possible to blind the participants or personnel as to whether they were receiving habit reversal treatment or not
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the dermatologist was not aware of which steroid was used during the 1st two weeks" Comment: the above is the only mention of blinding, therefore we cannot assume it was done for participants and other personnel, therefore any blinding of the dermatologist could still be compromised. In any case, it would not have been possible to blind the participants or personnel as to whether they were receiving habit reversal treatment or not
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 2 participants withdrew; no reason was given, it is not clear to which group they belonged, or how the relevant data were used. If these participants were from the same group that could potentially introduce bias as the maximum group size was 13.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available and so this cannot be assessed.
Other bias	Low risk	Comment: no other source of bias identified

Pei 2001

Study characteristics

Methods	**Trial design** Parallel-group RCT **Trial registration number** Not reported **Setting** A single paediatric dermatology outpatient clinic in Hong Kong **Date trial conducted** Not reported **Duration of trial participation** 6 weeks in total (run-in period of 2 weeks stabilisation prior to initial randomisation followed by 2 weeks application of TCS creams without occlusion, then participants were randomised again for whether they received WWT for the final 2 weeks). **Additional design details** Participants were only randomised in the last phase of the trial (i.e. WWT or no WWT) if they had failed to improve by > 50% after the initial 2 weeks. **Inclusion criteria** • Atopic dermatitis defined by the UK working party (Williams 1994) refinement of Hanifin and Rajka's Diagnostic criteria (Hanifin 1980). • Aged 1-15 years • Patients had to have active disease despite being under conventional treatment with a moderately potent topical steroid of Class II or above (UK classification with Class I being the weakest), as well as soap substitutes and emollients. • To be included within the trial, patients had to have a severity score of 40. **Exclusion criteria** • Systemic treatment with steroids, immunosuppressives or Chinese herbal medicine within the past 6 weeks • Presence of other skin conditions or any kind of infections • Antibiotic treatment within the past weeks **Notes** None
Participants	**Total number randomised** 40 initially randomised but it is unclear how many into each group during the WWT phase (where participants were re-randomised). **Age** Not reported **Sex** Not reported **Race/ethnicity**

Pei 2001 *(Continued)*

Not reported

Duration of eczema

Not reported

Severity of eczema

Quantification of the six signs of AD was carried out: erythema, oedema/papulation, oozing/crusting, excoriation, lichenification, and dryness. 8 areas of the body (head and neck, anterior trunk, back, genitalia, and 4 limbs) were graded on a scale of 0-3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Score < 40 = mild disease
Median (IQR): fluticasone with wet wrap 22 (10 to 45), fluticasone without wet wrap 41 (21 to 52), mometasone with wet wrap 29 (20.75 to 59), mometasone without wet wrap 20 (8 to 32)

Filaggrin mutation status

Not reported

Number of withdrawals

10 participants stopped before the end of the trial because their eczema had improved 50% from baseline. 1 child was unable to tolerate wet wraps in the fluticasone group and 2 stopped after the 1st week and dropped out of the trial because they felt their eczema was static.

Notes

None

Interventions

Run-in details

Participants and their carers initially received a talk about skin care and how to apply their topical treatment. Then, for a 2-week period, all participants applied standardised treatment of 0.005% fluocinolone acetonide cream twice daily on affected areas, used emulsifying ointment as a soap replacement, and used petrolatum as an emollient.

Groups

A: fluticasone propionate 0.005% ointment; diluted ointment (Glaxo Operation, UK) applied once daily for 2 weeks. Apply ointment to affected areas after a bath in the evening. Concurrent treatment: none

B: mometasone furoate 0.1% ointment; diluted preparation (one-tenth strength) ointment (Schering Plough, Canada) applied once daily for 2 weeks. Apply ointment to affected areas after a bath in the evening. Concurrent treatment: none

C: fluticasone propionate 0.005% ointment; diluted ointment (Glaxo Operation, UK) applied under wet wrap once daily for 2 weeks. TubiFast dressings (Seton Healthcare group) were soaked in warm water and placed on affected areas of the body. Dry TubiFast was then placed over the wet later. Undertaken in the evening at bedtime and dressing kept on overnight and removed in the morning (about 8 h duration). Concurrent treatment: none

D: mometasone furoate 0.1% ointment; diluted preparation (one-tenth strength) ointment (Schering Plough, Canada) applied under wet wrap once daily for 2 weeks. TubiFast dressings (Seton Healthcare group) were soaked in warm water and placed on affected areas of the body. Dry TubiFast was then placed over the wet later. Undertaken in the evening at bedtime and dressing kept on overnight and removed in the morning (about 8 h duration). Concurrent treatment: none

Adherence

All creams and ointments were weighed at each visit. No data presented

Co-interventions

We assumed that the standardised soap (emulsifying ointment) and emollient use (petrolatum) continued throughout the randomised phases. Petrolatum was applied to unaffected areas.

Pei 2001 *(Continued)*

	Notes None
Outcomes	• Disease severity score - quantifying the 6 signs of AD: erythema, edema/papulation, oozing/crusting, excoriation, lichenification, and dryness. 8 areas of the body (head and neck, anterior trunk, back, genitalia, and 4 limbs) were graded on a scale of 0-3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe) at week -2, 0, 2, 4 (only weeks 2 to 4 are relevant to this review - randomised to WWT or no WWT).* • Disease extent score - percentage of body area involved. The body was divided into 8 areas. 9% each for head and neck, right upper limb and left upper limb; 18% each for the dorsal aspect of the trunk, ventral aspect of the trunk, right lower limb, left lower limb; and 1% for genitalia at week −2, 0, 2, 4 (only weeks 2-4 are relevant to this review - randomised to WWT or no WWT). • Subjective assessment of AD impact on daily life (effects on school, work, play, social life, choice of clothing, sleep, sensations of itch and pain on a scale of 0-3) at week −2, 0, 2, 4 (only weeks 2-4 are relevant to this review - randomised to WWT or no WWT). *denotes relevance to this review
Funding source	Not stated. Schering Plough supplied the mometasone ointment.
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation involved the use of 50 envelopes with X or Y written inside" Comment: no report as to whether these envelopes were shuffled or if they were opaque.
Allocation concealment (selection bias)	Unclear risk	Quote: "Only the pharmacist distributing the ointment knew the treatment coding" Comment: not clear if the allocation was concealed appropriately
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: it would have not been possible to blind participants to the use of wet wraps.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "For the duration of the study the same blinded observer saw all patients at weekly intervals and recorded and assessed the disease" Comment: outcome assessors were blinded to treatment group.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Twenty-seven patients completed the study. Ten patients stopped before the end of the study because their eczema had improved more than 50% from the baseline. One child was unable to tolerate wet wraps in the fluticasone group and two stopped after the first week and dropped out of the study because they felt their eczema was static" Comment: it is not clear how many participants were randomised to the WWT groups and how many were randomised to no WWT. No trial flow diagram of participants is presented in the review.

Pei 2001 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available to unable to assess if preplanned outcomes were reported in the publication.
Other bias	High risk	Comment: no demographic data presented so unable to see how similar the groups were when they were randomised to WWT or no WWT, however there is a marked baseline mismatch in severity.

Peserico 2008

Study characteristics	
Methods	**Trial design** randomised, double-blind, placebo-controlled, parallel-group trial **Trial registration number** NCT00185510, EudraCT Number: 2004-002673-22 **Setting** 20 centres in Germany, Italy and Spain; no information about whether secondary care or general population **Date trial conducted** August 2005-January 2006 **Duration of trial participation** Non-randomised acute phase was up to 4 weeks (run-in period). Randomised maintenance phase was 16 weeks. **Additional design details** None **Inclusion criteria** • Current flare with IGA score ≥ 4 • ≥ 12 years of age • ≥ 2 years history of moderate-severe AD • ≥ 4 weeks since any systemic AD therapy, vaccination, or local tacrolimus or pimecrolimus • ≥ 1 week since last glucocorticoid therapy • ≥ 2 weeks since last antihistamine therapy **Exclusion criteria** • Pregnancy and lactation • Requirement for systemic AD therapy • Known sensitivity to any of the trial formulations • Known immune, hepatic or renal disease • Acute infections or infestations. **Notes** None
Participants	**Total number randomised**

Peserico 2008 *(Continued)*

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Age

The methylprednisolone aceponate group were aged 31.1 ± 14.7 and the emollient group were aged 30.6 ± 14.7 (mean ± SD).

Sex

Methylprednisolone aceponate = 66 participants were female (58.9%), emollient = 76 participants were female (69.7%).

Race/ethnicity

Methylprednisolone aceponate = 112 participants were white, emollient = 108 participants were white and 1 was Asian

Duration of eczema

Not reported

Severity of eczema

The methylprednisolone aceponate group had mean EASI of 17.2 at the point of screening and 1.9 at the end of the acute phase; the emollient group had mean EASI of 15.3 at the point of screening and 1.4 at the end of the acute phase. Baseline itch scores 8.7 100 mm VAS emollient, 10.1 100 mm VAS methylprednisolone aceponate.

Filaggrin mutation status

Not reported

Number of withdrawals

Methylprednisolone aceponate group = 5 (3 = lost to follow-up, 2 = protocol deviation), emollient group (2 = lost to follow-up, 1 = adverse event)

Notes

Participants were removed from the trial in the event of relapse.

Interventions

Run-in details

Participants were stabilised with once daily open-label methylprednisolone aceponate and emollient for a maximum of 4 weeks then randomised to maintenance phase once IGA ≤ 1

Groups

- Methylprednisolone aceponate 0.1% cream; participants applied once daily TCS and once daily Advabase twice weekly (weekends). Advabase was applied twice daily for the remaining 5 days in the week. Concurrent treatment: none
- No TCS; Advabase was applied twice daily. Concurrent treatment: none

Adherence

Unused cream was returned by the participants for weighing.

Co-interventions

None

Notes

Participants were asked to apply the creams to affected skin, including new lesions and those healed during the acute phase, once in the morning and once in the evening.

Peserico 2008 *(Continued)*

Outcomes	• Relapse rate from beginning of maintenance phase until relapse, measured up to the end of 16-week maintenance phase. Relapse defined as when the participant required or requested more intense therapy. New lesions were reported on separately.* • Time to relapse - number of days from start of maintenance phase until relapse, measured from beginning of maintenance phase until relapse • Participant's assessment of quality of sleep at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16* • Intensity of itching on a 100 mm VAS at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16* • Adverse events (signs of skin atrophy, striae formation and telangiectasia were monitored. The number of local bacterial, viral and fungal infections, and the degree of treatment-related pruritus, irritation and burning, were also documented as adverse events) at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16.* • CDLQI at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16 • EASI at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16 • Assessment of target lesions at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16 • DLQI at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16 • Affected BSA at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16 • PGA of response at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16 • IGA of response at beginning of maintenance phase (baseline), weeks 2, 6, 10 and 16 *denotes relevance to this review
Funding source	Not stated
Declarations of interest	None declared, although 2 authors employed by Intendis GmbH, Berlin. The trial was sponsored by Intendis GmbH, Berlin.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: ."Randomization at the end of the AP [acute phase] was carried out in blocks according to the patients' arrival at the study centre and aimed to achieve a 1: 1 randomization ratio overall and within each centre." Comment: randomisation method not fully described
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ."MP [maintenance phase] medication was packed in identical tubes to ensure blinding." Comment: unclear which personnel were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All assessments were performed under double-blind conditions." Comment: blinded assessments were performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The last-observation carried- forward principle was applied to impute missing values in secondary analyses.""Efficacy was assessed for the full analysis set (FAS), including all patients who entered the MP, and for the per protocol set (PPS), which excluded patients with major protocol violations." "Safety was assessed for all patients to whom AP medication was dispensed

Peserico 2008 *(Continued)*

		and for the FAS. The efficacy results from the FAS and PPS groups were comparable." "...213 completed 16 weeks of treatment or were treated until relapse (107/112 in the MPA group and 106/109 in the emollient group)." Comment: dropout rates were low and an ITT analysis was conducted.
Selective reporting (reporting bias)	Unclear risk	Comment: the publication failed to report dispersion data for some outcomes and did not present difference between groups or exact P values. Most data were presented in graphs.
Other bias	Low risk	Comment: no other sources of bias identified

Portnoy 1969

Study characteristics	
Methods	**Trial design** Randomised, double-blind, half-sided **Trial registration number** Not reported **Setting** Outpatients from the Manchester and Salford Hospital for Skin Diseases, UK according to the affiliation of the author and address given. **Date trial conducted** Not reported **Duration of trial participation** 1 week **Additional design details** None **Inclusion criteria** • Outpatients with bilateral, symmetrical eczema **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised** 39 participants treated on both sides of the body. **Age** Not reported **Sex**

Portnoy 1969 *(Continued)*

	Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** 1 participant dropped out ("defaulted") and it is not clear if this was an eczema or psoriasis participant. **Notes** None
Interventions	**Run-in details** Not reported **Groups** • HC 1%; applied twice daily for 1 week to the designated side without polythene occlusion. Concurrent treatment: none • Fluocortolone 0.2% (Ultralan D); applied twice daily for 1 week to the designated side without polythene occlusion. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Not reported **Notes** "In order to reduce the risk of admixture of the preparations applicators labelled "left" and "right" were supplied." "The preparations used were 1% hydrocortisone in a base composed of liquid paraffin, soft paraffin, cetyl alcohol, lauryl sulphate and propylene glycol and 0.1% fluocortolone trimethyl acetate and 0.1% fluocortolone caproate, in a base containing white wax, lanoline, mineral oil, white paraffin, amphocerin K and demineralized water."
Outcomes	• Preference for 1 steroid over the other (N.B. the paper states "only where the patient agreed with the trialist reading the result was a definitive positive finding recorded") at day 7.* *denotes relevance to this review
Funding source	None stated, however Schering A. G. Berlin were acknowledged as having provided materials and contributed to statistical analysis.
Declarations of interest	None declared, however Schering A. G. Berlin were acknowledged as having provided materials and contributed to statistical analysis.

Portnoy 1969 *(Continued)*

Notes	This trial included patients with eczema and psoriasis; only data for eczema participants was extracted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "order of application of the preparations was determined by using random number tables." Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Comment: no information given for this domain
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind", "the materials were packed in identical 30g tubes which were paired and labelled for use on the right or left side of the body" Comment: although it is likely the participants were blinded, it is unclear which other parties were also blinded, e.g. whether the personnel looking after the participant knew which treatment they were receiving or whether the investigator assessing the outcomes was aware of the treatment the participant was receiving
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: it is unclear which other parties were also blinded, e.g. whether the personnel looking after the participant knew which treatment they were receiving or whether the investigator assessing the outcomes was aware of the treatment the participant was receiving
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "a total of fifty patients was studied and one defaulted". Comment: whilst there is no information about which disease the withdrawn participant had, it is unlikely to contribute bias to the results especially in a half-sided trial.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias detected

Prado de Oliveira 2002

Study characteristics

Methods	**Trial design** Double-blind, randomised comparative trial **Trial registration number** Not reported **Setting** Dermatology Department of the Hospital das Clinicas, Faculty of Medicine, University of São Paulo, Brazil **Date trial conducted** Not reported

Prado de Oliveira 2002 *(Continued)*

Duration of trial participation

Last visit was 42 days however the paper states that there was a mean number of treatment days mometasone 26.8, desonide 25.7 and that the duration of treatment varied from 7-42 days.

Additional design details

None

Inclusion criteria

- Patients with AD
- Children aged 2-12 years of age
- Patient of any race or sex
- Atopic dermatitis involving 6% of the BSA
- Without other clinically significant disease
- Minimum total score* of 8 from the clinical variables and 2 for the erythema variable. * erythema, lichenification, desquamation, excoriation and pruritus were assessed. These were scored 0 - absent: no evident sign/symptom; 1 - slight: sign/symptom present, though ill defined and easily tolerated; 2 - moderate; sign/symptom present, well defined and uncomfortable, although still tolerable; 3 - intense: sign/symptom difficult to tolerate, interfering in the daily activities and/or during sleep

Exclusion criteria

- Abnormal results on laboratory examinations performed during baseline visits
- Previous serious disease
- Immunosuppression
- Evidence of cutaneous atrophy in the target area of treatment
- Use of TCS or any other therapies for dermatitis in the 7 days prior to the beginning of the trial
- Use of emollients in the 2 days prior to the trial
- History of previous hypersensitivity to desonide or mometasone furoate
- Use of any other medication in the 15 days before the beginning of the trial that could have clinical effect on the course of dermatitis
- Use of systemic corticosteroid in the 28 days prior to the beginning of the trial
- Use of antibiotics 1 week before beginning the trial

Notes

None

Participants

Total number randomised

25 (13 mometasone, 12 desonide)

Age

Mometasone: mean (SD) = 7.2 years (2.7), range 3-11 years. Desonide: mean (SD) = 4.8 years (3.1), range 2-12 years.

Sex

Not reported

Race/ethnicity

Mometasone: white = 8 participants, black = 0 participants, mixed = 4 participants. Desonide: white = 4 participants, black = 1 participant, mixed = 7 participants.

Duration of eczema

Prado de Oliveira 2002 *(Continued)*

Not reported, however the text states "several previous attempts at treatment were mentioned for AD, of which the most frequent were antihistamines, antibiotics, and topical corticoids, all with recurrence of the picture".

Severity of eczema

Mean sum of total scores was 9.1 in the mometasone group and 8.7 in the desonide group at baseline.

Filaggrin mutation status

Not reported

Number of withdrawals

1 participant in the desonide group interrupted treatment due to bronchopneumonia. All other participants completed the trial.

Notes

Differences in age and race not statistically different. The total number of participants in the desonide group provided in the race/ethnicity characteristics is 13 rather than 12 quoted in the rest of the paper. In table 1 it says characteristics are missing from 1 participant from each group, however, we think the participant is missing from the mometasone group.

Interventions

Run-in details

NA

Groups

- Desonide 0.05% cream; applied once daily after a bath for up to 42 days. Concurrent treatment: none
- Mometasone furoate 0.1% cream; applied once daily after a bath for up to 42 days. Concurrent treatment: none

Adherence

None

Co-interventions

During the trial participants were not allowed to use antibiotics, antihistamines, topical emollients, other corticosteroids or any other drug shown in clinic or laboratory to be associated with hepatotoxicity or that could induce an increase in hepatic enzymes.

Notes

None

Outcomes

- IGA: improvement of signs and symptoms were evaluated according to the following scores: scale 1 = disappearance of the lesions (100%), 2 = notable improvement (75%-100%), 3 = moderate improvement (50%-75%), 4 = slight improvement (< 50%), 5 = no alteration, 6 = exacerbation at assumed to be at days 3, 7, 14, 21, 35, and 42*
- Signs of cutaneous atrophy: thinning of the skin, striae, shiny skin, telangiectasia, loss of elasticity, loss of normal lines on the cutaneous surface were evaluated using the score system 0 = absent; 1 = slight; 2 = moderate; 3 = intense at assumed to be at baseline and days 3, 7, 14, 21, 35, and 42.*
- Tolerance to the drugs was evaluated according to the participant's complaints, whether spontaneous or prompted by questions, and whether or not these could be related to the treatment at assumed to be at days 3, 7, 14, 21, 35, and 42.*
- Laboratory tests including total blood count, glycaemia, TGO and TGP at baseline and day 42. TGO and TGP assumed to be aspartate (AST) and alanine transaminases (ALT) (Spanish translation of synonyms).
- Heart rate, blood pressure and respiratory rate in sitting and standing positions at 7 pretreatment control visits and after 3, 7, and 42 days of treatment.

Prado de Oliveira 2002 *(Continued)*

- Body surface involved based on evaluation of the palm of the participant's right hand, which is equal to 1% of the total body surface at assumed to be at baseline and days 3, 7, 14, 21, 35, and 42*
- Clinical severity scores for variables such as erythema, lichenification, desquamation, excoriation and pruritus. Classified using the following scale: 0 = absent (no evident sign/symptom), 1 = slight (sign/symptom present, though ill-defined and easily tolerated), 2 = moderate (sign/symptom present, well defined and uncomfortable, although still tolerable), 3 = intense (sign/symptom difficult to tolerate, interfering in the daily activities and/or during sleep) at assumed to be at baseline and days 3, 7, 14, 21, 35, and 42

*denotes relevance to this review

Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "allocated at random" "randomised" Comment: no detailed information regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind" Comment: no information as to which involved group (participants, personnel or outcome assessors) were blinded or the method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind" Comment: no information as to which involved group (participants, personnel or outcome assessors) were blinded or the method of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient in the desonide group interrupted treatment due to associated disease - bronchopneumonia - all the remaining patients concluded the study" Comment: only 1 participant did not finish the trial and so even if their data were not included in any analysis it is unlikely this would have made a difference
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias was identified

Queille 1984

Study characteristics

Methods	**Trial design** RCT **Trial registration number**

Queille 1984 *(Continued)*

Not reported

Setting

Inpatient settings in Switzerland and France

Date trial conducted

Not reported

Duration of trial participation

7 days run-in, then 6 days initial treatment phase followed by a phase of treatment on alternate days lasting up to between 19 and 180 days (unclear from when this is measured).

Additional design details

None

Inclusion criteria

- Children with severe AD (hospitalised)
- Clinical score ≥ 45 derived from assessment of the following signs and symptoms: erythema, oedema, vesicles, crusts, excoriations, scales, lichenification, pigmentation, pruritus, and loss of sleep (each ranked on an 8-point scale from 0-7) combined with an extent score up to 30 meaning generalised spread
- BSA involvement of ≥ 50%
- Patients who had not used TCSs within the preceding 2 weeks
- Patients who had never been treated with systemic corticosteroids

Exclusion criteria

None of the children had been treated with local corticosteroids for at least 2 weeks previously and never with systemic corticosteroids.

Notes

None

Participants	**Total number randomised** 26 **Age** Overall mean 3 years and 5 months (range 5 months-12 years) **Sex** 18 male and 8 female participants overall **Race/ethnicity** 20 participants were white, 3 were black, 3 were Asian overall **Duration of eczema** Not reported **Severity of eczema** Baseline severity data are available on an individual basis within the paper. **Filaggrin mutation status** Not reported

Queille 1984 *(Continued)*

Number of withdrawals

For 1 child, fluocortin butylester was replaced with another steroid in order to gain control.

Notes

None

Interventions	**Run-in details** For the 1st week of hospitalisation it is stated that "local treatment consisted of daily baths with trichlorocarban and the application of sodium fusidate ointment, a potent antistaphylococcal antibiotic. Systemic treatment consisted of hydroxyzine." Treatment then began on day 7 (0 in our extraction). **Groups** **A**: desonide 0.05% cream (proprietary: unspecified); applied once a day in the morning, without occlusion. Concurrent treatment: not reported **B**: fluocortin butylester 0.75% cream (proprietary: unspecified); applied once a day in the morning, without occlusion. Concurrent treatment: not reported **C**: clobetasone butyrate 0.05% cream (proprietary: unspecified); applied once a day in the morning, without occlusion. Concurrent treatment: not reported **D**: betamethasone dipropionate 0.05% cream (proprietary: unspecified); applied once a day in the morning, without occlusion. Concurrent treatment: not reported **E**: difluorocortolone valerianate 0.1% cream (proprietary: unspecified); applied once a day in the morning, without occlusion. Concurrent treatment: not reported **F**: halcinonide 0.1% cream (proprietary: unspecified); applied once a day in the morning, without occlusion. Concurrent treatment: not reported All TCS were applied daily for the first 6 days and then on alternate days until the participant was discharged. **Adherence** Amount of steroid used was calculated by weighing the tubes. It is stated that "the mean quantity applied over five days was 16.6 g (from 5 to 45 g), that is, 3.3g (1 to 9 g) per day. This quantity bears no relation either to the severity of the dermatitis as determined by the clinical score at entry, or to surface area treated for each child […] The quantity required to cover the same skin area varied for the same preparation according to the person who applied the treatment (23). Differences among the products may also be an additional factor in the variations." Individual usage data are given in the paper. **Co-interventions** Not reported; participants remained in hospital. **Notes** None
Outcomes	• Morning plasma cortisol (a series at 7:30, 8 and 8:30 am): competitive binding to transcortine after a double extraction with dichlormethane and then carbon tetrachloride at baseline (2 consecutive days in the week preceding the trial), and days 2, 4, 6, and at follow-up "in children with lowered levels" (19-180 days; unclear from when this is measured)* • Investigator assessment of signs and symptoms adapted from Clendenning and co-workers: erythema, oedema, vesicles, crusts, excoriations, scales, lichenification, pigmentation, pruritus, and loss of sleep (each ranked on an 8-point scale from 0-7) combined with an extent score up to 30 meaning generalised spread at admission (day 7), baseline (day 0) and day 6.* Notes: this is referred to as "lesional"

Queille 1984 *(Continued)*

	score in the outcome tables, with % BSA given separately, however it does state in the methods that "the total score thus obtained out of 100 permitted us to follow progress during treatment."
Funding source	None stated
Declarations of interest	None declared
Notes	Raw cortisol measurements given per person have been converted to number of participants with abnormal cortisol measurements using a reference range from the Royal College (Canada) 6-23 µg/dL or 170-635 nmol/L.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the preparation (selected by random choice)..." Comment: no information about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "differences among the products may also be an additional factor in the variations." "The investigator knew the day of administration and the medication the children received". Comment: nothing to suggest that the children, or the people applying their treatment, were blinded, or if the products were sufficiently similar to ensure blinding. Investigators were stated to be unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the investigator knew […] the medication the children received." Comment: this knowledge may have influenced the investigator's assessments.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "A single investigator made all the clinical observations on all children. This explains the fact that for some children a clinical score could be missing". Comment: no data reported at follow-up times for 8/26 participants, which is 30.8%, so incomplete data are a potential concern for bias. The study authors do not provide a full explanation for why these data were missing, but we felt we were unable to judge if this reason for missing data was likely to be related to the true outcome or not.
Selective reporting (reporting bias)	High risk	Comment: no protocol available In table 6, however, the mean difference at day 6 fails to take into account the case that worsened during the treatment period.
Other bias	Low risk	Comment: no additional sources of bias detected

Rafanelli 1993

Study characteristics

Methods	**Trial design** 3rd-party-blind, randomised, parallel-group trial **Trial registration number** Not reported

Rafanelli 1993 *(Continued)*

Setting

Not reported

Date trial conducted

Not reported

Duration of trial participation

3 weeks

Additional design details

None

Inclusion criteria

- Children with AD, otherwise in good general health
- Presence of the following signs in a target area: erythema, induration and pruritus
- Total severity score ≥ 6 according to a scale from 0 = none to 3 = severe (presumably scored for each sign, but this is not stated).
- Stable disease or disease that worsened for > a week

Exclusion criteria

- Participants had not received corticosteroids either topically in the week before the trial
- Participants had not received corticosteroids systemically in the 4 weeks before the trial
- Participants did not show signs of atrophy on physical examination (atrophy was assessed at baseline according to the scale 0 = none; 1 = mild; 2 = moderate; 3 = severe)
- Participants were not known to be hypersensitive to the drugs or to the components of the formulations.

Notes

No medication that might interfere with the drugs under investigation was allowed; all other medications given during the trial were recorded.

Participants

Total number randomised

60; 30 randomised to each group

Age

Mean 7.7 years ± SD 3.2 (range 2-12) in the mometasone once daily group compared to 6.8 ± 3.1 (2-12) in the clobetasone twice daily group.

Sex

12 male to 18 female in both groups

Race/ethnicity

Not reported

Duration of eczema

Mean 26.7 months ± SD 22.2 (range 1-72) in the mometasone once daily group compared to 16.4 ± 15.7 (1-48); P < 0.05 between the groups

Severity of eczema

Mean total signs and symptoms score* was 7.8 ± SD 1.1 in the mometasone once daily group compared to 7.2 ± 0.9 in the clobetasone twice daily group

Rafanelli 1993 *(Continued)*

	*sum of scores 0 = none to 3 = severe for each of erythema, induration, and pruritus. Mometasone percent body involved: up to 25% 93.3%, 26%-50% 6.7 Clobetasone percent body involved: up to 25% 100.0, 26%-50% 0 **Filaggrin mutation status** Not reported **Number of withdrawals** The paper states "all patients completed the study" **Notes** None
Interventions	**Run-in details** NA **Groups** • Clobetasone 0.05% cream (unspecified); applied twice daily for up to 3 weeks. Concurrent treatment: not reported • Mometasone furoate 0.1% cream (unspecified); applied once daily for up to 3 weeks. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** All other medications used by the participants during the trial were recorded. **Notes** None
Outcomes	• Laboratory tests, especially blood cortisol at baseline and at the end of treatment* • Total and individual signs and symptoms scores from 0 = none to 3 = severe, for erythema, induration, and pruritus at days 0, 2, 3, 4, 7, 14 and 21 • Safety evaluation involving questioning the participant/parents about side effects and a skin examination of alterations or atrophy at days 0, 2, 3, 4, 7, 14 and 21* • Physician global evaluation (according to the scale 1 = cleared (disappearance of all symptoms); 2 = marked improvement (> 75% clearance of symptoms); 3 = moderate improvement (50-75% clearance of symptoms); 4 = slight improvement (< 50% clearance of symptoms); 5 = no change (no improvement from baseline); 6 = exacerbation (worsening at evaluated sites)) at baseline and days 2, 3, 4, 7, 14, and 21* • Parents' evaluation of efficacy from 1 = excellent, 2 = good, 3 = fair, 4 = poor at baseline and days 2, 3, 4, 7, 14, and 21* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None
Risk of bias	

Rafanelli 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: no further detail provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "third-party blind" Comment: no mention of any placebo so unlikely participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "third-party blind" "always by the same physician (in blind)." Comment: it is likely that the assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients completed the study" Comment: if all participants completed the trial and contributed data for each outcome then this would not be a source of bias in this trial.
Selective reporting (reporting bias)	Unclear risk	Comment: a protocol for this trial is not available. There is also very little information regarding the participant-reported outcomes. Participant parents' data were not included in the trial report and there is very little information from the PGA.
Other bias	Low risk	Comment: no other source of bias was identified.

Rajka 1986

Study characteristics	
Methods	**Trial design** Randomised, double-blind, half-sided trial **Trial registration number** Not reported **Setting** Outpatients in Norway, assumed from the 1st author's affiliation **Date trial conducted** Not reported **Duration of trial participation** 4 weeks **Additional design details** None **Inclusion criteria** • Patients with symmetrical, bilateral AD

Rajka 1986 *(Continued)*

- Aged > 16 years of age
- Global severity of ≥ 2 (moderate on a 5-point scale) at baseline

Exclusion criteria

- Participants with a primary bacterial or viral skin infection (e.g. erysipelas, tuberculosis, syphilis, varicella, vaccinia, herpes zoster, herpes simplex)
- Participants with a secondarily infected dermatosis
- Participants with malignant disease
- Pregnant and lactating women, and women of childbearing age not taking adequate precautions to avoid pregnancy
- Participants requiring systemic steroids or who had used glucocorticoids within the preceding 2 weeks

Notes

None

Participants	**Total number randomised** States "30 patients were admitted to be randomised" however also mentions "drop-outs had to be replaced" **Age** Mean overall age was 28.5 years ± SD 11.6 (range 17-63) **Sex** Overall, there were 10 male and 20 female participants included in this trial **Race/ethnicity** Not reported **Duration of eczema** Mean duration overall was 16.7 years ± SD 8.4 (range 2-40). **Severity of eczema** Baseline assessment of "global severity of skin symptoms"* hydrocortisone 17-butyrate mean 2.8 SD 0.4 n = 30, desonide mean 2.8 SD 0.4 n = 30 *Physician assessed global severity of skin symptoms (0 = none, 1 = slight, 2 = moderate, 3 = severe and 4 = very severe). Only 1 skin lesion or area on each treated side was assessed. **Filaggrin mutation status** Not reported **Number of withdrawals** Although paper states "drop-outs had to be replaced", no dropouts are specifically reported in the paper. **Notes** None
Interventions	**Run-in details** Not reported **Groups**

Rajka 1986 *(Continued)*

- Desonide 0.1% ointment (proprietary: Apolar); applied twice daily to the designated side for 4 weeks "or until complete clearance of the lesions of the involved side had occurred, whichever was the shortest." Concurrent treatment: none
- HC 17-butyrate 0.1% fatty cream (proprietary: Locoid); applied twice daily to the designated side for 4 weeks "or until complete clearance of the lesions of the involved side had occurred, whichever was the shortest." Concurrent treatment: none

Adherence

Not reported

Co-interventions

Use of occlusive dressings was not permitted. Participants were asked to wash their hands between applications to avoid contamination between treatments.

Notes

None

Outcomes	• IGA improvement; considerable improvement, definite improvement, minimal improvement, no change, worsening of skin lesions. Skin lesions on both sides of the body were individually rated at week 4.* • Side effects (spontaneously reported) at up to week 4* • Participant preference for cosmetic acceptability at weeks 2 and 4 • Severity of erythema, induration and scaling were assessed according to Fredriksson, Lassus and Salde (1983). Skin lesions on both sides of the body were individually rated at weeks 0, 2 and 4 • IGA of the severity of skin symptoms on both sides (5-point scale: 0 = none to 4 = very severe). Only 1 skin lesion or area on each treated side was assessed at weeks 0, 2 and 4 *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared, however 1 author was affiliated to Research and Development, Gist-brocades.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were assigned to treatment with Locoid 0.1% fatty cream to skin lesions on one side of the body and Apolar 0.1 % ointment to the contralateral side according to a randomized code." Comment: there was no information as to how the code was generated and so it is not possible to assess the risk of bias associated with the method used.
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "According to this code tubes marked 'left' and 'right' were given for treatment of the skin lesions on the left and right sides of the body, respectively, after patients had given consent to participation" and "double-blind" Comment: it could be assumed that participants were blinded as they only received tubes marked 'left' and 'right', however there is no information given about which personnel were blinded, or how.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "double-blind"

Rajka 1986 *(Continued)*

All outcomes		Comment: there is no information given about which personnel were blinded, or how.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "drop-outs had to be replaced"; "patients have been included only if they experienced the symptom on at least one occasion during the trial period, some ten patients had no scaling, and erythema and induration were not observed in one patient (Table 2)"; "all reasons for withdrawing patients from the study were to be clearly noted on the patient card"
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias detected

Rampini 1992a

Study characteristics	
Methods	**Trial design** 3 multicentre trials (only 2 applicable the other trial is reported in Rampini 1992b), double-blind, randomised, controlled group comparisons **Trial registration number** Not reported **Setting** Multiple centres in Germany, Austria, and Italy **Date trial conducted** Not reported **Duration of trial participation** 21 days **Additional design details** None **Inclusion criteria** • Children with AD • No requirement for systemic corticosteroid therapy • TCS had not been applied during the preceding 3 days prior to the beginning of the trial • No requirement for other systemic or topical therapy that might influence the treatment results in any way **Exclusion criteria** No further criteria reported **Notes** None
Participants	**Total number randomised**

Rampini 1992a *(Continued)*

Methylprednisolone aceponate once daily versus prednicarbate twice daily n = 120, only 108 assessed (see withdrawals)

Age

4 months-14 years for comparison 2 (median 5.4 of 108 assessed)

Sex

Of 108 assessed for methylprednisolone aceponate once daily versus prednicarbate twice daily comparison 2, 50 were male and 58 female

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Not reported

Filaggrin mutation status

Not reported

Number of withdrawals

Only 108 out of the 120 participants originally enrolled in the methylprednisolone aceponate once daily versus prednicarbate twice daily are reported in the results. The paper does report "the treatment of one participant in each group was prematurely discontinued due to 'lack of efficacy". However, there is no explanation given for the other 10 participants missing from the results section.

Notes

Interventions	**Run-in details** None **Groups** • Methylprednisolone aceponate 0.1% ointment (proprietary: Advantan, Schering AG, Germany); the participants were treated with methylprednisolone aceponate once daily in the evening with an additional application of the ointment vehicle in the morning. Concurrent treatment: none • Prednicarbate 0.25% ointment (proprietary: Dermatop, Cassella-Riedel, Germany); applied twice daily for a maximum of 21 days. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Not reported **Notes** 1 participant in the methylprednisolone aceponate group received short-term antibiotic therapy for impetigo contagiosa.
Outcomes	• Global therapeutic effect categorised as complete healing, distinct improvement, moderate therapeutic effect, no therapeutic effect, deterioration (comparisons 1 and 2 only) at day 21* • Local and general adverse events recorded using a specifically designed form at up to day 21*

Rampini 1992a *(Continued)*

- Objective and subjective symptoms categorised as absent, mild, or severe (comparisons 1 and 2) at day 21 (assumed).

*denotes relevance to this review

Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised allocation" Comment: no information provided about how this was done
Allocation concealment (selection bias)	Unclear risk	Comment:no information provided about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind" "The patients were treated with MPA once-daily in the evening with an additional application of the ointment vehicle in the morning, or twice daily with the PC ointment". Comment: participants were treated with a vehicle at the time when participants in the other group would receive a second dose of steroid. However, it is not clear which personnel were blinded, or how this was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided about outcome assessment blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the numbers that were reported as the numbers of participants randomised are quite different to those included in the results section. For example, 120 participants were randomised however results were only reported for 108. There is no indication as to why these participants were excluded from the analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: there is no protocol available for this trial and so it is not possible to say whether all pre-planned outcomes are reported.
Other bias	Low risk	Comment: no other sources of bias detected

Rampini 1992b

Study characteristics

Methods	**Trial design** 3 multicentre trials (only 2 applicable, the other trial is reported in Rampini 1992a), double-blind, randomised, controlled group comparisons **Trial registration number** Not reported **Setting**

Rampini 1992b *(Continued)*

Multiple centres in Germany, Austria, and Italy

Date trial conducted

Not reported

Duration of trial participation

21 days

Additional design details

None

Inclusion criteria

- Children with AD
- No requirement for systemic corticosteroid therapy
- TCS had not been applied during the preceding 3 days prior to the beginning of the trial
- No requirement for other systemic or topical therapy that might influence the treatment results in any way

Exclusion criteria

No further criteria reported

Notes

None

Participants	**Total number randomised** Methylprednisolone aceponate twice daily versus prednicarbate twice daily n = 80, only 78 assessed (see withdrawals) **Age** 3-14 years (median of 78 assessed was 8.25 years) **Sex** Of 78 assessed for methylprednisolone aceponate twice daily versus prednicarbate twice daily comparison 1, 40 were male and 38 female **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Only 78 participants out of the 80 who were originally enrolled in methylprednisolone aceponate twice daily vs prednicarbate twice daily trial are reported in the results. No reasons are given for why this was the case.

Rampini 1992b *(Continued)*

	Notes
Interventions	**Run-in details** None **Groups** • Methylprednisolone aceponate 0.1% cream (proprietary: Advantan, Schering AG, Germany); applied twice daily for a maximum of 21 days. Concurrent treatment: none • Prednicarbate 0.25% cream (proprietary: Dermatop, Cassella-Riedel, Germany); applied twice daily for a maximum of 21 days. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Not reported **Notes** None
Outcomes	• Global therapeutic effect categorised as complete healing, distinct improvement, moderate therapeutic effect, no therapeutic effect, deterioration (comparisons 1 and 2 only) at day 21* • Local and general adverse events recorded using a specifically designed form at up to day 21* • Objective and subjective symptoms categorised as absent, mild, or severe (comparisons 1 and 2) at day 21 (assumed) *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised allocation" Comment: no information provided about how this was done
Allocation concealment (selection bias)	Unclear risk	Comment:no information provided about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind" "The patients were treated with MPA [methylprednisolone aceponate] once-daily in the evening with an additional application of the ointment vehicle in the morning, or twice daily with the PC [prednicarbate] ointment". Comment: in this comparison, it is not clear which personnel were blinded, or how this was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided about outcome assessment blinding

Rampini 1992b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 2 participants out of the 80 were not included in the results so this is unlikely to introduce bias.
Selective reporting (reporting bias)	Unclear risk	Comment: there is no protocol available for this trial and so it is not possible to say whether all pre-planned outcomes are reported.
Other bias	Low risk	Comment: no other sources of bias detected

Reidhav 1996

Study characteristics	
Methods	**Trial design** Randomised, double-blind, half-side trial **Trial registration number** Not reported **Setting** Trial authors were affiliated to Department of Dermatology, Central Hospital, S-29185 Kristianstad, Sweden. **Date trial conducted** Not reported **Duration of trial participation** 4 weeks **Additional design details** None **Inclusion criteria** • Consecutive patients with "typical" AD fulfilling "standardised criteria" (Svensson 1985; Svensson 1989). • Eczematous lesions had to be symmetrical and involve > 5% of the BSA • On entry a target area of symmetrical dermatitis on the trunk or extremities with a total severity score* of at least 5, which measured between 5 cm and 10 cm in diameter was selected for specific evaluation. *Sum of erythema, scaling, lichenification, excoriation, papules and vesicles scores from 0-3. The maximum possible score was 18. **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised** 30 participants (60 sides of the body), sides were randomised as to whether they received betamethasone valerate or mometasone furoate

Reidhav 1996 *(Continued)*

Age

Between 15 and 66 years (median 26.4 years)

Sex

Not reported

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Not reported

Filaggrin mutation status

Not reported

Number of withdrawals

1 participant did not attend the final visit (no reason provided) but did answer the questions about cosmetic quality of the products.

Notes

None

Interventions	**Run-in details** NA **Groups** • Betamethasone valerate 0.1% cream; cream applied once daily on 1 side of the body for 4 weeks. Concurrent treatment: none • Mometasone furoate 0.1% cream; cream applied once daily on the other side of the body for 4 weeks. Concurrent treatment: none **Adherence** Trial nurses contacted participants by telephone during weeks 2 and 3. The weight of medication used was recorded at 1 and 4 weeks, however weight data were missing for 6 participants at week 1 and 3 participants at week 4. After 1 week of treatment, there was no difference in the amount of treatment used - after 4 weeks 34.1 g of betamethasone and 31.4 g of mometasone cream was used per participant ($P < 0.05$ statistically significant difference). **Co-interventions** Locobase cream for use as an emollient was the only additional treatment permitted. **Notes** None
Outcomes	• Participant evaluation of cosmetic properties of the 2 preparations at week 1 and 4 • Participant-reported effectiveness (by preference) at week 1 and 4 (assumed)* • Participant-reported severity of pruritus and smarting pain - scale from 0-3 at baseline, at each visit (not sure if this is weekly or just at week 1 and 4)*

Reidhav 1996 *(Continued)*

- Target area severity score (investigator-assessed) - parameters erythema, scaling, lichenification, excoriation, papules and vesicles were assigned severity scores from 0-3 (maximum score 18). Target area for evaluation required to be between 5 and 10 at baseline, week 1, 4.*
- Participant compliance - monitored by trial nurse telephone contacts at week 2, 3
- Participant compliance - amount of medication determined by weight at each visit (not sure if this is weekly or just at week 1 and 4).

*denotes relevance to this review

Funding source	The trial authors acknowledge the support of Glaxo-Wellcome. No further information given.
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each patient was treated with one preparation on the left and the other preparation on the right side of the body, by random allocation." Comment: no description of randomisation method
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "randomized double-blind study" Comment: no description of who exactly was blinded and how blinding was achieved (e.g. labelling of tubes)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "randomized double-blind study" Comment: no description of who was exactly blinded and how blinding was achieved (e.g. labelling of tubes)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient did not attend the final visit but did answer the questions about cosmetic quality of the products. " For compliance data " Data were, however, missing for six patients after 1 week and for 3 patients after 4 weeks of treatment. " Comment: the trial authors stated where data were missing, however, this was with regards to the compliance data which is not an included outcome in this review. Only 1 participant was missing at the final visit.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. Only raw data given for the participant preference of cosmetic quality outcome - no raw data for symptom scores provided
Other bias	Low risk	Comment: no other risk of bias identified

Richelli 1990

Study characteristics

Methods	**Trial design**

Richelli 1990 *(Continued)*

Randomised, parallel-group trial

Trial registration number

Not reported

Setting

Not reported

Date trial conducted

Not reported

Duration of trial participation

7 days

Additional design details

None

Inclusion criteria

Children with AD who had not used topical steroids within the last fortnight

Exclusion criteria

Not reported

Notes

None

Participants

Total number randomised

30; 13 into the twice daily 8 am/3 pm group; 8 into the twice daily 3 pm/8 pm group; 9 into the once daily group

Age

Mean age 4.17 years in the twice daily 8 am/3 pm group; 5.25 years in the twice daily 3 pm/8 pm group; 5.56 years in the once daily group

Sex

7 male to 6 female participants in the twice daily 8 am/3 pm group; 5 male, 3 female in the twice daily 3 pm/8 pm group; 3 male, 6 female in the once daily group

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Mean sign severity scores were 1.27, 1.24, 1.21 in the twice daily 8 am/3 pm, twice daily 3 pm/8 pm, and once daily groups respectively, estimated using WebPlotDigitizer; symptoms (itching, burning, pain) and signs (erythema, oedema, exudation, blisters, bullae, scabs, scaling and lichenification) were classified and scored from 0 (none) to 3 (severe).

Filaggrin mutation status

Not reported

Richelli 1990 *(Continued)*

	Number of withdrawals Not reported **Notes** None
Interventions	**Run-in details** NA **Groups** **A**: clobetasone 17-butyrate 0.05% lotion (proprietary: Glaxo S.Pa, Verona, Italy); TCS applied twice daily at 8 am and 3 pm without occlusion. Concurrent treatment: none **B**: clobetasone 17-butyrate 0.05% lotion (proprietary: Glaxo S.Pa, Verona, Italy); TCS applied twice daily at 3 pm and 8 pm without occlusion. Concurrent treatment: none **C**: clobetasone 17-butyrate 0.05% lotion (proprietary: Glaxo S.Pa, Verona, Italy); TCS applied once daily at 9 pm without occlusion. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Not reported **Notes** Not reported
Outcomes	• Symptoms (itching, burning, pain) and signs (erythema, oedema, exudation, blisters, bullae, scabs, scaling and lichenification) were classified and scored from 0 (none) to 3 (severe) at baseline and day 1, 2, 3, 4, 5, 6, and 7.* • Serum cortisol and ACTH concentrations at baseline and day 7, 8 am and 4 pm* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "each patient was randomly assigned to one of three treatment groups". Comment: no information about how this was done
Allocation concealment (selection bias)	Unclear risk	Comment: no information about allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: no mention of blinding

Richelli 1990 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no mention of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: no mention of any withdrawals, yet the number of lines on the ACTH graph is lower (perhaps indicating the number of participants is reduced) on the after treatment graph rather than the before. This may mean some participants are missing.
Selective reporting (reporting bias)	Unclear risk	Comment: there was no protocol available
Other bias	Low risk	Comment: no other source of bias detected

Rossi 2002

Study characteristics	
Methods	**Trial design** Randomised, investigator-blinded, active controlled, parallel-group, trial **Trial registration number** Not reported **Setting** Secondary care in the UK, France, and Germany, assumed from the list of affiliations **Date trial conducted** Not reported **Duration of trial participation** 3 weeks **Additional design details** None **Inclusion criteria** Not reported, however title states AD **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised** 152 enrolled; unclear how many were randomised or to which group **Age**

Rossi 2002 *(Continued)*

	Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported **Notes** None
Interventions	**Run-in details** Not reported **Groups** • Desonide 0.05% lotion; applied for up to 3 weeks. Concurrent treatment: not reported • Fluocortolone 0.5% ointment; applied for up to 3 weeks. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** None
Outcomes	• Pruritus at baseline and end of treatment (week 3) at least, assumed* • The paper states safety was measured but contains no details on how this was measured, up to week 3, assumed.* • Efficacy: sum of scores for erythema, infiltration/papulation, excoriation, lichenification and oozing/crusting, further details not specified at baseline and end of treatment (week 3) at least, assumed* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Rossi 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" Comment: no other information given
Allocation concealment (selection bias)	Unclear risk	Comment: no details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "investigator-blinded" Comment: participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "investigator-blinded" Comment: no details were given for how blinding was achieved, and blinding may have been compromised as the participants were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no data were presented, only P values, so it is unclear whether all enrolled participants were included until the end of the trial
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available and insufficient detail
Other bias	Low risk	Comment: no other sources of bias detected

Roth 1973

Study characteristics

Methods

Trial design

Randomised, double-blind, half-sided

Trial registration number

Not reported

Setting

Assumed to be secondary care in the USA from the affiliations of the authors. Lead author affiliated to Atopic Dermatitis Clinic, University of California School of Medicine

Date trial conducted

Not reported

Duration of trial participation

2 weeks

Additional design details

Doesn't explicitly state half-sided but reporting of results and mention of 'symmetrical lesions' make it clear that it is.

Inclusion criteria

Roth 1973 *(Continued)*

- Patients with diagnoses of psoriasis or AD (only the latter subgroup is considered and data are extracted separately where it has been possible).
- Patients with symmetrical lesions

Exclusion criteria

Not reported

Notes

None

Participants	**Total number randomised** 31 AD participants were enrolled, 21 into the trial of mild (HC) versus moderate (fluocinonide) steroid **Age** Of the 31 AD participants, mean age was 23.4 years (range 18 months to 59 years). **Sex** Of the 31 AD participants, 13 were male and 18 were female. **Race/ethnicity** Not reported **Duration of eczema** Of the 31 AD participants, mean duration of eczema before the trial was 3.7 years (range 1 week-49 years). **Severity of eczema** Of the 31 AD participants, 13 were considered to have severe disease, 16 had moderate disease, and 2 were unclassified. **Filaggrin mutation status** Not reported **Number of withdrawals** "One patient was not seen after 7 days, and two were lost to follow-up." **Notes** Looking at the outcomes, of 21 AD participants entered into the trial, only 18 are reported on at week 1, and a further participant is missing at week 2. Not all of these are accounted for in the number of withdrawals.
Interventions	**Run-in details** Not reported **Groups** • HC 0.5% cream (unspecified); applied 4 times daily, unoccluded, to the designated side for 2 weeks. Concurrent treatment: none reported • Fluocinonide 0.05% cream (proprietary: Lidex, Syntex Laboratories, Inc., Palo Alto, Calif.); applied 4 times daily, unoccluded, to the designated side for 2 weeks. Concurrent treatment: none reported **Adherence** Not reported

Roth 1973 *(Continued)*

	Co-interventions Not reported **Notes** Fluocinonide 0.05% cream is FAPG cream.
Outcomes	• Global improvement relative to baseline, assumed to be investigator-assessed. Lesions were graded on a 5-point scale from +3 = clear to -1 = worse at weeks 1 and 2. • Comparative efficacy based on global improvement judgements; either greater improvement with moderate (fluocinonide), greater improvement with mild (HC), or no difference at weeks 1 and 2.* • Participant-reported adverse events at weeks 1 and 2* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned." Comment: unclear how sequence was generated and even which components were randomised
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided on allocation concealment method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind techniques were used." Comment: no information as to how blinding was done or who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind techniques were used." Comment: no information as to how blinding was done or who was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "one participant was not seen after 7 days and two were lost to follow-up." Comment: 3 of 21 enrolled are lost by the end of week 2.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias identified

Roth 1978a

Study characteristics

Methods	**Trial design**

Roth 1978a *(Continued)*

Double-blind, randomised, half-sided comparison

Trial registration number

Not reported

Setting

''patient population''; 1 author was affiliated to the Department of Dermatology, University of California, School of Medicine, San Francisco, California.

Date trial conducted

Not reported

Duration of trial participation

Up to 4 weeks or until clearance

Additional design details

None

Inclusion criteria

- Patients with bilateral lesions of chronic AD, primarily on the limbs

Exclusion criteria

- Pregnancy

Notes

None

Participants	**Total number randomised** 29 **Age** Not reported separately for each trial **Sex** Not reported separately for each trial **Race/ethnicity** Not reported **Duration of eczema** Mean 12.1 years **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** none reported

Roth 1978a *(Continued)*

	Notes None
Interventions	**Run-in details** Participants receiving systemic or topical steroids discontinued at least 2 weeks preceding the trial. participants receiving anti-metabolites were discontinued at least 3 months before. **Groups** • HC 1% cream (Cortdome); applied 3 times daily (morning, noon and night) for up to 4 weeks to lesions on the designated side. Concurrent treatment: not reported • HC valerate 0.2% cream (Westcort); applied 3 times daily (morning, noon and night) for up to 4 weeks to lesions on the designated side. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Some medications were permitted during the trial (e.g. antihistamines for allergic rhinitis, insulin for diabetes, antibiotics, tranquillisers), with the dosage kept at pre-trial levels or changed only as therapeutically necessary. However no anti-metabolites, steroids (systemic or topical) were permitted. **Notes** Participants were asked to wash their hands between applications, and to apply the cream marked 'left' with the right hand, and the cream marked 'right' with the left hand. Plastic gloves were provided for the participant to wear on the hand applying the medication if it were lesions on the hands being treated.
Outcomes	• Assessment of signs/symptoms: 5 symptoms evaluated at each visit (pruritus, erythema, scaling, excoriation, and lichenification) on a 10-point severity scale (0-9). Cleared was defined as a severity score of 0 for all symptoms at visits at 5-9 days, 12-16 days, 17-25 days and 26-35 days.* • Participant reports of adverse events at each visit (assumed; at 5-9 days, 12-16 days, 17-25 days and 26-35 days)* • Participant impression of which side had responded better at "the end of therapy"; presumed to be 26-35 days in most participants • Overall judgement as to which side had responded better at "the end of therapy"; presumed to be 26-35 days in most participants • Overall judgements of the response to the 2 medications (defined as cleared, excellent, good, no effect or worse) at "the end of therapy"; presumed to be 26-35 days in most participants* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared however 1 of the authors states Westwood pharmaceuticals Inc, Buffalo, New York as their affiliation.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised assignment of medications". "the tubes were labelled … as determined by a random table of numbers"

Roth 1978a *(Continued)*

		Comment: reference to a random number table suggests likely that an adequate randomisation method was used
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "at the first visit, each patient was given two tubes of cream (2oz each) one containing HCV and the other containing the control agent. The tubes were labelled identically except that one was marked "left" and one "right" as determined by a table of random numbers." Comment: although it was likely that the participants were blinded it is unclear which personnel were blinded and how this was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: although the trial is described as double-blinded there is no information as to how the parties other than the participants were blinded. Therefore it is unclear whether the personnel responsible for the participant's care were blinded or the outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: as participants left the trial when clearing was achieved (in 1 case within 7 days) there may have not been adequate time for any adverse events to develop. Also, if a participant was judged to be cleared at week 1 and then leaves the trial there is no way of knowing whether the participant would relapse before the end of the 4-week period. It is also unclear how many participants were initially randomised.
Selective reporting (reporting bias)	High risk	Comment: no trial protocol was available and so this cannot be assessed.
Other bias	Low risk	Comment: no other source of bias was identified.

Roth 1978b

Study characteristics	
Methods	**Trial design** Double-blind, randomised, half-sided comparison **Trial registration number** Not reported **Setting** ''patient population''; 1 author was affiliated to the Department of Dermatology, University of California, School of Medicine, San Francisco, California. **Date trial conducted** Not reported **Duration of trial participation** Up to 4 weeks or until clearance **Additional design details** None

Roth 1978b *(Continued)*

Inclusion criteria

- Patients with bilateral lesions of chronic AD, primarily on the limbs

Exclusion criteria

- Pregnancy

Notes

None

Participants	**Total number randomised** 19 **Age** Not reported separately for each trial **Sex** Not reported separately for each trial **Race/ethnicity** Not reported **Duration of eczema** Mean 7.2 years **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** None reported **Notes** None
Interventions	**Run-in details** Participants receiving systemic or topical steroids discontinued at least 2 weeks preceding the trial. Participants receiving anti-metabolites were discontinued at least 3 months before. **Groups** • HC valerate 0.2% cream (Westcort); applied 3 times daily (morning, noon and night) for up to 4 weeks to lesions on the designated side. Concurrent treatment: not reported • Betamethasone valerate 0.1% cream (Valisone); applied 3 times daily (morning, noon and night) for up to 4 weeks to lesions on the designated side. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions**

Roth 1978b *(Continued)*

	Some medications were permitted during the trial (e.g. antihistamines for allergic rhinitis, insulin for diabetes, antibiotics, tranquillisers), with the dosage kept at pre-trial levels or changed only as therapeutically necessary. However no anti-metabolites, steroids (systemic or topical) were permitted. **Notes** Participants were asked to wash their hands between applications, and to apply the cream marked 'left' with the right hand, and the cream marked 'right' with the left hand. Plastic gloves were provided for the participant to wear on the hand applying the medication if it were lesions on the hands being treated.
Outcomes	• Adverse events reported by participants presumed to be at each visit, timing of visits not given in the paper. As the participants were treated for up to 4 weeks it is likely that the last visit was around this time point.* • The severity of the condition scored on a 4-point scale: 1, clear; 2, slight; 3, moderate; 4, severe presumed to be at each visit, timing of visits is not given in the paper. As the participants were treated for up to 4 weeks it is likely that the last visit was around this time point. • Overall improvement evaluated on an 8-point severity scale ranging from "severely worse" (1) to “cleared” (8). The improvement score at the last visit was taken as the overall response to therapy at the timing of visits is not given in the paper. As the participants were treated for up to 4 weeks it is likely that the last visit was around this time point.*
Funding source	None stated
Declarations of interest	None declared however 1 of the authors states Westwood pharmaceuticals Inc, Buffalo, New York as their affiliation.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomised assignment of medications". "the tubes were labelled … as determined by a random table of numbers" Comment: reference to a random number table suggests likely that an adequate randomisation method was used
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "at the first visit, each patient was given two tubes of cream (2oz each) one containing HCV and the other containing the control agent. The tubes were labelled identically except that one was marked "left" and one "right"..." Comment: lengths were taken to blind participants, but no detail of which personnel were blinded or how
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: although the trial is described as double blinded there is no information as to how the parties other than the participants were blinded. Therefore it is unclear whether the personnel responsible for the participant's care were blinded or the outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no report on exactly how many initially randomised. Also, if a participant was judged to be cleared at week 1 and then leaves the trial there is no way of knowing whether the participant would relapse before the end of the 4 week period or develop adverse events.

Roth 1978b *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no trial protocol was available, however a severity assessment is also reported in the methods, but the data are not given.
Other bias	Low risk	Comment: no other source of bias was identified.

Rubio-Gomis 2018

Study characteristics

Methods

Trial design

Randomised, multicentric, placebo controlled, parallel-group, double-blind trial

Trial registration number

EudraCT Number:2008-005360-14; ClinicalTrials.gov Identifier: nCT01772056

Setting

20 centres of primary care and Dermatalogical Service Allergic Unit and Clinical Pharmacology Unit of a General Hospital in Valencia, Spain

Date trial conducted

December 2009-March 2012

Duration of trial participation

Up to 18 weeks (including 2-week stabilisation phase and the remaining 16-week, double-blind maintenance phase)

Additional design details

Participants' families were contacted by telephone at week 8 and week 16.

Inclusion criteria

- Patients with mild or moderate AD according to SCORAD < 50
- Aged 2-10 years (mentioned in the corresponding trial protocol but not in the paper itself)
- Patients were eligible for the double-blind maintenance phase if they achieved SCORAD < 5 or a ≥ 75% reduction of baseline SCORAD.

Exclusion criteria

- Any head involvement or > 30% body or head combined BSA
- Patients with any medical condition for which the trial preparations were contraindicated (e.g. fluticasone or vehicle allergy, rosacea, acne vulgaris, perioral dermatitis or severe fungal, bacterial, viral or parasitic infections)
- Patients with other dermatological conditions that may have prevented accurate assessment of AD
- Those who were receiving any concomitant medications that might have affected the trial's outcome (e.g. systemic glucocorticoid drugs, immunosuppressive agents or antihistamine drugs)
- Any other condition that meant the inclusion in the trial would be unadvised (e.g. cancer or mental illness)
- Other medical history that could interfere with the evaluation of trial treatment (from Clinical Trials registry)

Notes

None

Rubio-Gomis 2018 *(Continued)*

Participants	**Total number randomised** 61 participants assessed for eligibility; 7 failed screening and 54 entered the stabilisation phase. 49 were eligible for the double-blind maintenance phase; 26 randomised into the fluticasone propionate group and 23 into the vehicle group. **Age** Fluticasone propionate group mean 5.5 (SD 2.8), vehicle group mean 5.1 (SD 2.3), > 4 years old fluticasone propionate group 16 (61.5%), vehicle group 15 (65.2%) **Sex** 25 male, 29 female overall; 10 male and 16 female in the fluticasone propionate group; 13 male and 10 female in the vehicle group **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** At screening, retrospectively calculated (assumed) mean SCORAD was 28.3 (SD 8.8) overall, 28.3 (8.4) in the fluticasone propionate group, and 29.1 (9.6) in the vehicle group. Prior to the maintenance phase, SCORAD was 3.3 (2.9) in the fluticasone propionate group and 3.8 (3.0) in the vehicle group. Fluticasone propionate group proportion AD mild 9 (34.6%),vehicle group proportion AD mild 10 (43.5%). Mean % BSA was 7.2 (SD 7.1) overall, 6.4 (4.9) in the fluticasone propionate group, and 8.1 (9.4) in the vehicle group. **Filaggrin mutation status** Not reported **Number of withdrawals** 4; 2 in the fluticasone propionate group (both protocol deviations) and 2 in the vehicle group (1 protocol deviation, 1 withdrawal of consent). **Notes** 5 withdrew during the stabilisation phase (3 lack of fluticasone efficacy, 1 protocol deviation, 1 fluticasone adverse event) Participants were withdrawn from the trial at 16 weeks (length of the maintenance phase) or relapse.
Interventions	**Run-in details** All were treated with twice daily fluticasone propionate cream 0.05% for up to 2 weeks in an open-label stabilisation phase. **Groups** • Fluticasone propionate 0.05% cream; participants applied the TCS cream twice weekly on consecutive days for 16 weeks or until relapse. Concurrent treatment: none • No TCS (PFCO/W Base - Guinama S.L.U., Propyleneglycol and Aqua con-servans); participants applied vehicle only twice weekly on consecutive days for 16 weeks or until relapse. Concurrent treatment: none **Adherence**

Rubio-Gomis 2018 *(Continued)*

	Not reported **Co-interventions** Participants continued using the emollient cream. Systemic corticoids, immunomodulators drugs and antihistamines H1 were not allowed during the maintenance phase. **Notes** None
Outcomes	• Adverse event monitoring, especially skin atrophy, telangectasia, striae and hypertrichosis at up to week 22 according to the trial protocol. The causal relationship of the clinical events to the use of the medication trials was assessed by clinical researchers.* • Time to relapse. Relapse defined as SCORAD > 5 or ≥ 25% initial SCORAD before week 16* • Relapse rate (SCORAD > 5 or ≥ 25% initial SCORAD) before week 16* • Clinical manifestation and severity of AD (individual domains of SCORAD proportion of participants rated as without, mild, moderate, severe) at baseline (unclear if at screening or after active phase) week 16 or at relapse. • SCORAD (mean and SD) at enrolment (week −2), baseline (week 0) • Compliance monitoring at 18 weeks according to the trial protocol *denotes relevance to this review
Funding source	Trial conducted with a grant from ISCIII - Ministerio de Ciencia e Innovación, Spain.
Declarations of interest	1 declared
Notes	"The study was prematurely ended because financial resources were limited and the recruitment of participants was scarce."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was generated by a random number table; the list was produced by the statistical service of the Contract Research Organization (CRO. EXPERIOR SL)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "A blinded copy and clinical trial coded medication were received and stored by the clinical trials pharmacist at Consorcio Hospital General Universitario de Valencia (CHGUV). The pharmacist dispensed the research drugs packs according with the research assistants that used consecutively numbered packs to allocate new participants to treatment groups." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants and researchers were blinded to group assignment until the study completion" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants and researchers were blinded to group assignment until the study completion." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "An intention to treat analysis was done."

Rubio-Gomis 2018 *(Continued)*

		Comment: only 2 participants dropped out of each group. Numbers of participants reported in the results table are the number of participants in each group at randomisation
Selective reporting (reporting bias)	Low risk	Comment: prospective trial protocol found and is consistent with the publication
Other bias	Low risk	Comment: no other sources of bias identified, however it should be noted that the trial was prematurely ended owing to recruitment and financial reasons.

Ruiz 1976

Study characteristics

Methods

Trial design

Randomised, half-sided, double-blind trial. Participants had a mixture of conditions; we have only extracted data from those with atopic eczema where it is separated from the other data.

Trial registration number

Not reported

Setting

Affiliation with General Hospital of the State Medical Center Mexico, so assumed participants recruited from clinics there.

Date trial conducted

Not reported

Duration of trial participation

Up to 4 weeks (assumed from table 5 as not stated in the methods)

Additional design details

None

Inclusion criteria

- Bilateral and preferably symmetrical atopic eczema

Exclusion criteria

- Pregnant patients
- Patients with tuberculous processes, virosis (herpes) or vaccinated patients (as translated)

Notes

None

Participants

Total number randomised

6

Age

Participants were aged 4 months, 5 years, 15 years, 17 years, 18 years and 26 years.

Sex

Ruiz 1976 *(Continued)*

	5 male and 1 female **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported. 4 participants gave data after 4 weeks and 2 participants gave data after only 3 weeks (assumed from table 5). It is not clear why this was the case. **Notes** None
Interventions	**Run-in details** Not reported **Groups** • Flumethasone pivalate 0.2% ointment (unspecified); applied to the designated side ≥ 2 times daily according to the "clinical picture." Concurrent treatment: none • Diflucortolone valerate 0.1% ointment (unspecified); applied to the designated side ≥ 2 times daily according to the "clinical picture." Concurrent treatment: none **Adherence** Not reported **Co-interventions** Not reported **Notes** None
Outcomes	• Therapeutic success assessed by the doctor (in consultation with the participant) as good, moderate or poor at week 1, 2, 3, and 4* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	Translated into English

Risk of bias

Bias	Authors' judgement	Support for judgement

Ruiz 1976 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Double blind." "Each patient received a randomised preparation pack containing 2 x 2 tubes." Quoted from the English translation Comment: no information provided about sequence generation.
Allocation concealment (selection bias)	Unclear risk	Quote: "A red label marked the application for the left and a white for the right body part." "Each patient received a randomised preparation pack containing 2 x 2 tubes." Quoted from the English translation Comment: it is not clear who prepared the treatments against the allocation in order to be confident no bias was introduced.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double blind." "A red label marked the application for the left and a white for the right body part." "Each patient received a randomised preparation pack containing 2 x 2 tubes." Quoted from the English translation. Comment: whilst it is likely patients were blinded, there is no description on how this was achieved, and also no information about how personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Double blind." "A red label marked the application for the left and a white for the right body part." "Each patient received a randomised preparation pack containing 2 x 2 tubes." Quoted from the English translation. Comment: whilst it is likely participants were blinded, there is no description on how this was achieved, and also no information about how personnel were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: data are presented for all 6 participants, but it is not clear why some data are from week 3 and some are from week 4.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available participants were assessed at weekly visits, but only the final time point (assumed) is reported.
Other bias	Low risk	Comment: no other source of bias detected.

Ryu 1997

Study characteristics	
Methods	**Trial design** Randomised, single-blinded clinical trial **Trial registration number** Not reported **Setting** Department of Dermatology at Kangnam St. Mary's Hospital, Seoul, South Korea **Date trial conducted** April-June 1997 **Duration of trial participation** 2 weeks **Additional design details**

Ryu 1997 *(Continued)*

None

Inclusion criteria

- Aged ≥ 3 years
- Mild-moderate AD according to Hanifin and Rajka's criteria (Hanifin 1980).
- > 5% BSA involved with moderate or more severe disease
- Patient that had not received systemic steroid treatment or radiation treatment within the past month or topical steroids in the past week

Exclusion criteria

Not reported

Notes

We have assumed that the discrepancy between "mild and moderate" and "moderate or more severe disease" is that the former is a global assessment and the latter a local one referring to > 5% BSA.

Participants	**Total number randomised** 24; 12 per group **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** BSA (BSA): mometasone furoate 47%, fluocortin butylester 29%. 8 symptoms (erythema, oedema/vesicles/crusting, scaling, excoriation, lichenification, pig-/depigmentation, pruritus, loss of sleep) were scored according to 4 categories (0 = absent, 1 = mild, 2 = moderate, 3 = severe). The baseline average symptom and signs severity score of the "whole area" was 18.1 for the mometasone potent group and 17.6 for the fluocortin butylester mild group. The baseline average symptom and signs severity score of the "target area" was 16.3 for the mometasone potent group and 15.3 for the fluocortin butylester mild. **Filaggrin mutation status** Not reported **Number of withdrawals** Not specifically mentioned; however, 1 participant in the control (fluocortin butylester) group was not included in the analysis and the report says that 1 participant in this group stopped application due to worsening of involved area despite treatment. **Notes** Not clear from the paper whether the signs/symptoms were assessed by participants and doctors (though it seems from the lists of signs/symptoms that input would have been required from participants (i.e. loss of sleep) and doctors (i.e. lichenification).
Interventions	**Run-in details**

Ryu 1997 *(Continued)*

None

Groups

- Mometasone furoate 0.1% cream; once per day, applied thinly to involved area. Concurrent treatment: none
- Fluocortin butylester 0.75% cream; twice per day, applied thinly to involved area. Concurrent treatment: none

Adherence

Not reported

Co-interventions

None

Notes

Participants were advised not to use 'exterior use' makeup or other local topically applied medications with the exception of toner and lotion.

Outcomes	• BSA (according to the rule of 9s) at baseline and days 3, 8 and 14 • Participant subjective satisfaction with treatment (excellent, good, poor, exacerbation) at day 14 • Measurement of 8 signs/symptoms (erythema, edema/vesicles/crust, scales, excoriation, lichenification, pig-/depigmentation, pruritus, loss of sleep – were scored according to 4 categories (0 = absent, 1 = mild, 2 = moderate, 3 = severe)) in the most severe region ("target area") and over the whole body involved at baseline and days 3, 8 and 14 • Assessment in comparison to baseline scores as excellent (76%-100% decrease), good (51%-75% decrease), poor (0%-50% decrease), and exacerbation at baseline and days 3, 8 and 14. Assumed to be an IGA, however it could be a calculation in percentage reduction in symptoms or incorporate participant judgement.* • Adverse events, specifically steroidal acne, folliculitis, pigmentation change, maculopapular rash, and skin atrophy signs were recorded. The presence of other side effects were monitored as well at baseline and days 3, 8 and 14.* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomised into two groups according to patient number" (English translation). Comment: not enough information given to judge risk of selection bias. It seems like rather a big difference in BSA between the 2 groups.
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blinded" (English translation) Comment: it is not clear who was blinded and there is no mention of a placebo cream in the once daily arm.

Ryu 1997 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "single-blinded" (English translation) Comment: there is no information regarding which group (participants, personnel or outcome assessors) were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1 control (using fluocortin butylester) participant dropped out and was not analysed for the effectiveness outcomes (it is unclear exactly how handled for the safety outcomes), however as it was only 1 participant it is unlikely to make a difference.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or clinical trial registry entry so unable to judge reporting bias.
Other bias	Low risk	Comment: no other biases identified.

Sanabria-Silva 1991

Study characteristics

Methods

Trial design

Prospective, open, randomised, parallel-group

Trial registration number

Not reported

Setting

Outpatients; National Institute of Paediatrics, Mexico

Date trial conducted

May-December 1985

Duration of trial participation

4 weeks of treatment followed by 10 days of post-treatment follow-up

Additional design details

None

Inclusion criteria

- Age 3-12 years
- AD diagnosed by a doctor from the dermatology department
- Lesions on > 30% of the body surface
- The percentage affected was calculated based on the rule of 9s.
- Consent from parents

Exclusion criteria

- Under 3 years old (due to absorption being greater in this age group)
- Over 12 years old (due to AD being less common in adolescence)
- Secondary infection
- Hypersensitivity to corticosteroids
- Concurrent systemic illness
- Treated with topical or systemic steroids 4 weeks before the trial

Sanabria-Silva 1991 *(Continued)*

Notes

Original text in Spanish with English translation

Participants	**Total number randomised** 30 **Age** 28 pre-school children: 17 school children (includes 15 participants from a placebo arm that is not relevant to our review) **Sex** 14 female, 31 male (includes 15 participants from a placebo arm that is not relevant to our review) **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Potent TCS group (15): 8 participants with 30%-50% BSA affected, 6 with 51%-70%, and 1 with > 70%. Severity data not presented for the mild TCS group. **Filaggrin mutation status** Not reported **Number of withdrawals** None reported, however results in the text refer to 15 participants in each group, whilst the results in table 1 report only 12 participants included in the mild group and 13 in the potent. **Notes** Participants who did not comply with instructions, abandoned the trial, had adverse reactions or could not be assessed periodically were removed from the trial.
Interventions	**Run-in details** Not reported **Groups** • Betametasone dipropionate 0.05% cream (proprietary: Diprosone); applied every 12 h to affected skin for 4 weeks. Concurrent treatment: none • HC 1% cream (proprietary: Nutracort); applied every 12 h to affected skin for 4 weeks. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Parents/carers were instructed at baseline on how to apply the medications. Rules of care were also recommended: use of emollients when the skin appears dry; other medication was prohibited; bathing daily if possible; use of cotton underwear; avoidance of soap on the affected skin; avoidance of clothing made of woolens, nylon, or thick materials, which may cause irritation; avoidance of washing clothes with detergent or bleach; cutting the child's nails twice weekly

Sanabria-Silva 1991 *(Continued)*

	Notes None
Outcomes	• "Extensiveness of lesions" (noting percentage of skin affected, presence or absence of erythema, lichenification and scabs) at baseline, week 1, 2, 3 and 4. After treatment suspension participants were evaluated every 48 h for 10 days or whenever a new skin lesion appeared.* • Photographs at were taken of the lesions baseline, after 10 days treatment, at suspension of treatment and after suspension when any lesion appeared. • Number of participants relapsing (reappearance of lesions with equal or lower intensity) in following days after treatment cessation - does not mention if this was related to the signs/ symptoms score every 48 h for 10 days or whenever a new skin lesion appeared. • Number of participants experiencing rebound (symptoms of greater intensity) in following days after treatment cessation- does not mention if this was related to the signs/ symptoms score every 48 h for 10 days or whenever a new skin lesion appeared. • Clinical history at baseline • Adverse events up to 6 weeks* *denotes relevance to this review
Funding source	Not reported
Declarations of interest	Not reported
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated to the different groups on a random basis." Comment: no information about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Each group used one of the treatments in identical containers with similar colour, smell and texture"; "The researchers knew the contents of the three containers". Comment: whilst the intention was to blind participants, it is not clear to what extent this may have been compromised by researchers knowing who was randomised to which treatment, and the trial was described as "open". None of the researchers was blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The researchers knew the contents of the three containers". Comment: the trial was described as "open". None of the researchers was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote:"participants who did not comply with therapeutic instructions; those who abandoned the study; those who had adverse reactions and those who could not be assessed periodically" were removed from the trial. Comment: no withdrawals were reported however the numbers in the results table do not add up to 15. The paper states "all patients relapsed" but the number relapsed in the table does not add up to 15, the number randomised.

Sanabria-Silva 1991 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available. Individual-level relapse data are presented but do not include all participants. Unclear what measure of dispersion is for % clinical improvement.
Other bias	Low risk	Comment: no other source of bias identified

Savin 1976

Study characteristics	
Methods	**Trial design** Randomised, double-blind, half-sided trial **Trial registration number** None **Setting** Not reported; author affiliation was Yale University School of Medicine **Date trial conducted** Not reported **Duration of trial participation** 3 weeks **Additional design details** Assumed that participants were told to apply treatments for the full 3 weeks of the trial. Paper reports comparisons for psoriasis and AD - only AD reported here **Inclusion criteria** • The trial states that "Atopic dermatitis was to consist of discrete or confluent edematous papules which were intensely pruritic in the classical anatomical distribution and becoming lichenified from rubbing." It was to be a 'clear' diagnosis with an overall evaluation of moderate (average: easily discernable), severe, or very severe. **Exclusion criteria** • Pregnancy **Notes** None
Participants	**Total number randomised** 27 participants with AD **Age** Not reported **Sex** Not reported

Savin 1976 *(Continued)*

Race/ethnicity

Not reported

Duration of eczema

The trial states that "all patients had a long history of eczematous dermatitis with lichenification and intense pruritus in the classical anatomic distribution."

Severity of eczema

26 participants were considered moderate (easily discernable), none were severe (markedly evident), and 1 was very severe. The mean total symptom score was 7.0 in the mild (HC) group at baseline compared to 6.5 in the potent (betamethasone) group; there was no difference between the groups (no further details regarding the way total symptom score was assessed).

Filaggrin mutation status

Not reported

Number of withdrawals

Data were stated to be missing for 2 AD participants in the HC group, 1 at week 2 and 1 at week 3. However it is also stated that "All patients on betamethasone dipropionate kept their appointments", yet there are outcome data for 15 participants at week 1 for the betamethasone dipropionate group, and only 13 at week 2, and 11 at week 3.

Notes

None

Interventions

Run-in details

The trial states that "All patients were removed from topical medication for 1 week prior to the study and from systemic medication for 3 weeks prior to the study. Systemic medications such as diuretics and digitalis were continued prior to and throughout the study"

Groups

- HC 1% ointment; applied twice daily without occlusion. Concurrent treatment: none
- Betamethasone dipropionate 0.05% ointment; applied twice daily without occlusion. Concurrent treatment: none

Adherence

Not reported

Co-interventions

Participants requiring systemic medications, e.g. diuretics and digitalis, were permitted to take these throughout. All participants were asked to take a bath daily using 'ordinary soap' and not to use other topicals e.g. emollients or bath oils.

Notes

None

Outcomes

- Adverse reactions at weeks 0, 1, 2, and 3*
- Clinical effectiveness (physician's evaluation) rated as excellent (≥ 75% clinical control), good (50%-75% control), fair (25%-50% control) and poor (< 25% or worse) at weeks 1, 2, and 3*
- Mean total symptom score (no more details i.e. don't know if physician or participant reported) at weeks 0, 1, 2, and 3

*denotes relevance to this review

Savin 1976 *(Continued)*

Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" Comment: no information given about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no information on how participants were blinded to assess whether this was adequate, and no details provided on how investigators were blinded, and who exactly was blinded (single-author trial)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: no details provided on how investigators were blinded, and who exactly was blinded (single-author trial)
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Five patients [2 of the included AD patients] failed to keep appointments for follow-up in the second and third week; these failures to follow-up occurred only in patients on 1% HC. All patients on betamethasone dipropionate kept their appointments." Comment: in such a small trial, loss of 2 participants from 1 group and none from the other could be a source of bias. However, of more concern is the statement that no participants were lost in the betamethasone dipropionate arm, yet 4/15 participants are not accounted for in the week 3 data (table 2).
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other source of bias detected

Schlessinger 2006

Study characteristics

Methods	**Trial design** Multicentre, multiple-dose, randomised, open-label safety trial **Trial registration number** ISRCTN71227633 **Setting** Clinical outpatient setting, multicentre, USA **Date trial conducted**

Schlessinger 2006 *(Continued)*

June 2004-March 2005

Duration of trial participation

4 weeks (unless HPA axis suppression occurred; then participants were tested at week 4 and then every 4 weeks until within normal limits).

Additional design details

None

Inclusion criteria

- Male or female participants with moderate-severe clinically diagnosed AD that was ≥ 20% of the BSA
- Aged 3 months to < 18 years old
- Normally functioning HPA axis (tested for once randomised)
- Not pregnant, and using acceptable birth control

Exclusion criteria

Only reported in ISRCTN71227633.

- Pregnant or nursing
- Use of concomitant therapies for AD
- Untreated bacterial, tubercular, fungal or viral lesion of the skin
- Known sensitivity to any constituents of the trial drug
- Significant disease of the hepatic, renal, endocrine, musculoskeletal or nervous system or any gross physical impairment
- Irregular sleep schedules
- History of chronic drug or alcohol abuse

Notes

None

Participants

Total number randomised

126 randomised:

- cohort 1 (age 12 to < 18 years) 16 once daily vs 17 twice daily
- cohort 2 (age 6 to < 12 years) 16 vs 16
- cohort 3 (age 2 to < 6 years) 15 vs 15)
- cohort 4 (age 3 months to < 2 years) 16 vs 15

Age

Mean ages (years):

- Cohort 1 (12 to < 18): once daily 14.6, twice daily 14.4
- Cohort 2 (6 to < 12): once daily 8.6, twice daily 8.9
- Cohort 3 (2 to < 6): once daily 3.7, twice daily 3.3
- Cohort 4 (3 months to 2 years): once daily 1.3, twice daily 1.2

Sex

- Cohort 1: 7 (44%) male and 9 (56%) female (once daily) and 6 (35%) male and 11 (65%) female (twice daily)
- Cohort 2: 8 (50%) male and 8 (50%) female in each group
- Cohort 3: 6 (40%) male and 9 (60%) female (once daily) and 10 (67%) male and 5 (33%) female (twice daily)
- Cohort 4: 12 (75%) male and 4 (25%) female (once daily) and 10 male and 5 female (twice daily).

Schlessinger 2006 *(Continued)*

Race/ethnicity

- Cohort 1: 10 (62%) white, 4 (25%) black and 2 (12%) 'other' (once daily), and 13 (76%) white, 3 (18%) black and 1 (6%) other (twice daily)
- Cohort 2: 12 (75%) white, 1 (6%) black and 3 (19%) other (once daily), and 8 (50%) white, 5 (31%) black and 3 (19%) other (twice daily)
- Cohort 3: 9 (60%) white, 5 (33%) black and 1 (7%) other (once daily), and 11 (73%) white, 1 (7%) black and 3 (20%) other (twice daily)
- Cohort 4: 15 (94%) white, 0 (0%) black and 1 (6%) other (once daily), and 10 (67%) white, 3 (20%) black and 2 (13%) other (twice daily)

Duration of eczema

Mean duration:

- cohort 1: once daily 12.1 years, twice daily 11.8 years
- cohort 2: once daily 7.3 years, twice daily 7.0 years
- cohort 3: once daily 3.0 years, twice daily 3.0 years
- cohort 4: once daily 1.1 years; twice daily 1.2 years

Severity of eczema

BSA involvement % (mean (SD), range):

- cohort 1: once daily 36.1 (19.7) 20.0 to 92.0, twice daily 34.0 (14.9) 20.0 to 75.0
- cohort 2: once daily 40.7 (18.1), 20.0 to 90.0; twice daily 40.6 (22.7), 20.0 to 95.0
- cohort 3: once daily 34.9 (18.5) 20.0 to 57.0, twice daily 34.2 (12.0) 20.0 to 57.0
- cohort 4: once daily 43.1 (18.5) 23.0 to 80.0; twice daily 38.2 (18.1) 20.0 to 80.0

Filaggrin mutation status

Not reported

Number of withdrawals

2 participants allocated to the twice daily group in cohort 1 and 1 participant in the once daily group in cohort 2 did not receive the intervention because of baseline cortisol suppression. 1 participant in the once daily group of cohort 1 discontinued the intervention because of an adverse event (moderate urticaria). 1 participant in the once daily group of cohort 4 was also excluded from analysis because of "medication 7 days".

Notes

None

Interventions

Run-in details

NA

Groups

- Fluocinonide 0.1% cream (Vanos); once daily fluocinonide 0.1% cream. participants and/or guardians were instructed to apply thin layer to all treatable areas for 2 weeks. Concurrent treatment: none
- Fluocinonide 0.1% cream (Vanos); twice daily fluocinonide 0.1% cream. participants and/or guardians were instructed to apply thin layer to all treatable areas for 2 weeks. Concurrent treatment: none

Adherence

Not reported

Co-interventions

Not reported

Schlessinger 2006 *(Continued)*

	Notes None
Outcomes	• Severity of AD: "clear/almost clear", "improved (but less than clear/almost clear)", or "no improvement," or "worsened" at baseline, week 1, week 2, week 4* • Skin safety evaluation of 8 signs and symptoms of skin atrophy: telangiectasia, transparency, loss of elasticity, loss of normal skin markings, thinning, striae, pigmentation changes, and bruising at baseline, week 1, week 2, week 4* • Post-cosyntropin stimulation cortisol measurement (HPA suppression defined as serum cortisol level of 18 µg/dL or less (≤ 497 nmol/L) 30 min after IV cosyntropin stimulation) at baseline, week 1, week 2 (any participant with a post-stimulation cortisol level of 18 µg/dL or less was retested at week 4 and once every 4 weeks thereafter until the post-stimulation levels were within normal limits).* • Adverse events at Up to 4 weeks* *denotes relevance to this review
Funding source	Medicis, The Dermatology Company; a subsidiary of Medicis Pharmaceutical, who manufacture Vanos.
Declarations of interest	Last author and corresponding author (Todd Plott) is affiliated to the funding source and was involved in analysis and interpretation of data. They declare they had no affiliation with or financial involvement with any organization or entity discussed in the manuscript and no relevant financial interest in the manuscript. 'Members of the Vanos Study Group' was also listed as an author but they don't say how they were involved in the trial other than as participating clinical investigators and contributors.
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients who met the inclusion and exclusion criteria were randomized to receive topical fluocinonide either once or twice daily in an outpatient setting" Comment: no description of randomisation method
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients who met the inclusion and exclusion criteria were randomized to receive topical fluocinonide either once or twice daily in an outpatient setting" Comment: not clear if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no mention of blinding - but unlikely to be achieved as participants were applied the treatment either once or twice a day and there is no mention of using a vehicle in the once daily group.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no mention of whether the assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 5/126 participants withdrew (due to an adverse event) or were excluded from the trial (due to cortisol suppression at baseline or only taking medication for 7 days). 3 participants with once daily versus 2 with twice daily. Low risk of attrition bias
Selective reporting (reporting bias)	Unclear risk	Comment: there is a clinical trial registry entry (ISRCTN71227633) but it was retrospectively registered (in 2006).

Schlessinger 2006 *(Continued)*

Other bias	Low risk	Comment: no other source of bias detected

Sefton 1984a

Study characteristics

Methods

Trial design

Randomised, double blind, half-sided trials

Trial registration number

Not reported

Setting

Multiple centres in the USA

Date trial conducted

Not reported

Duration of trial participation

14 days

Additional design details

None

Inclusion criteria

- Patients with bilateral, symmetrical lesions of stable, chronic AD
- Mild- to moderate-severity disease

Exclusion criteria

- Patients experiencing an acute flare or a rebound effect from prior treatment
- Patients with atypical AD, also those with "a generalised exfoliative or vesicular, exudative stage"
- Patients with disease confined to hands and feet
- Patients with known sensitivity to components of the trial medication
- Patients with secondary infection
- Pregnant patients

Participants

Total number randomised

The information below includes data from Sefton 1984a, Sefton 1984b and Sefton 1984c, across the 3 trials 145 were randomised, 131 were evaluated. All received HC valerate; 68 received betamethasone valerate, 37 received triamcinolone acetonide, and 26 received fluocinolone acetonide on the contralateral side.

Age

Of 131 evaluated, the mean age was 26 years

Sex

Of 131 evaluated, 42 were male and 89 were female.

Race/ethnicity

Sefton 1984a *(Continued)*

Of 131 evaluated, 99 were white, 4 were Hispanic, 24 were black and 4 were Asian.

Duration of eczema

Of 131 evaluated, the average duration of eczema was 13 years.

Severity of eczema

IGA of severity using an analogue scale (0 = clear 100 = most severe): in the HC valerate v triamcinolone acetonide-treated participants, severity was 46.4 and 47.9.

Filaggrin mutation status

Not reported

Number of withdrawals

Only 131/145 were evaluated for efficacy; 14 did not complete the trial because of protocol violations or missed follow-up visits. All records were reviewed to capture the safety data.

Notes

None

Interventions	**Run-in details** Participants did not take TCSs in the 2 weeks preceding the trial, or parenteral steroids in the 4 weeks preceding **Groups** • HC valerate 0.2% ointment (proprietary: Westcort, Westwood Pharmaceuticals, Inc.); applied twice daily to the designated side for 2 weeks. Concurrent treatment: none • Triamcinolone 0.1% ointment (proprietary: Kenalog, E. R. Squibb & Sons, Inc); applied twice daily to the designated side for 2 weeks. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Both written and oral instructions were given to all participants. Other topical medications and concurrent systemic corticosteroids were prohibited during the trial. **Notes** None
Outcomes	• Adverse experiences: all written comments from case report forms, therefore some may be symptoms of the disease process at up to day 14.* • Participant preference (cosmetic; collecting through a questionnaire) at day 14 • Investigator assessment of individual signs and symptoms using an analogue scale from 'none'/'clear' to most severe (100): pruritus (paper explicitly states investigator-assessed), erythema, scaling, papulation, lichenification, vesiculation at baseline and days 3, 7, and 14 • IGA using an analogue scale (0 = clear 100 = most severe) at baseline and days 3, 7, and 14* *denotes relevance to this review
Funding source	none stated, however the authors are affiliated to Bristol-Myers Pharmaceutical Research and Development Division, Buffalo, New York. Also Neutrogena Corporation supplied Melanax® and Herbert Laboratories supplied the Total Eclipse® 15 and its placebo vehicle.

Sefton 1984a *(Continued)*

Declarations of interest	None declared, however the trial authors are affiliated to Bristol-Myers Pharmaceutical Research and Development Division, Buffalo, New York. Also Neutrogena Corporation supplied Melanax® and Herbert Laboratories supplied the Total Eclipse® 15 and its placebo vehicle.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "the allocation of treatments in each study was accomplished by a restricted randomization process to ensure equal frequencies of the treatments to each side in small sequences of consecutively numbered patients." Comment: method of sequence generation could allow investigators to guess the allocation.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient detail in allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "the test preparations were supplied to investigators in coded identical tubes". Comment: whilst it is likely that participants were adequately blinded as the trial preparations were similarly packaged, it is unclear which personnel were blinded and whether blinding might be compromised.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the test preparations were supplied to investigators in coded identical tubes". Comment: it is unclear which personnel were blinded and whether blinding might be compromised.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "data on fourteen patients were excluded from the efficacy analyses due to their failure to make any of the subsequent visits or because of significant protocol violations. However, all patients' records were reviewed and included for the tabulation of possible adverse experiences." Comment: this is just over 10% of data, so could be a problem given overall low numbers included
Selective reporting (reporting bias)	Unclear risk	Comment: individual signs and symptom data not presented, we have assumed for brevity; results are alluded to in the text. No protocol available
Other bias	High risk	Comment: the paper does not fully explain how the reported trials differed in terms of methodology.

Sefton 1984b

Study characteristics

Methods	**Trial design** Randomised, double blind, half-sided trials **Trial registration number** Not reported **Setting**

Sefton 1984b *(Continued)*

Multiple centres in the USA

Date trial conducted

Not reported

Duration of trial participation

14 days

Additional design details

None

Inclusion criteria

- Patients with bilateral, symmetrical lesions of stable, chronic AD
- Mild- to moderate-severity disease

Exclusion criteria

- Patients experiencing an acute flare or a rebound effect from prior treatment
- Patients with atypical AD, also those with "a generalised exfoliative or vesicular, exudative stage"
- Patients with disease confined to hands and feet
- Patients with known sensitivity to components of the trial medication
- Patients with secondary infection
- Pregnant patients

Participants	**Total number randomised** The information below includes data from Sefton 1984a, Sefton 1984b and Sefton 1984c, across the 3 trials 145 were randomised, 131 were evaluated. All received HC valerate; 68 received betamethasone valerate, 37 received triamcinolone acetonide, and 26 received fluocinolone acetonide on the contralateral side. **Age** Of 131 evaluated, the mean age was 26 years **Sex** Of 131 evaluated, 42 were male and 89 were female. **Race/ethnicity** Of 131 evaluated, 99 were white, 4 were Hispanic, 24 were black and 4 were Asian. **Duration of eczema** Of 131 evaluated, the average duration of eczema was 13 years. **Severity of eczema** IGA of severity using an analogue scale (0 = clear, 100 = most severe): in the HC valerate v betamethasone valerate-treated participants, severity was 44.1 and 43.4 on the respective sides. **Filaggrin mutation status** Not reported **Number of withdrawals** Only 131/145 were evaluated for efficacy; 14 did not complete the trial because of protocol violations or missed follow-up visits. All records were reviewed to capture the safety data.

Sefton 1984b *(Continued)*

	Notes None
Interventions	**Run-in details** Participants did not take TCSs in the 2 weeks preceding the trial, or parenteral steroids in the 4 weeks preceding. **Groups** • HC valerate 0.2% ointment (proprietary: Westcort, Westwood Pharmaceuticals, Inc.); applied twice daily to the designated side for 2 weeks. Concurrent treatment: none • Betamethasone 17-valerate 0.1% ointment (proprietary: Valisone, Schering Corp.); applied twice daily to the designated side for 2 weeks. Concurrent treatment: none **Adherence** Not reported **Co-interventions** Both written and oral instructions were given to all participants. Other topical medications and concurrent systemic corticosteroids were prohibited during the trial. **Notes** None
Outcomes	• Adverse experiences: all written comments from case report forms, therefore some may be symptoms of the disease process at up to day 14* • Participant preference (cosmetic; collecting through a questionnaire) at day 14 • Investigator assessment of individual signs and symptoms using an analogue scale from 'none'/'clear' to most severe (100): pruritus (paper explicitly states investigator-assessed), erythema, scaling, papulation, lichenification, vesiculation at baseline and days 3, 7, and 14 • IGA using an analogue scale (0 = clear 100 = most severe) at baseline and days 3, 7, and 14.* *denotes relevance to this review
Funding source	None stated, however the trial authors are affiliated to Bristol-Myers Pharmaceutical Research and Development Division, Buffalo, New York. Also Neutrogena Corporation supplied Melanax® and Herbert Laboratories supplied the Total Eclipse® 15 and its placebo vehicle.
Declarations of interest	None declared, however the trial authors are affiliated to Bristol-Myers Pharmaceutical Research and Development Division, Buffalo, New York. Also Neutrogena Corporation supplied Melanax® and Herbert Laboratories supplied the Total Eclipse® 15 and its placebo vehicle.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "the allocation of treatments in each study was accomplished by a restricted randomization process to ensure equal frequencies of the treatments to each side in small sequences of consecutively numbered patients." Comment: method of sequence generation could allow investigators to guess the allocations
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient detail in allocation concealment

Sefton 1984b *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "the test preparations were supplied to investigators in coded identical tubes". Comment: whilst it is likely that participants were adequately blinded as the trial preparations were similarly packaged, it is unclear which personnel were blinded and whether blinding might be compromised.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the test preparations were supplied to investigators in coded identical tubes". Comment: it is unclear which personnel were blinded and whether blinding might be compromised.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "data on fourteen patients were excluded from the efficacy analyses due to their failure to make any of the subsequent visits or because of significant protocol violations. However, all patients' records were reviewed and included for the tabulation of possible adverse experiences." Comment: this is just over 10% of data, so could be a problem given overall low numbers included
Selective reporting (reporting bias)	Unclear risk	Comment: individual signs and symptom data not presented, we have assumed for brevity; results are alluded to in the text. No protocol available.
Other bias	High risk	Comment: the paper does not fully explain how the reported trials differed in terms of methodology.

Sefton 1984c

Study characteristics

Methods

Trial design

Randomised, double blind, half-sided trials

Trial registration number

Not reported

Setting

Multiple centres in the USA

Date trial conducted

Not reported

Duration of trial participation

14 days

Additional design details

None

Inclusion criteria

- Patients with bilateral, symmetrical lesions of stable, chronic AD
- Mild- to moderate-severity disease

Exclusion criteria

Sefton 1984c *(Continued)*

- Patients experiencing an acute flare or a rebound effect from prior treatment
- Patients with atypical AD, also those with "a generalised exfoliative or vesicular, exudative stage"
- Patients with disease confined to hands and feet
- Patients with known sensitivity to components of the trial medication
- Patients with secondary infection
- Pregnant patients

Notes

None

Participants	**Total number randomised** The information below includes data from Sefton 1984a, Sefton 1984b and Sefton 1984c**,** across the 3 trials 145 were randomised, 131 were evaluated. All received HC valerate; 68 received betamethasone valerate, 37 received triamcinolone acetonide, and 26 received fluocinolone acetonide on the contralateral side. **Age** Of 131 evaluated, the mean age was 26 years **Sex** Of 131 evaluated, 42 were male and 89 were female. **Race/ethnicity** Of 131 evaluated, 99 were white, 4 were Hispanic, 24 were black and 4 were Asian. **Duration of eczema** Of 131 evaluated, the average duration of eczema was 13 years. **Severity of eczema** IGA of severity using an analogue scale (0 = clear 100 = most severe): in the HC valerate v fluocinolone acetonide-treated participants, severity was 27.1 and 26.9. **Filaggrin mutation status** Not reported **Number of withdrawals** Only 131/145 were evaluated for efficacy; 14 did not complete the trial because of protocol violations or missed follow-up visits. All records were reviewed to capture the safety data. **Notes** Data are across both trials.
Interventions	**Run-in details** Participants did not take TCSs in the 2 weeks preceding the trial, or parenteral steroids in the 4 weeks preceding **Groups** • HC valerate 0.2% ointment (proprietary: Westcort, Westwood Pharmaceuticals, Inc.); applied twice daily to the designated side for 2 weeks. Concurrent treatment: none • Fluocinolone acetonide 0.025% ointment (proprietary: Synalar, Syntex Laboratories, Inc.); applied twice daily to the designated side for 2 weeks. Concurrent treatment: none

Sefton 1984c *(Continued)*

	Adherence Not reported **Co-interventions** Both written and oral instructions were given to all participants. Other topical medications and concurrent systemic corticosteroids were prohibited during the trial. **Notes** None
Outcomes	• Adverse experiences: all written comments from case report forms, therefore some may be symptoms of the disease process at up to day 14* • Participant preference (cosmetic; collecting through a questionnaire) at day 14 • Investigator assessment of individual signs and symptoms using an analogue scale from 'none'/'clear' to most severe (100): pruritus (paper explicitly states investigator-assessed), erythema, scaling, papulation, lichenification, vesiculation at baseline and days 3, 7, and 14 • IGA using an analogue scale (0 = clear 100 = most severe) at baseline and days 3, 7, and 14* *denotes relevance to this review
Funding source	None stated, however the trial authors are affiliated to Bristol-Myers Pharmaceutical Research and Development Division, Buffalo, New York. Also Neutrogena Corporation supplied Melanax® and Herbert Laboratories supplied the Total Eclipse® 15 and its placebo vehicle.
Declarations of interest	None declared, however the trial authors are affiliated to Bristol-Myers Pharmaceutical Research and Development Division, Buffalo, New York. Also Neutrogena Corporation supplied Melanax® and Herbert Laboratories supplied the Total Eclipse® 15 and its placebo vehicle.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "the allocation of treatments in each study was accomplished by a restricted randomization process to ensure equal frequencies of the treatments to each side in small sequences of consecutively numbered patients." Comment: method of sequence generation could allow investigators to guess the allocations.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient detail in allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "the test preparations were supplied to investigators in coded identical tubes". Comment: whilst it is likely that participants were adequately blinded as the trial preparations were similarly packaged, it is unclear which personnel were blinded and whether blinding might be compromised.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the test preparations were supplied to investigators in coded identical tubes". Comment: it is unclear which personnel were blinded and whether blinding might be compromised.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "data on fourteen patients were excluded from the efficacy analyses due to their failure to make any of the subsequent visits or because of signifi-

Sefton 1984c *(Continued)*

		cant protocol violations. However, all patients' records were reviewed and included for the tabulation of possible adverse experiences." Comment: this is just over 10% of data, so could be a problem given overall low numbers included.
Selective reporting (reporting bias)	Unclear risk	Comment: individual signs and symptom data not presented, we have assumed for brevity; results are alluded to in the text. No protocol available
Other bias	High risk	Comment: the paper does not fully explain how the reported trials differed in terms of methodology.

Sikder 2005

Study characteristics

Methods

Trial design

Open, randomised, comparative, multicentre, parallel-group trial

Trial registration number

Not reported

Setting

3 centres in Dhaka, Bangladesh

Date trial conducted

October 2004-February 2005

Duration of trial participation

6 weeks (4 weeks treatment, 2 weeks post-treatment follow-up)

Additional design details

None

Inclusion criteria

- Patients aged 7-15 years of either sex
- Diagnosis of moderate or severe AD (Hanifin and Rajka (Hanifin 1980)).
- Patients with disease involvement of 5%-50% of the total BSA

Exclusion criteria

- Patients having a serious skin disease other than AD that required treatment
- Patients with a history of eczema herpeticum
- Patients who had received topical treatment for AD within 2 weeks and/or systemic drug for AD within 4 weeks of the trial

Notes

None

Participants

Total number randomised

45 participants, however, they mention that 57 participants meeting the enrolment criteria were approached, and it's not clear if they were all randomised.

Sikder 2005 *(Continued)*

There are 3 arms to this trial: TCI arm A, TCS arm B, and TCS/TCI arm C. Data only extracted for B and C as A does not contain a steroid treatment. Only 2 groups are relevant to this review (n = 30).

Age

TCS alone: mean 10.7 (SD 1.8). TCS/TCI: mean 10.5 (SD 2.7). TCS alone: 7-9 years (n = 3, 20%), 10-12 years (n = 9, 60%), 13-15 years (n = 3, 20%). TCS/TCI: 7-9 years (n = 7, 46.7%), 10-12 years (n = 3, 20%), 13-15 years (n = 5, 53.3%).

Sex

TCS alone: male n = 11 (73.3%), female n = 4 (26.7%). TCS/TCI: male n = 8 (53.3%), female n = 7 (46.7%).

Race/ethnicity

Not reported

Duration of eczema

Mean duration (mean ± SD) TCS 6.7 ± 3.2, TCS/TCI 5.7 ± 3.2

In the TCS arm the number of participants with < 6 month duration was 9 (60.0%), > 6 month duration n = 6 (40.0%), TCS/TCI < 6 month duration n = 11 (73.3%), > 6 month duration n = 4 (26.7%).

Severity of eczema

Modified EASI mean (SD): TCS alone 15.6 (5.3); TCI/TCS 14.4 (5.7). Number of participants with a score 21 (%): TCS alone 2 (13.3%); TCI/TCS 1 (6.7%). Baseline BSA (BSA) mean (SD): TCS alone 25.4 (4.8); TCI/TCS 24.9 (5.0). Number of participants with BSA of 18%-24% (%): TCS alone 6 (40%); TCI/TCS 9 (60%). Number of participants with BSA of 25%-30% (%): TCS alone 8 (53.3%); TCI/TCS 4 (26.7%). Number of participants with BSA of 31%-36% (%):TCS alone 1 (6.7%); TCI/TCS 2 (13.3%)

Filaggrin mutation status

Not reported

Number of withdrawals

1 participant was lost during treatment who received TCS only. Another dropout was observed at the end of follow-up who received combination regimens.

Notes

"Among three treatment groups there were no significant differences in age, gender, socioeconomic status, duration of current episode of disease, side of involvement, affected BSA and severity (mEASI)." P values and numbers of participants are provided for all these parameters.

Interventions

Run-in details

Not reported

Groups

- Clobetasone butyrate 0.05% cream (Ezex); applied twice daily in a thin layer to areas of active disease for 4 weeks
- Clobetasone butyrate 0.05% cream (Ezex); applied once daily in the morning in a thin layer to areas of active disease for 4 weeks. Concurrent treatment: tacrolimus 0.03% ointment was applied in the evening to areas of active disease for 4 weeks.

Adherence

Not reported

Co-interventions

Sikder 2005 *(Continued)*

	Other topical and systemic drugs used in AD were prohibited. Bath oil and emollients were allowed. Inhaled or intranasal corticosteroids were limited to 1 mg/day where required. **Notes** None
Outcomes	• Adverse events (not mentioned in the methods) at up to week 6.* • Investigator assessment of overall clinical response (cleared = 100% improvement, excellent = 90-99% improvement, marked = 75-89% improvement, moderate = 50-74% improvement, slight = 30-49% improvement, no = 0-29% improvement at weeks 0, 2, 4, 6 (assumed). • participant assessment of intensity of itching experienced during previous 24 h using a 10cm visual analogue scale (0cm = no itch, 10cm = "severe intractable itch") at weeks 0, 2, 4, 6 (assumed).* • Modified EASI (mEASI) calculated using EASI and participant assessment of itching converted to an ordinal scale of 0-3 and multiplied by the total affected area score (0-6) for maximum itching score of 18. The EASI was summed with the itching score to get mEASI (maximum = 72+18 = 90) at weeks 0, 2, 4, 6 (assumed).* • Investigator assessed total percentage BSA (0%-100%) for 4 body regions (head and neck, upper limbs, trunk and lower limbs) at weeks 0, 2, 4, 6 (assumed) *denotes relevance to this review
Funding source	None stated, however Square Pharmaceuticals Ltd. Dhaka provided the trial medication.
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were stratified by age and disease severity and randomized in parallel group (1:1:1) to receive a commercial preparation of 0.03% tacrolimus ointment alone, 0.05% clobetasone butyrate cream alone or both" Comment: randomisation method not described
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open label study" Comment: participants would have known which treatment they were receiving.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open label study" Comment: outcome assessors could have possibly known what the participant was receiving.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three patients lost during treatment, of them two received 0.03% tacrolimus ointment and one received 0.05% clobetasone butyrate. Another dropout observed at the end of follow-up who received combination regimens." Comment: only 1 dropout in steroid only arm and 1 dropout in combination arm (tacrolimus arm not relevant to this review)

Sikder 2005 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available for this trial.
Other bias	Low risk	Comment: no other sources of biases identified

Sillevis 2000

Study characteristics	
Methods	**Trial design** Prospective, randomised, double-blind trial **Trial registration number** Not reported **Setting** Participants recruited from an outpatient clinic at Amsterdam Medische Centrum, a large University hospital. **Date trial conducted** Not reported **Duration of trial participation** 12 weeks: 8 weeks of treatment + 4 weeks of follow-up (we were supplied with additional information for this trial in June 2019; email correspondence). **Additional design details** None **Inclusion criteria** From the short paper: children with constitutional eczema. From email correspondence: • Children (0.5-14 years old) with AD (Hanifin and Rajka criteria (Hanifin 1980)). • Patients with a requirement for corticosteroid treatment; SCORAD > 15; Rajka and Langeland moderate-severe • Patients with 1-month duration of AD • Patients able to stop current treatment for 2 weeks **Exclusion criteria** From email correspondence: • Patients with acute uncontrolled bacterial, viral (herpes) or fungal infections • Unco-operative patients (or parents) who were unlikely to comply with medical prescriptions and/or who were not willing to, or not capable of attending the required appointments at the clinic • Patients with a known history of an allergic reaction in the past to 1 of the components of clobetasone butyrate ointment. **Notes** Inclusion criteria stated "patients had to be able to stop current treatment for two weeks" - this could indicate a potential run-in period

Sillevis 2000 *(Continued)*

Participants	**Total number randomised** 40; 20 in each group (from June 2019 email correspondence) **Age** June 2019 email: overall mean age was 5.1 ± SD 3.5, pulse group 4.2 ± 3.3; continuous 6.0 ± 3.7. There were 8 (20%) aged 0-1 years overall; 6 in the pulse group and 2 in the continuous group. There were 18 (45%) aged 1-5 years overall; 10 in the pulse group and 8 in the continuous group. There were 14 (35%) aged over 5 years overall; 4 in the pulse group and 10 in the continuous group. **Sex** June 2019 email: there were 26 male and 14 female overall; 13 (65%) male and 7 (35%) female in both groups. **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** June 2019 email; total baseline SCORAD was mean 45.5 ± SD 13.5; 46.3 ± 14.7 for the continuous group and 44.8 ± 12.5 for the pulse group. objSCORAD: 33.9 ± 10.5 in total; 34.6 ± 11.5 for the continuous group and 33.3 ± 9.8 for the pulse group. **Filaggrin mutation status** Not reported **Number of withdrawals** June 2019 email: There were 6 dropouts in the continuous group and 4 in the pulse group (no reasons given). **Notes** None
Interventions	**Run-in details** Not reported **Groups** • Clobetasone butyrate 0.05% ointment; 2 tubes of medication were supplied to each participant, 1 was applied for 4 days twice daily, the other for the remaining 3 days twice daily. In this group both tubes contained TCS **(**continuous treatment group**)**. Concurrent treatment: none • Clobetasone butyrate 0.05% ointment; 2 tubes of medication were supplied to each participant, 1 was applied for 4 days twice daily the other for the remaining 3 days twice daily. In this group the tube applied for 4 days contained TCS the other basic (placebo) ointment **(**pulse treatment group). Concurrent treatment: basic ointment was used instead of TCS on the remaining 3 days. The treatment was continuous regardless of response (June 2019 email). **Adherence** Not reported **Co-interventions**

Sillevis 2000 *(Continued)*

	Not reported **Notes** None
Outcomes	• SCORAD (also relevant, but ObjSCORAD higher in our hierarchy) at baseline and weeks 2, 4, 6, 8 and 12. • Adverse events (June 2019 email) at (assumed) 0-12 weeks (last 4 weeks follow-up only).* • ObjSCORAD at baseline and weeks 2, 4, 6, 8 and 12 (last 4 weeks follow-up only)* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	Translated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "forty consecutive children were randomised" June 2019 email: "A computer-generated randomization list was used to assign patients in one of the two treatment groups". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "The investigators were not allowed to break the code for any patient, unless the occurrence of severe or serious adverse events, until the trial was completed. Clobetasone butyrate ointment was supplied to the pharmacology department of the Academic Medical Center at the University of Amsterdam.' (from email correspondence) Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" From June 2019 email: "The investigators were not allowed to break the code for any patient, unless the occurrence of severe or serious adverse events, until the trial was completed. Clobetasone butyrate ointment was supplied to the pharmacology department of the Academic Medical Center at the University of Amsterdam. Sets of two 30 gram tubes were prepared. Two tubes were distributed, one for the first part of the week and one for the second part of the week. Both tubes looked the same in both groups, it was impossible to discern the ointment containing Clobetasone butyrate from the ointment containing no steroid. Physicians and patients were blinded for the allocation of treatment." Comment: blinding appears adequate as both groups of participants received virtually identical treatments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	From June 2019 email Quote: "The outcome assessors were blinded for the treatment of the patients. In most cases, assessments were done by the same investigator for each patient." Comment: as the treatments were so similar it is unlikely the participant would be able to disclose to the assessor what treatment they were receiving. There is no reason that the assessor would be able to tell what treatment the participant was receiving and so it is likely blinding was adequate.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data from June 2019 email: Quote "An ITT analysis was performed". "There were 6 drop outs in the continuous group and 4 in the pulse group".

Sillevis 2000 *(Continued)*

		Comment: no information was provided as to what imputation was used for the missing data in the 2 groups.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol, no comprehensive methods section
Other bias	Low risk	Comment: no other sources of bias detected

Sparkes 1974

Study characteristics	
Methods	**Trial design** Half-sided RCT **Trial registration number** Not reported **Setting** Most participants were outpatients, some were inpatients. Clinicians were mostly dermatologists at a variety of centres in the UK, Sweden, Finland and Belgium. **Date trial conducted** Not reported **Duration of trial participation** 1 week **Additional design details** None **Inclusion criteria** Bilateral lesions of eczema where there was minimal difference in severity between sides. **Exclusion criteria** Not reported **Notes** Only extracted data for eczema participants
Participants	**Total number randomised** Not reported for eczema alone **Age** Not reported **Sex** Not reported **Race/ethnicity**

Sparkes 1974 *(Continued)*

Not reported

Duration of eczema

Not reported

Severity of eczema

Not reported

Filaggrin mutation status

Not reported

Number of withdrawals

Not reported for eczema participants alone

Notes

Number reported is 1150, but this is inclusive of psoriasis and eczema participants. There was 1 withdrawal out of 1150 owing to worsening of disease; unclear if a psoriasis or eczema participant.

Interventions

Run-in details

Not reported

Groups

A: clobetasol propionate 0.05% cream (unspecified); applied at least twice daily (more if the clinician decided) to the designated side, with or without polythene occlusion. Concurrent treatment: not reported

B: betamethasone valerate cream (proprietary: Betnovate); applied at least twice daily (more if the clinician decided) to the designated side, with or without polythene occlusion. Concurrent treatment: not reported

C: fluclorolone acetonide cream (proprietary: Topilar); applied at least twice daily (more if the clinician decided) to the designated side, with or without polythene occlusion. Concurrent treatment: not reported

D: clobetasol propionate 0.05% ointment (unspecified); applied at least twice daily (more if the clinician decided) to the designated side, with or without polythene occlusion. Concurrent treatment: not reported

E: betamethasone valerate ointment (proprietary: Betnovate); applied at least twice daily (more if the clinician decided) to the designated side, with or without polythene occlusion. Concurrent treatment: not reported

F: fluclorolone acetonide ointment (proprietary: Topilar); applied at least twice daily (more if the clinician decided) to the designated side, with or without polythene occlusion. Concurrent treatment: not reported

G: fluocinonide FAPG (proprietary: Metosyn); applied at least twice daily (more if the clinician decided) to the designated side, with or without polythene occlusion. Concurrent treatment: not reported

Adherence

Not reported

Co-interventions

All participants were asked to wash their hands between treatment applications.

Notes

Sparkes 1974 *(Continued)*

	It is unclear who were randomised to which comparisons and how many eczema patients were treated. All that is known is that all participants received a clobetasol propionate preparation. *FAPG "said to have the properties of both a cream and an ointment (Portney & Sarkany, 1972)". Visual approximation from published figure of number evaluated in each group.
Outcomes	• Side effects were reported, and many participants were explicitly asked about sensation on application at up to day 7 however, the discussion states that side effects were not looked for. • Investigator preference for which side gave the best response (extracted in preference to the IGA as the IGA was not reported) at near day 7* • IGA: clinician (assumed) rated the lesions on a 4-point scale as 'healed', 'improved', 'static' or 'worse at near day 7 • Participant assessment (equal response, preference for clobetasol, preference for other steroid) at near day 7. However, the paper reported "Differences between these 2 assessments were extremely rare, so that all analysis of data that follows is based only upon the clinician's choice". *denotes relevance to this review
Funding source	None stated, however trial authors were affiliated to Glaxo Laboratories Ltd.
Declarations of interest	None declared, however trial authors were affiliated to Glaxo Laboratories Ltd.
Notes	The trial included eczema and psoriasis patients; however it was necessary to use WebPlotDigitizer to get the number of eczema patients randomised to each comparison. Participants were not randomised to occlusion/non-occlusion.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "allocated at random to left or right sides" Comment: no information on sequence generation or the extent to which this might be predicted
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient detail of allocation method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "identical looking tubes were labelled accordingly. Neither the clinician nor the patient was aware of their distribution." Comment: it is likely that the participants were adequately blinded by the use of similar preparations in identical tubes compared against one another, with the exception of FAPG. However, we are not given details on who prepared or distributed the medication and whether they were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "identical looking tubes were labelled accordingly. Neither the clinician nor the patient was aware of their distribution." "In order to eliminate [the ability to detect FAPG base versus other preparations] all patients in all sections of the trial were asked not to use the preparations on the day they returned to their doctor for assessment." "The trial code was held by a trial coordinator." Comment: suggests were adequately blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: at no point are we given the numbers of eczema patients randomised to each comparison, therefore we cannot scrutinise the data here. No detail is given on missing data or withdrawals.
Selective reporting (reporting bias)	High risk	Comment: no protocol available, IGA was not presented, and we are given no numerical outcome data or group sizes.

Sparkes 1974 *(Continued)*

Other bias	Low risk	Comment: no other source of bias detected

Stewart 1973

Study characteristics

Methods	**Trial design** Within-participant **Trial registration number** Not reported **Setting** Not reported **Date trial conducted** Not reported **Duration of trial participation** 4 weeks **Additional design details** None **Inclusion criteria** • Not reported **Exclusion criteria** • Not reported **Notes** None
Participants	**Total number randomised** 34 participants with AD (the initial test group contained patients with all dermatological conditions, not just AD, this group included 128 participants) **Age** Not reported separately for AD participants **Sex** Not reported separately for AD participants **Race/ethnicity** Not reported separately for AD participants **Duration of eczema** Not reported

Stewart 1973 *(Continued)*

	Severity of eczema Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Within the AD group 34 participants started the trial but only 23 were still included at week 4. no reason for withdrawals were given. **Notes** None
Interventions	**Run-in details** Not reported **Groups** • Betamethasone 17-valerate 0.1% cream; each drug was applied twice daily as a thin layer without occlusion to bilaterally symmetrical lesions. The labelling indicated clearly to the participant whether the medication was to be applied to the right or to the left side. Concurrent treatment: not reported • Desonide 0.05% cream; each drug was applied twice daily as a thin layer without occlusion to bilaterally symmetrical lesions. The labelling indicated clearly to the participant whether the medication was to be applied to the right or to the left side. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** Concentrations chosen are those recommended by the manufacturer for clinical use.
Outcomes	• Response to therapy was evaluated by decrease in erythema, vesicle formation, pruritus and induration in the inflammatory dermatoses. The results were scored as right side superior, left side superior, equally effective, or neither side effective at week 1, 2, 3 and 4* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared, however Miles Laboratories, Schering Corporation Ltd. And E. R. Squibb and Co. Ltd. are acknowledged as having provided TCS powders for the trial.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized". Comment: no information about sequence generation

Stewart 1973 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind". Comment: taking into account the above statement and that assessors recorded judgements by 'side' we have assumed that blinding was adequate.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 23 AD participants remain at 4 weeks of 34 enrolled; no details of withdrawals given
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Unclear risk	Comment: it is unclear how patches were selected and by whom, and whether this decision could be a source of bias.

Sudilovsky 1981

Study characteristics	
Methods	**Trial design** Double-blind, randomised, paired (right-side, left-side) trial **Trial registration number** None **Setting** Multiple centres; there is a list of 15 international investigators. No further information given **Date trial conducted** Not reported **Duration of trial participation** 3 weeks **Additional design details** If complete remission was obtained in < 3 weeks, treatment could be stopped at that time. **Inclusion criteria** • Patients with AD (or psoriasis vulgaris; results presented separately) • Bilateral lesions of similar severity and chronicity • Had not received corticosteroid medication for at least 1 week preceding the trial **Exclusion criteria** • Patients with a previous history of poor response to TCSs

Sudilovsky 1981 *(Continued)*

Notes

None

Participants	**Total number randomised** 149 participants **Age** Not reported separately for atopic eczema population **Sex** Not reported separately for atopic eczema population **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** Not reported, however if complete remission was achieved before the end of 3 weeks, treatment could be stopped. This might explain why weekly outcomes had progressively smaller numbers: 149 at week 1, 138 at week 2, 116 at week 3. **Notes** None
Interventions	**Run-in details** NA **Groups** • Halcinonide 0.1% cream (Halciderm, Halog); placebo cream was applied twice daily (morning and afternoon) plus halcinonide once daily at bedtime to 1 side of the body. Concurrent treatment: none • Halcinonide 0.1% cream (Halciderm, Halog); participants applied halcinonide 3 times daily to the other side of the body. Concurrent treatment: none **Adherence** Not reported **Co-interventions** During the course of the trial, participants did not receive any concomitant local or systemic therapy that could have affected their condition. **Notes** None

Sudilovsky 1981 *(Continued)*

Outcomes	• Comparative response (comparing bilateral lesions for factors such as erythema, edema, and changes in size and thickness of the lesions. Categorised as 'markedly superior' = easily discernible difference, 'slightly superior' = barely discernible difference, 'equal response' = no difference. "In determining a MARKEDLY SUPERIOR response, a difference of 1 or more steps on the above scale was required, A SLIGHTLY SUPERIOR response could be judged even when responses were in the same category." at week 1, 2 and 3 • Absolute response ('excellent' = 75%-100% improvement: cleared or essentially cleared, including those cases with residual pinkness of the skin, no oedema, and little or no thickening; 'good' = 50%-74% improvement: substantial, easily perceived improvement; 'fair' = 25%-49% improvement: some discernible improvement in at least 1 parameter; 'poor' = < 25% improvement: no significant improvement of worsening). Considered as an IGA at week 1, 2 and 3* • Overall IGA taking into account the comparative and absolute responses during the entire course of therapy at up week 3 (end of treatment period) • Side effects (not mentioned in the methods) at up week 3 (end of treatment period)* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None stated
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The part of the study to which a patient was assigned (I or II) and the side of the body chosen for a specific treatment was unknown to the investigators, and was determined by a table of random numbers." Comment: it is likely that the randomisation method was adequate.
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding the actual method of allocation (e.g. whether it was an open table of random numbers).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The cream base vehicle was used as placebo. Both halcinonide cream, 0.1 %, and placebo were packaged in identical 15-gm tubes." "Patients received placebo twice daily (morning and afternoon) plus halcinonide hs [at bedtime] on one side, and halcinonide tid on the opposite side." "The part of the study to which a patient was assigned (I or II) and the side of the body chosen for a specific treatment was unknown to the investigators." Comment: the investigators took steps to ensure that it was not likely that the participants or the personnel involved would be able to identify which treatment they were receiving.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The part of the study to which a patient was assigned (I or II) and the side of the body chosen for a specific treatment was unknown to the investigators." Comment: investigators who measured the outcomes were blinded to trial group assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "If a complete remission was obtained in less than three weeks, treatment could be stopped at that time." Comment: number and reasons for withdrawal were not reported, however if complete remission was achieved before the end of 3 weeks, treatment could be stopped. This might explain why weekly outcomes had progressively smaller numbers: 149 at week 1, 138 at week 2, 116 at week 3

Sudilovsky 1981 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available
Other bias	Low risk	Comment: no other sources of bias detected

Tharp 1996

Study characteristics	
Methods	**Trial design** Double-blind, parallel, RCT **Trial registration number** None **Setting** 9 centres, presumed to be in secondary care settings in the USA as the author is a dermatologist. **Date trial conducted** August-December 1991 **Duration of trial participation** 4 weeks **Additional design details** 3-arm trial, however, only 2 arms are relevant. Data not extracted from the vehicle arm. **Inclusion criteria** • Aged ≥ 12 years • An "established" diagnosis of eczema **Exclusion criteria** • "Prescribed medications with associated washout periods" • Comorbidities that might interfere (unspecified) • Sensitivity to the trial preparations or steroid therapy in general • Individuals unable to give consent or comply with the trial protocol • Patients with eczema that was acute, self-limited, or likely to resolve spontaneously ("allergic contact eczema" given as an example) selection of the target lesion excluded the scalp, face, axillae and groin. **Notes** None
Participants	**Total number randomised** 238 enrolled; 79 enrolled into the once daily, 79 into the twice daily group, and 80 into the vehicle group (data not extracted further) **Age** The mean age was 37 years (SE 1.1, range 12-87) overall, 38 (1.9, 14-77) in the once daily group, and 38 (1.8, 14-82) in the twice daily group.

Tharp 1996 *(Continued)*

Sex

There were 160 male and 78 female participants overall, 54 male and 25 female in the once daily group, and 50 male and 29 female in the twice daily group.

Race/ethnicity

There were 162 white participants, 37 black, 15 Asian and 24 "other" overall; 55 white participants, 15 black, 4 Asian and 5 "other" in the once daily group; and 50 white participants, 11 black, 6 Asian and 12 "other" in the twice daily group.

Duration of eczema

The median length of eczema history was 11 years (range 0-71) overall, 13 (0.4-70) in the once daily group, and 10.5 (0-60) in the twice daily group. The median length of the current flare was 8 weeks (range 1-1820) overall, 8 (1-1300) in the once daily group, and 6 (1-1820) in the twice daily group.

Severity of eczema

A 7-point scale (0.5 increments from 0 = absent to 3 = severe) was used to rate the severity of target lesion signs and symptoms at baseline. Each group scored a mean of 2.3 for erythema, 2.5 for pruritus, 2.1 for skin thickening, 1.6 for lichenification, 0.6 for vesiculation, and the scores for crusting were 0.8 (once daily) and 0.9 (twice daily). All participants had a combined score of ≥ 6 (the sum of the scores for erythema, skin thickening and pruritus).

Filaggrin mutation status

Not reported

Number of withdrawals

55 participants withdrew; 14 from the once daily group (2 for treatment failure, 5 for early cure, 1 because of an adverse event, 2 for protocol violations and 4 for other noncompliance/personal reasons) and 19 from the twice daily group (4 for treatment failure, 12 for early cure, 1 because of an adverse event, 1 for protocol violation and 1 for another noncompliance/personal reason). 2 participants from each group did not return for any follow-up visits.

Notes

None

Interventions

Run-in details

None

Groups

- Fluticasone propionate 0.05% cream (proprietary: Cutivate); TCS was applied to the target lesion (and others if required, although these were not assessed) in the evening; vehicle cream was applied in the morning. Concurrent treatment: none
- fluticasone propionate 0.05% cream (proprietary: Cutivate); TCS was applied morning and evening. Concurrent treatment: none

Adherence

No difference between treatment groups in percentage of participants missing at least 1 trial medication application.

Co-interventions

No other treatments or medications for eczema could be used by participants during the trial.

Notes

Tharp 1996 *(Continued)*

	The 1st treatment was supervised by an investigator or research nurse to ensure correct application, and occlusive dressings were not used.
Outcomes	• Occurrence of adverse events: monitored throughout the trial. Relationship to trial medication was judged by investigator (possibly, probably, or almost certainly related were reported) at up to 29 days.* • Participant's subjective assessment of treatment effects (4-point ordinal scale from 1 = excellent to 4 = poor) at baseline and days 8, 15, 22 and 29* • Physician's gross assessment of target lesion (6-point ordinal scale: 1 = cleared, 2 = 75%-99% improvement, 3 = 50%-74% improvement, 4 = 25%-49% improvement, 5 = ≤ 25% improvement, 6 = worse) at baseline and days 8, 15, 22 and 29* • Physician's score for each sign and symptom of the target lesion (7-point ordinal scale from 0 = absent to 3 = severe, with 0.5 increments, for the following signs and symptoms: erythema, pruritus, skin thickening, lichenification, vesiculation, and crusting at baseline and days 8, 15, 22 and 29 • Total severity score (sum of the individual sign and symptom severity scores for erythema, pruritus and skin thickening) at days 8, 15, 22 and 29 *denotes relevance to this review
Funding source	Not reported
Declarations of interest	None declared, however 2/4 references are to Glaxo documentation and data on file, and Cutivate is a product of Glaxo.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Qualifying patients were randomly assigned". Comment: no information about how randomisation was done
Allocation concealment (selection bias)	Unclear risk	Quote: "Qualifying patients were randomly assigned". Comment: not clear if allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "This multi-center, double-blind, randomized, parallel, four-week, vehicle controlled study…" Quote: "Study medications were packaged in identical 30 gm tubes". Comment: efforts were made to blind participants but not clear if trial personnel knew treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "This multi-center, double-blind, randomized, parallel, four-week, vehicle controlled study…" Quote: "Study medications were packaged in identical 30 gm tubes". Comment: not clear if outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Thus 232 patients (seventy-seven fluticasone QD, seventy-seven fluticasone BID, and seventy-eight vehicle patients) were evaluated and included in the analyses of efficacy and safety". Quote: "Fifty-five patients (24% of those treated) withdrew from the study prior to completion of day 29 evaluation". Comment: even though the authors said they included 232 participants in the efficacy analyses, figure 4 only shows data for those who completed the trial. There is no mention of any ITT analysis. Furthermore, more participants in the twice daily group withdrew for early cure.

Tharp 1996 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: no clinical trial register or protocol available
Other bias	Low risk	Comment: no other biases identified

Thomas 2002

Study characteristics	
Methods	**Trial design** Pragmatic, double-blind, parallel-group, RCT **Trial registration number** Not reported **Setting** Participants were recruited from the Queen's Medical Centre eczema clinic and from 13 general practices in the Nottingham, UK, area; participants recruited from the community were identified through doctors' records on the basis of a diagnosis of eczema or the use of TCSs in the past year. **Date trial conducted** Recruitment from October 1999-October 2000. Follow-up assessments completed by March 2001. **Duration of trial participation** 18 weeks **Additional design details** The trial authors had intended to recruit from dermatology outpatient clinics at 3 teaching hospitals; however, to achieve recruitment targets they also had to enrol from the community. **Inclusion criteria** • Children aged 1-15 years with atopic eczema as defined by Hanifin and Rajka's modified diagnostic criteria (Williams 1994). • Patients who had had mild or moderate atopic eczema within the past month **Exclusion criteria** • Children with severe eczema on ethical grounds • Known sensitivity to the trial treatments • Eczema confined to the face or nappy area **Notes** None
Participants	**Total number randomised** 207 participants (33 from hospital, 174 from community). Mild (HC) arm = 104 participants (17 from hospital, 87 from community), potent (betamethasone valerate) arm = 103 participants (16 from hospital, 87 from community). **Age**

Thomas 2002 *(Continued)*

Mild hospital-recruited participants had a mean age of 5 years (SD 3.2); mild community-recruited participants 5 (3.8); potent hospital-recruited participants 6 (3.0); potent community-recruited participants 6 (4.0).

Sex

There were 8 male (47%) recruited from the hospital in the mild arm; 49 (56%) from the community in the mild arm; 10 (63%) from the hospital in the potent arm; 36 (41%) from the community in the potent arm.

Race/ethnicity

Mild arm (hospital participants) = 14 white (82%). Mild arm (community participants) = 77 white (89%). Potent arm (hospital participants) = 15 white (94%). Potent arm (community participants) = 79 white (91%)

Duration of eczema

Not reported

Severity of eczema

Number of participants with mild eczema: mild arm (hospital participants) = 6 (35%); mild arm (community participants) = 62 (71%); potent arm (hospital participants) = 6 (38%); potent arm (community participants) = 52 (60%). Mean (SD) disease severity (according to SASSAD): mild arm (hospital participants) = 13.6 (8.7); mild arm (community participants) = 8.2 (6.1); potent arm (hospital participants) = 16.2 (9.7); potent arm (community participants) = 9.0 (6.3)

Filaggrin mutation status

Not reported

Number of withdrawals

31 (36%) withdrew from the mild arm; 6 participants dropped out due to uncontrolled eczema, 10 dropped out for other reasons (15 participants used concurrent treatment but remained in the trial). 22 (25%) withdrew from the potent arm; 3 due to uncontrolled eczema, 8 for other reasons (11 participants used concurrent treatments but remained in the trial)

Notes

None

Interventions

Run-in details

NA

Groups

- HC 1% ointment; twice daily for 7 days as a burst when required, over 18 weeks. Concurrent treatment: none
- Betamethasone valerate 0.1% fatty ointment (proprietary: Betnovate; GlaxoWellcome.); twice daily for 3 consecutive days out of 7 as a burst when required, over 18 weeks. Concurrent treatment: after the 3 days of TCS application, base emollient (white soft paraffin) was used for 4 days.

Adherence

Participants returned tubes for weighing.

Co-interventions

None stated in the methods however the paper mentions participants used similar quantities of emollients.

Notes

Thomas 2002 *(Continued)*

	None
Outcomes	• Number of undisturbed nights at daily diary over 18 weeks* • Number of scratch-free days; scratching was recorded by the child (or carer) in a daily diary. Scratch scores were graded in response to "how much has your eczema made you scratch today?" from 1 (not at all) to 5 (all the time). Scores of ≤ 2 were considered as scratch-free days at daily diary over 18 weeks* • Median number of relapses. Participants were assumed to be in relapse if they scored > 2 on the scratch-score for at least 3 consecutive days at up to 18 weeks. • Proportion of treatment failures (number of participants who used concurrent treatments or who were lost to follow-up) at up to 18 weeks • Quality of life using the Children's Life Quality Index and the DFI questionnaire at baseline and week 18. • Success of blinding by asking participants or parents of younger children to guess their treatment group at week 18 • Economic evaluation of the costs of the 2 treatments to the NHS at week 18 • Adverse events; self-reported (though not mentioned as an outcome in the methods section of the paper) and including clinical evidence of skin thinning at up to week 18* • Disease severity using SASSAD, with the proportion of participants achieving > 20% improvement in scores at baseline, week 6, week 12, week 18* • Short-term control, based on the median duration of the 1st relapse and the median duration of the 1st remission in daily diary over the 18 weeks • Skin thickness (epidermis and dermis) was measured a 20 MHz B mode ultrasound scanner (Longport International, Reading). 6 measurements at elbows, knees, forearm, and calf were taken and from which mean skin thickness was calculated. Clinically important thinning of the skin was defined as > 25% reduction in skin thickness compared to baseline at baseline and week 18. *denotes relevance to this review
Funding source	NHS research and development programme (Trent)
Declarations of interest	1 trial author received funds from the NHS health technology assessment programme. The trial authors reported that it is possible that the NHS could gain from this research. Another trial author was a consultant to Medical Solutions, a company that markets benzoyl peroxide formulations and anti-eczema products.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was computer generated in blocks of four. The list was produced and stored by the clinical trials pharmacist at Queen's Medical Centre. Treatment packs were prepared and labelled at the pharmacy. The research assistants used consecutively numbered packs to allocate new participants to treatment groups." Comment: randomisation method was fully described
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was computer generated in blocks of four. The list was produced and stored by the clinical trials pharmacist at Queen's Medical Centre. Treatment packs were prepared and labelled at the pharmacy. The research assistants used consecutively numbered packs to allocate new participants to treatment groups." Comment: as the packs were prepared in the pharmacy and distributed by the research assistants it is unlikely that those personnel handing out the packs would have known what group they were allocating to the participant.

Thomas 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants and assessors were blinded to group assignment during collection of the data", "Both treatments were dispensed in white tubes labelled A and B to maintain blinding of the treatment allocation. The contents of tube A were applied for three days then tube B for four days. In the mild arm both tubes contained hydrocortisone whereas in the potent arm tube A contained betamethasone valerate and tube B contained the base emollient." Comment: steps were taken to ensure that participants and personnel (plain unidentifiable packaging) would not be able to identify the treatment that they were receiving or allocating to participants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants and assessors were blinded to group assignment during collection of the data." Comment: outcome assessment was blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "We conducted our analysis on an intention to treat basis and imputed missing data by carrying forward the last known value". Comment: as the missing data were imputed as last known value and a large number of participants dropped out of the trial (36% mild, 25% potent) this may have introduced bias into the trial results. They did not exclude participants requiring concurrent treatment, however they did have to exclude 9 participants where the diaries were not returned (for participant reported outcomes).
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. The data presented for SASSAD were also limited.
Other bias	Unclear risk	Comment: more cases of mild eczema in the mild TCS potency arm and disease severity was higher in the potent TCS arm. participants recruited from a hospital setting had more severe eczema, but the data were often only presented for the community participants in the results section.

Ulrich 1991

Study characteristics	
Methods	**Trial design** Double-blind, randomised trial **Trial registration number** None **Setting** 7 centres, assumed to be in Germany from the affiliations of the authors. **Date trial conducted** Not reported **Duration of trial participation** 14 days **Additional design details** None

Ulrich 1991 *(Continued)*

Inclusion criteria

- Patients with acute episodes of AD up to 40% (10% in infants) of their total BSA
- Able to have topical treatment only

Exclusion criteria

- Pregnancy and breastfeeding
- Microbial secondary infection of the outbreaks
- Concomitant tuberculosis, syphilitic or viral infections
- Accompanying diseases such as diabetes mellitus, leukaemia, parasitic manifestations (scabies, pediculosis), hypogammaglobulinaemia, perioral dermatitis, rosacea or vaccination reactions
- Concomitant treatment with another topical preparation other than the trial medication
- Accompanying systemic therapy with antihistamines, immunosuppressants, corticosteroids or ACTH
- Known hypersensitivity reactions of the skin compared to the active ingredients or propylene glycol, cetyl alcohol, stearyl alcohol, benzyl alcohol, polysorbate 60, paraffin, edetic acid, sorbitan monostearate

Notes

None

Participants	**Total number randomised** 165 were enrolled; 81 potent (halometasone) and 84 moderate (prednicarbate) **Age** Average 26 years (range 8 months-63 years). "The two treatment groups were comparable in terms of […] age" Quoted from the English translation **Sex** 88 male, 77 female. "The two treatment groups were comparable in terms of […] sex" Quoted from the English translation **Race/ethnicity** Not reported **Duration of eczema** "The two treatment groups were comparable in terms of […] duration of current episode." Quoted from the English translation **Severity of eczema** In the potent (halometasone) group, 24/81 had up to 9% BSA involvement, 37 had 10%-20%, and 20 had 21%-40%; 5 were judged to have mild disease, 33 were moderate, and 43 were severe. In the moderate (prednicarbate) group, 32/84 had up to 9% BSA involvement, 39 had 10%-20%, and 13 had 21%-40%; 2 were judged to have mild disease, 45 were moderate, and 37 were severe. **Filaggrin mutation status** Not reported **Number of withdrawals** 20 participants (10 from each group) healed within 12 days, therefore treatment was discontinued, however their data were included in the analysis. **Notes**

Ulrich 1991 *(Continued)*

	"The two treatment groups were comparable in terms of number of participants, age, sex and duration of current episode."
Interventions	**Run-in details** Not reported **Groups** • Halometasone 0.05% cream (proprietary: Sicorten); applied twice daily without occlusion to affected areas for 2 weeks. Concurrent treatment: not reported • Prednicarbate 0.25% cream (unspecified); applied twice daily without occlusion to affected areas for 2 weeks. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** Not reported **Notes** There is a discrepancy between the German and English summary on the strength of halometasone used. English summary states 0.5%, German consistently states 0.05%. We have assumed 0.05% as this is a standard Sicorten preparation.
Outcomes	• Cosmetic acceptance at week 2 (assumed as not stated) • Adverse drug reactions at up to week 2 (assumed as not stated)* • Clinical efficacy, collected by the doctor, assessed on a 5-point scale with the scores: 1 = healing, 2 = definite improvement, 3 = moderate improvement, 4 = mild or no improvement, 5 = worsening at week 2 (assumed)* • Severity of the disease and the onset of the illness, as indicated by the 1st signs or symptoms of recovery, were recorded at baseline and week 2. *denotes relevance to this review
Funding source	None stated, however 1 of the trial authors is affiliated to Zyma GmbH, Munich.
Declarations of interest	None declared, however 1 of the trail authors is affiliated to Zyma GmbH, Munich.
Notes	Translated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "According to the randomization criteria, the patients were assigned to one of the two treatment groups.' Quoted from the English translation. Comment: no information about sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind' Comment: no further information given. Whilst it can be assumed that the participants were blinded it is unclear which investigators were blinded, and how this was achieved.

Ulrich 1991 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind' Comment: no further information given. It is unclear which investigators were blinded, and how this was achieved.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Because of healing in less than twelve days, treatment was discontinued prematurely in 20 patients (10 from each group) (Table 5). However, the data from these patients were included in the evaluation.' Quoted from the English translation. Comment: probably done and appears to be the case in table 4
Selective reporting (reporting bias)	Unclear risk	Quote: "Taking into account the unequal initial situation with regard to the severity of the disease when enrolled in the study (53% clinically severe cases in the halometasone group, and 44% in the prednicarbate group), the therapeutic efficacy in clinically severe cases was assessed by layer adjustment (Table 5).' Quoted from the English translation. Comment: as there is no protocol or analysis plan available it is not clear what analyses were prespecified. The choice to perform the subgroup analysis could have been data driven.
Other bias	Low risk	Comment: no other source of bias detected

Van Del Rey 1983

Study characteristics

Methods

Trial design

Randomised, double-blind, parallel-group trial

Trial registration number

Not reported

Setting

Assumed to be a secondary care setting in Brazil from the affiliations of the authors

Date trial conducted

Not reported

Duration of trial participation

3 weeks

Additional design details

None

Inclusion criteria

- Patients of any race or gender > 12 years old
- Diagnosed with atopic dermatis > 1 year ago
- Erythema, induration and pruritus all present. When scored from 0 = absent to 3 = severe, the sum of the scores was at least 6
- Stable disease (resistant to common treatments) or worsened > 1 week ago

Exclusion criteria

Van Del Rey 1983 *(Continued)*

- Pregnancy
- Patients requiring other topical steroidal anti-inflammatory drugs in addition to trial medication
- Patients requiring systemic treatment for any other reason

Notes

None

Participants	**Total number randomised** 30; 15 into each group **Age** < 18: moderate (alclometasone) group = 2, potent (HC butyrate) group = 1, total = 3. 18-30 years: moderate group = 7, potent group = 11, total = 18. 31-40 years: moderate group = 4, potent group = 2, total = 6. 41-50 years: moderate group = 1, potent group = 0, total = 1. 51-60 years: moderate group = 1, potent group = 0, total = 1. Baseline data not available for 1 individual and this was manually calculated to combine separately presented male and female data. **Sex** There were 13 male and 16 female overall (baseline data not available for 1 individual). There were 7 male and 8 female in the moderate (alclometasone) group. There were 6 male and 8 female in the potent (HC butyrate) group. **Race/ethnicity** White: potent group = 12, moderate group = 13, total = 25. Black: potent group = 2, moderate group = 1, total = 3. Others: potent group = 0, moderate group = 1, total = 1. Baseline data not available for 1 individual **Duration of eczema** Overall, 26 participants had disease duration of 1-5 years, 2 had 6-10 years and 1 > 10 years. 14 had disease duration of 1-5 years and 1 had 6-10 years in the moderate (alclometasone) group. 12 had disease duration of 1-5 years, 1 had 6-10 years and 1 > 10 years in the potent (HC butyrate) group. Baseline data not available for 1 individual. **Severity of eczema** Overall 26 participants has BSA involvement up to 25%, 1 had 25%-50%, and 2 had 50%-75%. In the moderate (alclometasone) group 12 had up to 25% involvement, 1 had 25%-50%, and 2 had 50%-75%. All 14 in the potent (HC butyrate) group had BSA involvement of up to 25%. In the moderate (alclometasone) group the mean (assumed) sum of scores for erythema, induration and pruritus was 7.20 (SE 0.31). In the potent (HC butyrate) group, the mean sum was 7.14 (0.29). Disease state: stable (resistant to common treatments): moderate group = 4, potent group = 4, total = 8. Worsened > a week ago: moderate group = 11, potent group = 10, total = 21 **Filaggrin mutation status** Not reported **Number of withdrawals** 1 individual was excluded retrospectively as the primary diagnosis was seborrhoeic dermatitis. **Notes** None
Interventions	**Run-in details** Not reported

Van Del Rey 1983 *(Continued)*

Groups

- Alclometasone dipropionate (unspecified); applied twice daily (assumed from "12-12 hour" description) for 3 weeks. Concurrent treatment: not reported
- HC butyrate (unspecified); applied twice daily (assumed from "12-12 hour" description) for 3 weeks. Concurrent treatment: not reported

Adherence

Failure to apply treatment > twice, or > 2 additional applications were said to invalidate the report for that case.

Co-interventions

Not reported

Notes

We have assumed standard strengths of these TCS in order to classify their potency as they are not clearly given in the paper.

Outcomes	• Dermogram at baseline • Participant opinion on cosmetic acceptability at weeks 1, 2, and 3, end of trial (no time given) • Participant assessment of efficacy at baseline and weeks 1, 2, and 3, end of trial (no time given)* • Clinical observation for side effects (e.g. irritation, local sensitisation, folliculitis, stretch marks) at up to week 3* • Investigator assessment of clinical signs and symptoms including erythema, induration and pruritus (assumed although translation is not certain about exact signs) scored on a 4-point scale from 0 = absent to 3 = severe at baseline and weeks 1, 2, and 3, end of trial (no time given) • IGA of changes in the target areas: 1 = eliminated (100%, only residual discolouration remaining), 2 = 'sensitive' improvement (75%-< 100% elimination of the signs and symptoms being monitored), 3 = moderate improvement (50%-< 75% elimination), 4 = small improvement (< 50% elimination), 5 = no change (no visible improvement with respect to the assessment made at the beginning of treatment), 6 = exacerbation at weeks 1, 2, and 3, end of trial (no time given)* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	Translated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were divided into two treatment groups according to the randomization adopted (Table A2)'. Quoted from the English translation. Comment: no information provided about sequence generation. Equal numbers in groups leads to the suspicion it may not have been a totally random process.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind". Quoted from the English translation. Comment: no information about how blinding was achieved

Van Del Rey 1983 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind". Quoted from the English translation. Comment: no information about which personnel were blinded or how blinding was achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: although up to 2 participants in the moderate (alclometasone) group and 1 participant in the potent (HC butyrate) group were lacking observations at follow-up visits, data are shown in an ITT format in the endpoint assessment. The single observation missing from the week 1 data is unlikely to contribute a significant source of bias.
Selective reporting (reporting bias)	High risk	Quote: "to evaluate the efficacy and safety of alclometasone compared to HC butyrate." AND 'At each follow-up appointment, the patient was asked to evaluate their efficacy and the cosmetic acceptability of the treatment, which was included in the form." Quoted from the English translation Comment: reports measuring safety but not included this in the results and we assume that participant assessment data have not been reported.
Other bias	Low risk	Comment: no other source of bias detected

Van Der Meer 1999

Study characteristics

Methods

Trial design

Multicentre, double-blind, placebo-controlled

Trial registration number

Not reported

Setting

18 hospitals in the Netherlands

Date trial conducted

Not reported

Duration of trial participation

20 weeks (included stabilisation phase - see section on "run-in" details)

Additional design details

None

Inclusion criteria

- Aged 15-50 years
- Moderate/severe chronic/chronically recurring AD (Hanifin and Rajka (Hanifin 1980)).
- Symptom severity of 4/9 (combined score of erythema, oedema/papulations, and excoriations graded from 0 = absent to 3 = severe) for a target lesion either on the neck, hands or flexural areas of elbows or knees
- For inclusion to the maintenance phase, each of the three main symptoms of the target lesion were scored either 0 or had improved by ≥ 2 stages compared to baseline

Exclusion criteria

Van Der Meer 1999 *(Continued)*

- The presence of concurrent systemic disease prohibiting topical treatment with corticosteroids
- Psoriasis
- AD only on the face, feet or hands
- Systemic treatment for AD (including PUVA or ultraviolet B) in the month preceding the trial
- Topical treatment with tar
- Use of corticosteroids other than low-potency in the week preceding the trial
- A requirement for > 100 g/week of a potent TCS during active episodes
- Use of high-dose (> 1600 micrograms) inhaled corticosteroids

Notes

None

Participants	**Total number randomised** 112 participants were enrolled in the treatment (stabilisation) phase (results not reported as not a comparison of interest) and randomised at this-point; 54 participants proceeded to the maintenance phase: 23 to fluticasone propionate and 31 to placebo. **Age** Mean age 25 years (range 15-46) **Sex** 22 male, 32 female **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Mean objSCORAD of 56 participants who were completely healed who entered the maintenance phase (2 subsequently dropped out before the randomised phase began) 15.9 ± 13.0. Mean objSCORAD at the start of maintenance phase was 16.5 ± 14.5 in fluticasone group and 13.8 ± 9.6 in the placebo group. **Filaggrin mutation status** Not reported **Number of withdrawals** Of the 56 participants who entered the randomisation period, 2 withdrew as they were satisfied with their condition. 21/31 (68%) of the placebo group and 9/23 (39%) in the fluticasone group withdrew because of recurrence and relapse of their AD during the long-term phase. **Notes** Mean (SD) values of the participants that continued into the maintenance phase and those who did not are reported. The SCORAD score of all 112 participants in the trial was 42.1 ± 12.8 which reduced to 25.8 ± 18.9 after the 4 week initial non-randomised phase.
Interventions	**Run-in details** There was a 4-week treatment phase for all participants: during the first 2 weeks fluticasone propionate 0.005% ointment was applied once daily at bedtime to existing and new lesions; then the treatment was reduced to Thursday, Friday, Saturday and Sunday for the next 2 weeks. participants were told to apply the treatment to all sites even if it appeared that their AD was under control. Participants were

Van Der Meer 1999 *(Continued)*

also permitted to use up to 2 oral tablets (20 mg) hydroxyzine dihydrochloride at bedtime for pruritus where it was likely to disturb sleep.

Groups

- Fluticasone propionate 0.005% ointment (proprietary: Cutivate); TCS was applied to the known healed AD sites and any newly occurring sites once daily at bed time on 2 consecutive days (Friday/Saturday) per week. Concurrent treatment: none
- No TCS; placebo was applied to the known healed AD sites and any newly occurring sites once daily at bedtime on 2 consecutive days (Friday/Saturday) per week. Concurrent treatment: none

Adherence

None

Co-interventions

All participants were instructed to use bath oil after bathing or showering and emollient cream as necessary when their skin felt dry. Investigators were permitted to prescribe HC (0.1%) or clobetasone butyrate ointment for face treatment if they were unwilling to recommend trial treatments for the face.

Notes

None

Outcomes

- Skin thickness (3 mm punch biopsy); number of participants with atrophy at enrolment (week −4), week −2, and week 16.* To assess skin thickness, using identical materials and according to identical procedures defined by the trial protocol,investigators took 3-mm punch biopsies at specified clinic visits. All measurements in the same participant were performed at the same location on the body, preferably at flexural sites on elbows or knees. Where these sites were not lesional, another site was selected. Skin thickness was measured from the top of the granular layer to the bottom of the squamous cell layer, perpendicular to the surface of the skin. Samples were stored in formalin solution and sent for analysis to The Laboratory for Public Health in Friesland, Leeuwarden, The Netherlands. The samples were stained and visually assessed for thickness by 2 pathologists according to a 4-point scale where 0 = no atrophy, 1 = possibly atrophy, 2 = probably atrophy, 3 = atrophy. Subsequently, any biopsies judged as 1 or 2 underwent an additional analysis by a third pathologist together with an equally sized random control sample of biopsies originally judged as 0. This time skin thicknesses were judged both subjectively, by visual assessment, and objectively using an interactive image analysis system running Videoplan v2.2 (Kontron Elektronik, Germany). Skin thickness was measured according to criteria for measurement of malignant melanomas. Each biopsy was measured in 10 different, evenly spaced, places. Before starting the procedure, a control measurement of a calibrated 2-mm graticule was performed.
- Serum cortisol (fasting); mean ± SD at enrolment (week −4), baseline (week 0), and (assumed) week 16.* Serum cortisol levels were assessed from venous blood samples taken, where possible, in the morning of each clinic visit from fasting participants. The sample taken at the pre-trial visit was taken before any trial ointment was applied.
- SCORAD ((0.2 x extent) + (3.5 x intensity)); mean ± SD and mean difference with 95% CI at enrolment (week −4), baseline (week 0), and week 16 or at the point of withdrawals or relapse.
- Extent of body affected (rule of 9s) at enrolment (week −4), baseline (week 0), and week 16 or at the-point of withdrawals or relapse.
- Intensity of clinical signs (sum of scores for erythema, oedema/papulation, oozing/crusts, excoriations, lichenification and dryness both at the target lesion and over the body as a whole. Maximum score of 18) at enrolment (week −4), week −2, baseline (week 0), and week 16 or at the-point of withdrawals or relapse.
- Adverse events at "throughout the course of the study" up to 20 weeks in total, 4 weeks run in and 16 weeks maintenance.* Notes: Investigators were asked to assess the causal relationship of the event to the use of trial medication as not related, unlikely, possibly, probably or almost certainly related to the use of trial medication.
- Relapse-free period at up to 16 weeks.* Notes: Relapse is not explicitly defined. Participants experiencing at relapse at any point in the trial were to return to clinic where the investigator could perform an extra assessment scoring intensity and extent of the disease in order to calculate the SCORAD val-

Van Der Meer 1999 *(Continued)*

ue. An exacerbation was scored as the same index lesion as at the start of the trial. However in cases where this initial index lesion did not show any worsening of symptoms another index lesion could be chosen, this lesion being symptomatic for the overall severity of the disease.

- Time to relapse (days) at up to 16 weeks (see outcome above for details of relapse)*
- Relapse rate (hazard ratio and 95% CI) at week 16 (see outcome above for details of relapse)*

*denotes relevance to this review

Funding source	The trial was performed for and supported by Glaxo Wellcome who manufacturers of Cutivate, the preparation used in this trial.
Declarations of interest	In addition to being supported by Glaxo Wellcome, the second trial author is an employee of the company.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: the trial states that "randomization had taken place", however no further detail is provided.
Allocation concealment (selection bias)	Unclear risk	Comment: no detail was provided on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind'. Comment: no detail was provided about how participants and non-pathology personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "visual assessments were performed under blinded conditions, and the pathologists were not aware of the site or sequence of each specimen'. Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 2 participants withdrew for reasons other than recurrence or relapse and so this is unlikely to affect the results of the trial.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was found. Only mean values of serum cortisol from each group were compared. This does not mean that all participants did not experience cortisol suppression.
Other bias	Low risk	Comment: no other sources of bias detected

Veien 1984

Study characteristics

Methods	**Trial design** Randomised, double-blind, half-sided trial **Trial registration number** Not reported

Veien 1984 *(Continued)*

Setting

Outpatients from Dermatology Clinics in Denmark, assumed from the affiliations of several authors

Date trial conducted

Not reported

Duration of trial participation

4 weeks

Additional design details

Not reported

Inclusion criteria

- Patients with chronic, symmetrical and bilateral AD
- Aged under 10 years
- Either sex

Exclusion criteria

Not reported

Notes

None

Participants

Total number randomised

40

Age

Mean 4.1 years ± SD 2.9 (range 10 months-10 years)

Sex

23 male and 17 female

Race/ethnicity

Not reported

Duration of eczema

Not reported (other than "chronic")

Severity of eczema

The global severity at baseline was moderate in 18 participants, severe in 21, and very severe in 1 participant. Mean score was 2.6 ± SD 0.6 based on a 5-point scale from 0 = none to 4 = very severe.

Filaggrin mutation status

Not reported

Number of withdrawals

1 participant missed the 2-week assessment, otherwise no dropouts were reported.

Notes

None

Veien 1984 *(Continued)*

Interventions	**Run-in details** Not reported **Groups** • HC 1% cream (proprietary: Uniderm); applied twice daily until clearance or up to 4 weeks to the designated side, unoccluded. Concurrent treatment: not reported • HC 17-butyrate 0.1% cream (proprietary: Locoid); applied twice daily until clearance or up to 4 weeks to the designated side, unoccluded. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** To prevent contamination, all participants' parents/carers were told to wash their hands before applying each treatment. **Notes** None
Outcomes	• Side-effects were spontaneously reported at up to week 4.* • Number reported completely healed (with no relapse) as a ratio and a percentage at 2 weeks and 4 weeks • Participant/parent preferences rated as −2 = very much worse, −1 = worse, 0 = the same, 1 = better, 2 = very much better at weeks 2 and 4* • Investigator-assessed global severity of all lesions using a 5-point scale (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe); therapeutic results rated as moderate for a 1-point improvement, good for a 2-point improvement and excellent for a 3-point improvement at baseline and weeks 2 and 4* *denotes relevance to this review
Funding source	None stated, however the lead author is affiliated to Gist-brocades, The Netherlands.
Declarations of interest	None declared, however the lead author is affiliated to Gist-brocades, The Netherlands.
Notes	Uniderm, the brand of HC used, was considered to be an "advanced base formulation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned to treatment […] according to a randomized, double-blind code. According to this code tubes marked 'left' and 'right' were given for treatment of the skin lesions on the left and right sides of the body, respectively." Comment: no detail
Allocation concealment (selection bias)	Unclear risk	Quote: "assigned to treatment […] according to a randomized, double-blind code. According to this code tubes marked 'left' and 'right' were given for treatment of the skin lesions on the left and right sides of the body, respectively." Comment: no detail

Veien 1984 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "assigned to treatment […] according to a randomized, double-blind code. According to this code tubes marked 'left' and 'right' were given for treatment of the skin lesions on the left and right sides of the body, respectively." Comment: it is likely that participants were adequately blinded, however it is not clear which personnel were blinded and how this was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "assigned to treatment […] according to a randomized, double-blind code." Comment: it is not clear which personnel were blinded and how this was achieved.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient missed the assessment at 2 weeks." Comment: whilst we do not know what was done with the data from this participant, it is only 1 participant out of 40 in a half-sided trial, so unlikely to contribute much of a risk of bias.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol available. Reported outcomes are complete with respect to those stated in the methods.
Other bias	Low risk	Comment: no other sources of bias detected

Vernon 1991

Study characteristics

Methods

Trial design

Blinded, randomised, parallel-group trial

Trial registration number

Not reported

Setting

2 centres

Date trial conducted

Not reported

Duration of trial participation

7 weeks: 6 weeks treatment, followed by assessment 1 week after the end of treatment

Additional design details

At the end of the 3rd week participants whose dermatitis had cleared or shown no improvement were dropped from the trial.

Inclusion criteria

- Children with AD aged between 6 months and 12 years
- Initial BSA involved ≥ 15%
- Target area scoring ≥ 8/15 in severity based on the sum of 5 signs and symptoms: erythema, lichenification, skin surface disruption i.e. crusting and scaling, excoriation, and pruritus, each scored between 0 = none and 3 = severe. The erythema score was required to be ≥ 2

Exclusion criteria

Vernon 1991 *(Continued)*

- Patients receiving systemic steroids within 28 days of enrolment
- Patients using TCSs within 7 days of enrolment

Notes

The participants were randomised by age group and by BSA involvement of ≥ 25%. Only participants with acceptable laboratory values (blood cell count, blood electrolytes, glucose, liver enzymes, triglycerides, cholesterol, plasma cortisol) were entered into the trial. It is unclear whether this inclusion criteria is run-in criteria i.e. whether participants were excluded if they received topical steroids in the last 7 days or whether the they were told not to apply steroids in the 7 days before starting the trial.

Participants	**Total number randomised** 48; 24 randomised to each arm **Age** Overall, 12 participants were aged 7 months to < 2 years, 22 were aged 2-6 years, and 14 were > 6 years to 12 years **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** The baseline mean target area score was 11.3 in the mometasone group and 11.7 in the HC group based on the sum of 5 signs and symptoms: erythema, lichenification, skin surface disruption i.e. crusting and scaling, excoriation, and pruritus, each scored between 0 = none and 3 = severe **Filaggrin mutation status** Not reported **Number of withdrawals** 15 participants in each arm completed the trial early owing to clearing of their dermatitis (median duration 3 weeks). In the HC group 3 participants discontinued because of lack of response, 1 experienced a flare of asthma and commenced systemic steroids, and 1 was lost to follow-up, leaving 4 participants who completed the trial. In the mometasone group 1 participant discontinued after 36 days because of a *Staphylococcus aureus* infection of the scalp, leaving 8 participants who completed the trial. **Notes** None
Interventions	**Run-in details** Antihistamines and emollients stopped 2 days before the start of the trial **Groups** • HC 1% cream (proprietary: Hytone; Dermik Laboratories, inc. Blue Bell, Pa.); TCS applied twice daily in a thin layer on the pre-selected target treatment area as well as on all other involved areas for up to 6 weeks. Concurrent treatment: none

Vernon 1991 *(Continued)*

- Mometasone furoate 0.1% cream (proprietary: Elocon; Schering Corp., Kenilworth, N.J.); TCS applied once daily in a thin layer on the pre-selected target treatment area as well as on all other involved areas for up to 6 weeks. Concurrent treatment: none

Adherence

The amount of medication used each week was weighed and recorded.

Co-interventions

Instructions for application were given by an unblinded investigator. Bathing was not permitted for ≥ 8 h after application, and occlusive dressings were not allowed. The participants' usual bathing routine and soaps were to be continued unchanged throughout the trial, and any food/environmental allergens that the participant had avoided prior to the trial were to be similarly avoided for the duration of the trial.

Notes

All medications were monitored and participants were withdrawn if antibiotics, antihistamines, or other topical emollients or therapies were used.

Outcomes	• Adverse events were reported, including skin atrophy at up to week 7.* • Laboratory tests including complete blood cell count, blood electrolytes, glucose, liver enzymes, triglycerides, cholesterol (no data reported in the paper) at baseline and on the last day of treatment • Morning plasma cortisol levels (8 am-9 am) at baseline, week 1, and on the last day of treatment* • Global evaluations of improvement relative to baseline: numerical score from 1 = cleared (100% clearance of signs and symptoms), 2 = marked improvement (≥ 75% clearance), 3 = moderate improvement (≥ 50% clearance), 4 = slight improvement at (assumed) weekly until week 7 or 1 week after early completion • Percent BSA involvement using an age-appropriate estimate of BSA: 100* (end point-baseline)/baseline at baseline and (assumed) weekly until week 7, or 1 week after early completion • Prespecified target lesion severity score: sum of 5 signs and symptoms: erythema, lichenification, skin surface disruption i.e. crusting and scaling, excoriation, and pruritus, each scored between 0 = none and 3 = severe. Also presented as % improvement at baseline and (assumed) weekly until week 7, or 1 week after early completion* • Parents' evaluation of efficacy of treatment; does not appear to be reported in the paper *denotes relevance to this review
Funding source	Supported by a grant from Schering-Plough Research, Kenilworth, N.J.
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quotes: "The patients were randomized by age group and by body surface area involvement of greater or less than 25%." "Center 2 enrolled two sets of twins, 2-year-old white boys and 9-year-old white girls, who were assigned to different drug groups." Comment: the trial authors have clearly influenced the allocations.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were given tubes of medication and instructions for application by "unblinded" investigator." Comment: it is unclear whether the "unblinded" investigators in this trial were involved in the allocation.

Vernon 1991 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "blinded" "Patients were given tubes of medication and instructions for application by "unblinded" investigator." Comment: the trial is described as blinded however it is unclear whether this refers to participants or the outcome assessors (which were blinded) and so this may refer to this group of people involved in the trial. It is unclear what steps were taken, if any, to maintain blinding in the participants as this is not mentioned (e.g. tubes labelled with A or B). The personnel involved in counselling the participants were not blinded and this may have influenced how they spoke to the participants and hence the outcome of the trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Evaluations were done before giving the test medication and on each weekly follow-up visit by a "blinded" investigator." Comment: the investigator is unlikely to have influenced the outcome of the trial.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "At the end of the third week patients whose dermatitis had cleared or had shown no improvement were dropped from the study" "Data obtained up to the-point of patient withdrawal were included in the analysis" Comment: participants who responded to treatment were excluded from the trial, however these participants may have gone on to relapse or had adverse events at a later date. These participants were grouped with results from participants from 6 weeks so it appears that participants did not develop atrophy when treated up to 6 weeks, however most participants were not treated for 6 weeks. Also, with regards to the cortisol measurements, it is likely that not many were done 8 am-9 am as the last day of treatment for most participants was not at the end of week 6, therefore the investigators would have assessed most participants as cleared at prior weekly visits at which morning plasma cortisol was not routinely being tested.
Selective reporting (reporting bias)	High risk	Comment: no protocol available but some of the outcomes stated in the methods were not reported e.g. parents' evaluation of efficacy of treatment and global evaluations of improvement.
Other bias	Low risk	Comment: no other bias identified

Wilson 2009

Study characteristics	
Methods	**Trial design** Randomised, open label, controlled trial **Trial registration number** NCT00693693 **Setting** Not reported. Author affiliations: Departments of Dermatology, Pathology, and Public Health Sciences, and the Center for Dermatology Research, Wake Forest University School of Medicine, Winston-Salem, North Carolina **Date trial conducted** November 2006-September 2008 (trial registry) **Duration of trial participation**

Wilson 2009 *(Continued)*

	2 weeks **Additional design details** None **Inclusion criteria** • Patients ≥ 18 years of age with mild-moderate AD using IGA criteria (2 or 3 on severity scale). • > 5% to < 30% BSA involvement • Women of child bearing potential using at least 1 form of birth control **Exclusion criteria** • Known allergy or sensitivity to topical Locoid cream, ointment or lipocream • Inability to complete all trial-related visits • Use of other topical or systemic prescription medication for AD during the trial • Requiring > 130 g of cream over 2 weeks • Facial or groin involvement • Pregnant women and women who are breast feeding **Notes** Exclusion criteria all from trial registry
Participants	**Total number randomised** 25 (7 in ointment group, 9 in lipocream group, 9 in cream group) **Age** Range 19-74 years (of the 20 who completed the trial) **Sex** 11 male and 14 female overall; 4 male and 5 female received cream; 3 male and 4 female received ointment; 4 male and 5 female received lipocream **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Overall EASI was 8.30 ± SD 8.38 (of the 20 who completed the trial) **Filaggrin mutation status** Not reported **Number of withdrawals** Total = 5; lost to follow-up: ointment group = 1, lipocream group = 1, cream group = 2; excluded from analysis = 1 **Notes** None
Interventions	**Run-in details**

Wilson 2009 *(Continued)*

Not reported

Groups

- HC 17-butyrate 0.1% cream (proprietary: Locoid, Ferndale Laboratories, Ferndale, MI.); applied twice daily (morning and evening) to all affected areas of AD. Concurrent treatment: not reported
- HC 17-butyrate 0.1% fatty cream (proprietary: Locoid, Ferndale Laboratories, Ferndale, MI.); applied twice daily (morning and evening) to all affected areas of AD for 2 weeks. Concurrent treatment: not reported
- HC 17-butyrate 0.1% ointment (proprietary: Locoid®, Ferndale Laboratories, Ferndale, MI.); applied twice daily (morning and evening) to all affected areas of AD for 2 weeks. Concurrent treatment: not reported

Adherence

This trial had the primary aim of measuring adherence; the manufacturer's original tube was fitted with a Medication Event Monitoring System (MEMS) cap. This cap records dates and times the assembly is opened and this data can be downloaded and tabulated with the associated software. Overall adherence was 70% (SD 0.23) and did not differ between groups (F test; P = 0.39). The trial registry contains results of adherence measures in more detail if required.

Co-interventions

Not reported

Notes

None

Outcomes	• EASI; 0 = clear to 72 = severe) at baseline and week 2* • IGA; 0 = clear to 5 = severe) at baseline and week 2 • Target Lesion Assessments (TLA; 0 = clear to 12 = severe) at baseline and week 2 • Adverse events (assumed as adverse events are reported in the results) at up to week 2* *denotes relevance to this review
Funding source	None stated, however states "supported by Ferndale laboratories" (manufacturers of Locoid TCS).
Declarations of interest	States "none declared". Also states "supported by Ferndale laboratories" (manufacturers of Locoid TCS).
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: no information regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open label" Comment: unlikely that any of the involved parties would have been blinded to the treatments a participant was receiving. The protocol also mentions that the treatment is supplied in the manufacturers original tube.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "investigator blinded"

Wilson 2009 *(Continued)*

All outcomes		Comment: without further detail, particularly as elsewhere the trial is also described as "open label", it is difficult to assess whether this blinding was adequate or not.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "'Twenty subjects 19 to 74 years of age completed the study.'' Comment: only 20 of the 25 participants who enrolled completed the trial (20% data lost).
Selective reporting (reporting bias)	Unclear risk	Comment: there were outcomes reported in the letter that were not reported in the trial registry, however the trial registry focus was on adherence and the same adherence measure was used as the primary outcome. The investigators did not switch primary outcome, but it is unclear if the other analyses were prespecified.
Other bias	Low risk	Comment: no other source of bias was identified.

Wolkerstorfer 1998

Study characteristics	
Methods	**Trial design** Randomised, double-blind, parallel-group **Trial registration number** Not reported **Setting** Not stated but the trial authors were from The Netherlands. **Date trial conducted** Not reported **Duration of trial participation** 7 weeks (1 week run-in period, up to 4 weeks treatment, 2 weeks follow-up) **Additional design details** Treatment was stopped if ObjSCORAD decreased to below 9 (clinically healed), or after 4 weeks. During a 2-week follow-up period, only basic skin care with no anti-inflammatories was permitted. **Inclusion criteria** • Moderately active AD (Hanifin et al, Acta Derm Venereol Suppl (Stockh), 1980, 92:44-7) • Aged 3-8 years • No systemic treatment for AD in the month preceding the trial **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised**

Wolkerstorfer 1998 *(Continued)*

22 were initially randomised. 12 participants received potent TCS once daily (fluticasone propionate), 10 received moderate (clobetasone butyrate)TCS twice daily. 1 participant withdrew because of varicella.

Age

Of the 21 completing the trial, the age in the fluticasone propionate group was 4.9 ± 1.7 years and in the clobetasone butyrate group was 4.1 ± 1.1 years (assume they are mean, SD)

Sex

Fluticasone propionate cream: 4 male, 8 female. Clobetasone butyrate cream: 7 male, 2 female

Race/ethnicity

Not reported

Duration of eczema

Not reported

Severity of eczema

Initial SCORAD (assume they are mean, SD): fluticasone propionate cream: 29 ± 6.2. Clobetasone butyrate cream: 32 ± 5.6

Filaggrin mutation status

Not reported

Number of withdrawals

1 dropped out of clobetasone group because of varicella.

Notes

None

Interventions

Run-in details

1 week washout with only emollient, HC acetate 1%, and antihistamine when required

Groups

- Fluticasone propionate 0.05% cream; vehicle cream was applied in the morning and fluticasone propionate 0.05% cream in the evening until SCORAD was below 9 (clinically healed) or after 4 weeks. Concurrent treatment: not reported
- Clobetasone butyrate 0.05% cream; twice daily application of clobetasone butyrate 0.05% cream in the morning and evening until SCORAD was below 9 (clinically healed) or after 4 weeks. Concurrent treatment: not reported

Adherence

Not reported

Co-interventions

During the trial all children used the same basic skin care (emollient, bath oil)

Notes

None

Outcomes

- Measurement of cortisol excretion in 24 h at baseline, week 4 (end of treatment), then week 6 (end of follow-up)*

Wolkerstorfer 1998 *(Continued)*

- Objective SCORAD (modified consensus of the European Task Force on Atopic Dermatitis) at baseline, then week 1, 2, 3, 4 and 6 (end of follow-up)*
- Occurrence of adverse events (reported in methods but no results given) at baseline, week 1, week 2, week 3, week 4*

*denotes relevance to this review

Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: ."Thereafter, the children were randomized to receive either 0.05% FP [fluticasone propionate] cream once daily or 0.05% CB cream twice daily in a double-blind setting" Comment: no description of randomisation method
Allocation concealment (selection bias)	Unclear risk	Quote: "Thereafter, the children were randomized to receive either 0.05% FP [fluticasone propionate] cream once daily or 0.05% CB cream twice daily in a double-blind setting" Comment: no information provided for how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote:"Thereafter, the children were randomized to receive either 0.05% FP [fluticasone propionate] cream once daily or 0.05% CB cream twice daily in a double-blind setting. To keep the study blinded, patients in the once-daily group received vehicle cream in the morning and FP cream in the evening." Comment: efforts were made to blind the participants; however, we don't know if trial personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Thereafter, the children were randomized to receive either 0.05% FP [fluticasone propionate] cream once daily or 0.05% CB cream twice daily in a double-blind setting. To keep the study blinded, patients in the once-daily group received vehicle cream in the morning and FP [fluticasone propionate] cream in the evening." Comment: efforts were made to blind the participants; however, we don't know if outcome assessment was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twenty-one children completed the study (one dropout in the CB group because of varicella)." Comment: only 1 participant dropped out of the trial.
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol so not clear if they reported on all preplanned outcomes. The methods section says the researchers measured occurrence of adverse events, however only data on cortisol levels are presented. Also, no participant-reported outcomes are mentioned.
Other bias	Low risk	Comment: no other biases identified

Wortzel 1975

Study characteristics

Methods	**Trial design** Randomised, parallel-group, double-blind trial **Trial registration number** Not reported **Setting** Outpatients, multiple centres involving 20 investigators; led by a dermatologist in the USA according to the affiliation. **Date trial conducted** Not reported **Duration of trial participation** 22 days (with 21 day treatment period) **Additional design details** None **Inclusion criteria** • AD and psoriasis patients (data only extracted for AD patients) **Exclusion criteria** Not reported **Notes** None
Participants	**Total number randomised** 128; 62 in the mild (HC) arm and 66 in the potent (betamethasone dipropionate) arm **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported, although these were not hospitalised because of the severity of their condition. **Filaggrin mutation status** Not reported

Wortzel 1975 *(Continued)*

	Number of withdrawals Not reported **Notes** None
Interventions	**Run-in details** Not reported **Groups** • HC 1% ointment (unspecified); applied twice daily for 21 days. Concurrent treatment: not reported • Betamethasone dipropionate 0.05% ointment (proprietary: Diprosone); applied twice daily for 21 days. Concurrent treatment: not reported **Adherence** Not reported **Co-interventions** both groups received same dosages and identical observation schedules. **Notes** None
Outcomes	• Physician's opinion of drug effects at 8 days, 15 days and 22 days (1 week, 2 weeks, 3 weeks) • Overall therapeutic response, assume assessed by the physician: 5-point scale (excellent, good, fair, poor, exacerbation) at day 22 (assumed)* • Adverse events at up to day 22* *denotes relevance to this review
Funding source	None stated, however Diprosone was supplied by Schering Corporation, Bloomsfield, N. J. when it was not generally available.
Declarations of interest	None declared, however Diprosone was supplied by Schering Corporation, Bloomsfield, N. J. when it was not generally available.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Each patients upon entering the study received a sequential admission number. The clinical treatment for each individual was determined by this number, which corresponded to a treatment unit outline on a randomization schedule." Comment: no details given about how the sequence was generated, or the extent to which it might be predicted from the admission number.
Allocation concealment (selection bias)	Unclear risk	Quote: "Each patients upon entering the study received a sequential admission number. The clinical treatment for each individual was determined by this number, which corresponded to a treatment unit outline on a randomization schedule. Both control and drug-treated groups received the same dosages and had identical observation schedules. The ointment - identical in appearance and packaging for both preparations - was applied twice daily."

Wortzel 1975 *(Continued)*

		Comment: no information given about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Both control and drug-treated groups received the same dosages and had identical observation schedules. The ointment - identical in appearance and packaging for both preparations - was applied twice daily." Comment: it is very possible that participants were adequately blinded, however it is not clear which personnel were blinded or how this was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Both control and drug-treated groups received the same dosages and had identical observation schedules. The ointment - identical in appearance and packaging for both preparations - was applied twice daily." Comment: it is not clear which personnel were blinded or how this was achieved.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all 416 participants "initiated" appear to be accounted for in the outcome tables.
Selective reporting (reporting bias)	High risk	Quote: "The Incidence per proportion of subjects with respect to sex, chronicity, recent previous therapy, concomitant medication, overall adverse events at each visit, cures, failures, and symptom-free patients was evaluated using the chi-square statistic with Yates' correction; there were at least 4 responses in each category. Fisher's Exact Probability was used. Analysis of variance procedures was used to evaluate age." "initial severity, results of previous therapy, physician's opinions of drug effects and visits two, three, and 4, and last present visit, and physician's overall evaluation were evaluated using Wilcoxon's two Sample Test". Comment: only the overall therapeutic response is presented in full; other analyses were listed in the methods, but corresponding data were not shown.
Other bias	Low risk	Comment: no other source of bias detected

Yasuda 1976

Study characteristics	
Methods	**Trial design** Double-blind, half-sided, comparative trial **Trial registration number** Not reported **Setting** Multicentre involving 29 medical institutes across Japan (author provides a list of these institutes) **Date trial conducted** Not reported **Duration of trial participation** 7 days **Additional design details**

Yasuda 1976 *(Continued)*

None

Inclusion criteria

- Patients with AD, acute eczematous dermatitis, and psoriasis vulgaris (data only extracted for those with AD)

Exclusion criteria

Not reported

Notes

None

Participants	**Total number randomised** 29 participants were included in the relevant comparison (unclear how many were initially randomised) **Age** Not reported **Sex** Not reported **Race/ethnicity** Not reported **Duration of eczema** Not reported **Severity of eczema** Not reported **Filaggrin mutation status** Not reported **Number of withdrawals** 7 were defined as dropouts as they were deemed unsuitable for analysis; 32 were "not yet evaluated". **Notes** None
Interventions	**Run-in details** Not reported **Groups** • HC acetate 1% ointment (unspecified); applied twice daily to lesions (symmetrical) on the designated side for 7 days. Concurrent treatment: none • HC 17-butyrate 0.1% ointment (proprietary: Locoid); applied twice daily to lesions (symmetrical) on the designated side for 7 days. Concurrent treatment: none **Adherence** Not reported

Yasuda 1976 *(Continued)*

	Co-interventions No other local or systemic medications were permitted if they were thought to affect the lesions. **Notes** Other comparisons were included, but they compared potent to either another potent steroid or placebo. Plastibase (for ointment base) was used for all 3 interventions.
Outcomes	• Adverse events, if detected, were to be described in detail at 1st, 3rd and 7th day (assumed).* • Overall comparison of therapeutic response relative to baseline between groups (considering decreases in erythema, scaling, oedema, and subjective symptoms such as pruritus and burning sensation; rapidity of onset of response, maximum degree of response, and maintenance of response were also considered). The overall evaluation was recorded as remarkably excellent, excellent, good, fair, poor, and worsening (assuming that comparative response is generated from this overall evaluation) at 1st, 3rd and 7th day.* *denotes relevance to this review
Funding source	None stated
Declarations of interest	None declared
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "On entering the study, the patients were assigned a number, and drugs were allotted according to a table of numbers that assured random distribution. Following initial evaluation for diagnosis and clinical severity, patients were assigned drug regimes in a randomized fashion." Comment: reference to a random number table suggests randomisation was adequate.
Allocation concealment (selection bias)	Unclear risk	Quote: "On entering the study, the patients were assigned a number, and drugs were allotted according to a table of numbers that assured random distribution. Following initial evaluation for diagnosis and clinical severity, patients were assigned drug regimes in a randomized fashion." "As the test drugs were packed in coded tubes of identical appearance, neither the investigators nor the patients were aware of the two test tubes contained the active drug or corticosteroid to be tested". Comment: as there were multiple arms (i.e. could be comparing potent steroid to either moderate, mild or non-medicated ointment base), it is not clear who was aware of this randomisation and allocation at this stage, and possible that the person aware of allocation also assigned them to the drug regime.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "As the test drugs were packed in coded tubes of identical appearance, neither the investigators nor the patients were aware which of the two test tubes contained the active drug or corticosteroid to be tested. Paired tubes of ointment clearly labelled with the patient's assigned number, and right and left sides, were applied on lesions in symmetrical positions." Comment: it is probable that participants were blinded, however unclear which personnel were blinded, and how that was achieved.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "As the test drugs were packed in coded tubes of identical appearance, neither the investigators nor the patients were aware which of the two test

Yasuda 1976 *(Continued)*

All outcomes		tubes contained the active drug or corticosteroid to be tested. Paired tubes of ointment clearly labelled with the patient's assigned number, and right and left sides, were applied on lesions in symmetrical positions." Comment: it is unclear which personnel were blinded, and how that was achieved.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Those cases which were proved to be unsuitable for analysis at the end of the study were defined as 'dropouts'" and "12 patients 'dropouts' were excluded." Comment: 7 of the quoted 'dropouts' were AD patients and it was unclear why they were excluded. A further 8 observations were missing at day 7 and no explanation was given. 23 observations were also missing at day 3. It is stated in the methods that participants could withdraw if lesions on both sides disappeared, but also that participants could discontinue for other reasons. Taken with the fact that we don't know how many were randomised to that comparison in the first place means this study has been judged high risk for this domain.
Selective reporting (reporting bias)	High risk	Quote: "A significant difference […] was noted between the test drugs at the end of 3 and 7 days of therapy and after 1 day medication in cases of acute eczematous dermatitis." Comment: no protocol available and it is unclear why observations made at day 1 were not reported for AD participants. The quote above suggests it may have been omitted because it was not statistically significant. Also adverse events were not reported on in the results.
Other bias	Low risk	Comment: no other sources of bias detected

Yawalkar 1991

Study characteristics	
Methods	**Trial design** Double-blind, parallel-group, randomised trial **Trial registration number** Not reported **Setting** 11 dermatologists, multiple centres, in West Germany **Date trial conducted** Not reported **Duration of trial participation** 14 days (12-17 for the day 14 examination) **Additional design details** None **Inclusion criteria** • Patients with AD (non-infected, acute, severe exacerbation)

Yawalkar 1991 *(Continued)*

- Age ≥ 15 years
- Affecting up to 20% of total BSA and suitable for topical therapy

Exclusion criteria

- Age < 15 years
- Pregnancy or breastfeeding
- Secondary microbial infection of lesions
- Concomitant tuberculosis, syphilitic or viral infections
- Diabetes mellitus
- Leukaemia
- Parasitic infestations
- Perioral dermatitis

Notes

None

Participants	**Total number randomised** This paper reports 2 trials, the 1st, which was a comparison of halobetasol propionate with another very potent steroid (not included, therefore not extracted), and the second, which was a comparison of halobetasol propionate with betamethasone dipropionate (included). The paper therefore reports results for a total of 248 participants (264 were originally included) however only results from 117 are relevant to this review. The paper states "The treatment groups were comparable with regard to the number of patients [...]." **Age** Not reported separately for this trial. Range of all 248 evaluated was 15-89 years. "The treatment groups were comparable with regard to […] age […]." **Sex** Not reported separately for this trial. 104 male and 144 female of all 248 evaluated. "The treatment groups were comparable with regard to […] sex […]." **Race/ethnicity** Not reported **Duration of eczema** "The treatment groups were comparable with regard to […] duration of present attack […]." **Severity of eczema** "The treatment groups were comparable with regard to […] severity and extent of the disease." **Filaggrin mutation status** Not reported **Number of withdrawals** 16 participants were excluded for protocol violations or non-compliance with the planned treatment schedule (unclear how many of these were from the included comparison). **Notes** "The treatment groups were comparable with regard to the number of participants, age, sex, duration of present attack, and severity and extent of the disease."

Yawalkar 1991 *(Continued)*

Interventions	**Run-in details** Not reported **Groups** • Betamethasone dipropionate 0.05% cream (unspecified); "two nonoccluded applications per day were permitted" for 14 days. Concurrent treatment: not reported • Halobetasol propionate 0.05% cream (proprietary: Ultravate); "two nonoccluded applications per day were permitted" for 14 days. Concurrent treatment: not reported **Adherence** Not reported, but assumed to be measured in some way as it is reported that 16 participants (across both trials reported in the paper) were excluded because of "protocol violations or noncompliance- with the treatment schedule". **Co-interventions** Not reported **Notes** None
Outcomes	• Disease severity (4-point scale) at weeks 1 and 2; day 14 visit could be 12-17 days • Adverse events at weeks 1 and 2 (assumed); day 14 visit could be 12-17 days* • Participant-reported cosmetic acceptability and ease of application at weeks 1 and 2 (assumed); day 14 visit could be 12-17 days • IGA of therapeutic effect (4-point scale: 1 = healed, 2 = marked improvement, 3 = moderate improvement, 4 = slight/no improvement) at week 2; day 14 visit could be 12-17 days* • Onset of therapeutic action indicated by 1st sign of improvement at day 3. *denotes relevance to this review
Funding source	Supported by an educational grant from Westwood-Squibb Pharmaceuticals, a Bristol-Myers Squibb company.
Declarations of interest	None declared in addition to the above, but 2 employees from Ciba-Geigy Limited (now Novartis) are acknowledged for their roles in organising the trial and commenting on the manuscript.
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "treatment allocations were in accordance with predetermined randomization lists. […] The medication packs had consecutive numbers. To ensure randomized allocation of the treatment, each patient was given the medication from the pack with the lowest available number." Comment: no information given about sequence generation or the extent to which it could be predicted
Allocation concealment (selection bias)	Low risk	Quote: "The medication packs had consecutive numbers. To ensure randomised allocation of the treatment, each patient was given the medication from the pack with the lowest available number."

Yawalkar 1991 *(Continued)*

		Comment: method put in place to ensure person recruiting participants cannot change allocation of participants
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind"; "trial medications were identical in appearance and were supplied in identical tubes" Comment: it is likely that the participants were blinded, however there is no information about which personnel were blinded or how blinding was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind"; "trial medications were identical in appearance and were supplied in identical tubes" Comment: there is no information about which personnel were blinded or how blinding was achieved.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "After excluding 16 patients because of protocol violations or non-compliance with the treatment schedule stated in the trial plan, the evaluable trial population consisted of 248 patients." Comment: it is not clear which trial/group the excluded participants were from, however 16/264 is a small proportion and may not cause significant bias. Not an ITT analysis.
Selective reporting (reporting bias)	High risk	Quote: "The follow-up vitis were scheduled for days 7 and 14, and disease severity was rated with a 4-point scale." Comment: whilst visits were held at day 7 and day 14, the onset of therapeutic response data were reported at day 3, and the success rates were reported at day 11. There is no explanation for this discrepancy. Also, no data on disease severity were reported although it was included in the stated outcomes.
Other bias	Low risk	Comment: no other source of bias detected

ACTH: adrenocorticotropic hormone; **AD:** atopic dermatitis; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **BSA:** body surface area; **CDLQI:** Children's Dermatology Life Quality Index; **CI:** confidence interval; **DFI:** Dermatitis Family Impact; **DLQI:** Dermatology Life Quality Index; **EASI:** Eczema Area and Severity Index; **FAPG:** fatty alcohol propylene glycol; **HC:** hydrocortisone; **HPA:** hypothalamic pituitary axis; **HDM:** house dust mite; **IDQOL:** Infants Dermatology Quality of Life Index; **IGA:** Investigator Global Assessment; I**gE:** immunoglobulin E; **IQR:** interquartile range; **ITT:** intention-to-treat; **IV:** intravenous; **NA:** not applicable; **O/W:** oil in water; **PGA:** Patient Global Assessment; **POEM:** Patient Oriented Eczema Measure; **PSGA:** Physician Static Global Assessment; **PUVA:** psoralen + ultraviolet light A **QPCAD:** quality of life in primary caregivers of children with AD; **RCT:** randomised controlled trial; **SCORAD:** SCORing Atopic Dermatitis; **SASSAD:** Six Area, Six Sign Atopic Dermatitis severity score; **SD:** standard deviation; **SE:** standard error; **SPGA:** Physician Global Assessment of Psoriasis scale; **TAA:** Target Area Assessment; **TARC:** thymus and activation-regulated chemokine; **TCI:** topical calcineurin inhibitors; **TCS:** topical corticosteroid; **TEWL:** transepidermal water loss; **TIS:** Three-Item Severity score; **TSS:** Total Sign Score; **UVB:** ultraviolet light B; **VAS:** visual analogue scale; **WWT:** wet wrap therapy

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abrahams 1975	Ineligible comparator
ACTRN12618000864224	Ineligible comparator
Aerce 1972	Ineligible comparator
Aertgeerts 1973	Ineligible intervention
Afzelius 1979	Same potency TCS

Study	Reason for exclusion
Ahumada Padilla 1982	Ineligible intervention
Albrecht 1994	Eczema data not presented separately
Alexander 1973	Same potency TCS
Almeyda 1974	Ineligible intervention
Alonso 1999	Eczema data not presented separately
Amerio 1975	Eczema data not presented separately
Anonymous 1969	Eczema data not presented separately
Anonymous 1976	Eczema data not presented separately
Anonymous 1979	Ineligible intervention
Anonymous 1981a	Eczema data not presented separately
Anonymous 1981b	Same potency TCS
Anonymous 1981c	Eczema data not presented separately
Anonymous 1991a	Eczema data not presented separately
Anonymous 1991b	Eczema data not presented separately
Anonymous 2004	Ineligible comparator
Anonymous 2017	Ineligible comparator
Anonymous 2018	Ineligible intervention
Ashton 1987	Eczema data not presented separately
Ashurst 1970	Same potency TCS
Ashurst 1972	Ineligible comparator
Atherton 1984	Ineligible comparator
August 1985	Same potency TCS
Aussems 1972	Ineligible intervention
Aussems 1974	Eczema data not presented separately
Bagatell 1974	Same potency TCS
Baran 1971	Eczema data not presented separately
Barsky 1976	Eczema data not presented separately
Beck 1981	Eczema data not presented separately

Study	Reason for exclusion
Belliboni 1973	Eczema data not presented separately
Bergoend 1982	Eczema data not presented separately
Berti 1977	Eczema data not presented separately
Bhutani 1980	Ineligible comparator
Bickers 1984	Does not meet criteria for adequate diagnosis of atopic dermatitis.
Binder 1972	Same potency TCS
Binder 1977	Ineligible comparator
Binet 1979	Eczema data not presented separately
Bjornberg 1975	Eczema data not presented separately
Bleeker 1989	Eczema data not presented separately
Bluefarb 1972	Eczema data not presented separately
Blum 1984	Same potency TCS
Borelli 1973	Eczema data not presented separately
Breneman 2006	Ineligible comparator
Brock 1967	Ineligible comparator
Brunner 1991	Eczema data not presented separately
Buckley 1964	Same potency TCS
Bureau 1963	Ineligible intervention
Bystron 2005	Ineligible intervention
Camacho 1996	Same potency TCS
Camarasa 1975	Eczema data not presented separately
Carbonaro 1986	Eczema data not presented separately
Carbone 1970	Same potency TCS
Cardona 2020	Ineligible intervention
Carvajal 1976	Eczema data not presented separately
Castro 1977	Eczema data not presented separately
Celleno 1991	Eczema data not presented separately
Chapman 1979	Ineligible comparator

Study	Reason for exclusion
Charney 1975	Ineligible comparator
Chiarenza 1982	Ineligible comparator
ChiCTR-IOR-15007140	Ineligible intervention
ChiCTR-TRC-12002591	Ineligible comparator
ChiCTR-TRC-13003551	Ineligible comparator
ChiCTR-TRC-14004331	Ineligible intervention
Christiansen 1977	Eczema data not presented separately
Cullen 1973	Ineligible comparator
Cunliffe 1974	Same potency TCS
Danto 1963	Eczema data not presented separately
Da Rocha 1973	Eczema data not presented separately
Delescluse 1996	Eczema data not presented separately
Del Rosso 2007	Ineligible comparator
Desmons 1977	Ineligible comparator
Dobozy 1977	Eczema data not presented separately
Doherty 1979	Same potency TCS
Dohil 2009	Ineligible comparator
Dominguez 1973	Eczema data not presented separately
Dominguez 1990	Eczema data not presented separately
Dotti 1978	Eczema data not presented separately
Draelos 2015	Ineligible intervention
Duke 1983	Same potency TCS
Dumitriu 1973	Eczema data not presented separately
Eichenberger-de-Beer 1972	Ineligible comparator
Eichenberger-de-Beer 1982	Eczema data not presented separately
Eichenfield 2006	Ineligible comparator
Elgart 1978	Same potency TCS
English 1989	Eczema data not presented separately

Study	Reason for exclusion
EUCTR2008-006422-33-ES	Ineligible intervention
EUCTR2009-017407-28-DE	Ineligible comparator
EUCTR2018-001043-31	Ineligible intervention
Fadrhoncova 1976	Eczema data not presented separately
Filgueiras 1977	Ineligible comparator
Fischer 1984	Same potency TCS
Fisher 1979	Same potency TCS
Fontanini 2013	Ineligible intervention
Fowler 2005	Eczema data not presented separately
Fredriksson 1973	Eczema data not presented separately
Fredriksson 1979	Eczema data not presented separately
Fredriksson 1980	Eczema data not presented separately
Fuller 1976	Ineligible comparator
Gada 2009	Ineligible comparator
Garretts 1975	Eczema data not presented separately
Gartner 1984	Eczema data not presented separately
Gayraud 2015	Ineligible intervention
Gelmetti 1978	Same potency TCS
Gelmetti 1994	Same potency TCS
Gharpuray 1980	Eczema data not presented separately
Gip 1982	Same potency TCS
Gip 1983	Eczema data not presented separately
Gip 1987	Eczema data not presented separately
Giungi 1974	Eczema data not presented separately
Gomez 1977	Eczema data not presented separately
Gordon 1999	Ineligible comparator
GP Medical Research Unit 1967	Ineligible comparator
Grater 1967	Eczema data not presented separately

Study	Reason for exclusion
Grejs 1978	Same potency TCS
Groel 1968	Ineligible comparator
Grosshans 2000	Eczema data not presented separately
Guenther 1981	Same potency TCS
Guillet 1989	Eczema data not presented separately
Guillot 1983	Same potency TCS
Haim 1973	Same potency TCS
Handa 1988	Eczema data not presented separately
Haribhakti 1973	Eczema data not presented separately
Harman 1972	Eczema data not presented separately
Helander 1982	Same potency TCS
Hersle 1982	Eczema data not presented separately
Ishibashi 1987	Eczema data not presented separately
Ishibashi 1989a	Eczema data not presented separately
Ishibashi 1989b	Eczema data not presented separately
Ishibashi 1995	Eczema data not presented separately
Jablonska 1979	Eczema data not presented separately
Jaffe 1974	Eczema data not presented separately
Jardim 1981	Eczema data not presented separately
Jegasothy 1985	Eczema data not presented separately
Jorizzo 1997	Ineligible comparator
JPRN-UMIN000005158	Ineligible intervention
JPRN-UMIN000008726	Ineligible intervention
JPRN-UMIN000009864	Ineligible intervention
JPRN-UMIN000010009	Ineligible comparator
JPRN-UMIN000010299	Ineligible study design (pseudorandomised)
JPRN-UMIN000025722	Ineligible intervention
Juhlin 1996	Eczema data not presented separately

Study	Reason for exclusion
Kassis 1982	Same potency TCS
Katsambas 1986	Eczema data not presented separately
Kejda 1984	Eczema data not presented separately
Kimmelman 1975	Same potency TCS
Klaschka 1989	Eczema data not presented separately
Konzelmann 1983	Eczema data not presented separately
Kowarz-Sokolowska 1969	Ineligible intervention
Kuokkanen 1974	Eczema data not presented separately
Laakso 1981	Eczema data not presented separately
Lassus 1979	Eczema data not presented separately
Lassus 1981	Eczema data not presented separately
Lassus 1984	Same potency TCS
Lawless 1978	Eczema data not presented separately
Leeming 1974	Same potency TCS
Leibsohn 1974	Same potency TCS
Lessard 1980	Same potency TCS
Levy 1974	Ineligible comparator
Lewis 1978	Eczema data not presented separately
Liu 2002	Ineligible intervention
Loeffler 1976	Eczema data not presented separately
Lowy 1977	Eczema data not presented separately
Lundell 1974	Same potency TCS
Lundell 1975	Does not meet criteria for adequate diagnosis of atopic dermatitis.
MacDonald 1974	Eczema data not presented separately
Mackey 1974	Eczema data not presented separately
Mackey 1977	Does not meet criteria for adequate diagnosis of AD
Majerus 1986	Same potency TCS
Manusov 1974	Ineligible intervention

Study	Reason for exclusion
Marchetti 1972	Eczema data not presented separately
Marks 1973	Eczema data not presented separately
Mattelaer 1978	Eczema data not presented separately
Mauracher 1983	Eczema data not presented separately
McKenna 2006	Ineligible intervention
Medansky 1972	Ineligible comparator
Medansky 1976	Ineligible comparator
Meenan 1972	Eczema data not presented separately
Melichar 1979	Eczema data not presented separately
Meyer 1975	Eczema data not presented separately
Miura 1978	Ineligible comparator
Moreno 1977	Same potency TCS
Morley 1976	Ineligible comparator
Morresi 1990	Eczema data not presented separately
Mudaliyar 2020	Ineligible comparator
Munro 1977	Same potency TCS
Nagreh 1988	Ineligible comparator
Nakagawa 1998	Ineligible comparator
Natarajan 1974	Same potency TCS
NCT00106496	Ineligible comparator
NCT00119158	Ineligible comparator
NCT00121316	Ineligible intervention
NCT00121381	Ineligible intervention
NCT00130364	Ineligible intervention
NCT00576238	Ineligible comparator
NCT00689832	Ineligible comparator
NCT00690105	Ineligible comparator
NCT00828412	Ineligible comparator

Study	Reason for exclusion
NCT00980135	Ineligible intervention
NCT01020994	Ineligible intervention
NCT01119313	Ineligible comparator
NCT01691209	Ineligible intervention
NCT02732314	Ineligible intervention
NCT03050294	Ineligible intervention
NCT03386032	Ineligible intervention
NCT04194814	Ineligible comparator
NCT04271007	Ineligible intervention
Neering 1972	Does not meet criteria for adequate diagnosis of AD
Neumann 1971	Same potency TCS
Nicholls 1972	Eczema data not presented separately
Nierman 1981	Ineligible comparator
Nilsson 1992	Ineligible comparator
Nolting 1985	Same potency TCS
Nordwall 1974	Eczema data not presented separately
Nurmukhambetov 2020	Ineligible comparator
Pala 1982	Same potency TCS
Palmerio 1977	Eczema data not presented separately
Panja 1988	Eczema data not presented separately
Parish 1976	Eczema data not presented separately
Pelfini 1975	Eczema data not presented separately
Peltonen 1984	Eczema data not presented separately
Pfitzer 1971	Ineligible intervention
Phillips 1967	Eczema data not presented separately
Pilgaard 1978	Eczema data not presented separately
Planitz 1993	Eczema data not presented separately
Polano 1973	Eczema data not presented separately

Study	Reason for exclusion
Puccinelli 1983	Eczema data not presented separately
Rajan 1976	Eczema data not presented separately
Ramelet 1982	Same potency TCS
Rampini 1977	Eczema data not presented separately
Reckers 1976	Eczema data not presented separately
Reckers 1977	Eczema data not presented separately
Reinel 1985	Eczema data not presented separately
Reinhard 1974	Eczema data not presented separately
Reitamo 2002	Ineligible comparator
Rieder 1979	Eczema data not presented separately
Rocha 1976	Eczema data not presented separately
Rodriguez 1977	Same potency TCS
Roessel 1977	Same potency TCS
Ronn 1976	Eczema data not presented separately
Rosenberg 1971	Same potency TCS
Rosenberg 1979	Eczema data not presented separately
Rozzoni 1982	Eczema data not presented separately
Salavec 2004	Ineligible intervention
Sanchez 1978	Eczema data not presented separately
Sarkany 1971	Same potency TCS
Savin 1978	Ineligible comparator
Schachner 1996	Ineligible comparator
Schachner 1998	Ineligible intervention
Scherwitz 1980	Eczema data not presented separately
Schmid 1981	Eczema data not presented separately
Schmidt 1984	Eczema data not presented separately
Schmidt 1987	Eczema data not presented separately
Schmitz 1982a	Ineligible comparator

Study	Reason for exclusion
Schmitz 1982b	Ineligible comparator
Schuppli 1983	Same potency TCS
Schwarz 1982	Eczema data not presented separately
Sefton 1983	Same potency TCS
Sehgal 1991	Same potency TCS
Silverman 1979	Same potency TCS
Simon 1976	Eczema data not presented separately
Singh 1973	Eczema data not presented separately
Smith 1973	Eczema data not presented separately
Smitt 1993	Same potency TCS
Soto 1977	Eczema data not presented separately
Stahle 1965a	Does not meet criteria for adequate diagnosis of AD
Stahle 1965b	Does not meet criteria for adequate diagnosis of AD
Sudilovsky 1975	Same potency TCS
Tamilselvi 2014	Eczema data not presented separately
Texier 1978	Eczema data not presented separately
Thormann 1976a	Same potency TCS
Thormann 1976b	Eczema data not presented separately
Toda 1993	Ineligible intervention
Tollofsrud 1974	Eczema data not presented separately
Torok 2003	Ineligible comparator
Traulsen 1997	Same potency TCS
Turnbull 1975	Same potency TCS
Turnbull 1982	Eczema data not presented separately
Van Leent 1998	Ineligible intervention
Van Leent 1999	Ineligible intervention
Van Zuiden 1978	Same potency TCS
Verfaillie 1973	Ineligible intervention

Study	Reason for exclusion
Viglioglia 1990	Eczema data not presented separately
Viktorinova 1979	Ineligible comparator
Vollum 1979	Same potency TCS
Von Fischer 1984	Same potency TCS
Walsh 1989	Same potency TCS
Wang 1995	Ineligible comparator
Wang 1997	Eczema data not presented separately
Wang 2003	Same potency TCS
Wang 2011	Does not meet criteria for adequate diagnosis of AD
Weikersthal 1999	Eczema data not presented separately
Weitgasser 1973	Eczema data not presented separately
Weitgasser 1975	Eczema data not presented separately
Weitgasser 1985	Eczema data not presented separately
Wendt 1978	Same potency TCS
Wilson 1973	Does not meet criteria for adequate diagnosis of AD
Zaun 1980	Eczema data not presented separately
Zhang 2014	Ineligible intervention
Zuccati 1982	Ineligible comparator

AD: atopic dermatitis; **TCS:** topical corticosteroid

Characteristics of studies awaiting classification *[ordered by study ID]*

Adam 1978

Methods	An open paired-comparison clinical trial; otherwise unclear
Participants	Unclear
Interventions	Desoximetasone vs betamethasone valerate; otherwise unclear
Outcomes	Unclear
Notes	No abstract, full text, or contact information for the trial authors available

Albrecht 1986

Methods	Open, multicentre trial; otherwise unclear
Participants	383 participants with AD amongst other diagnoses; unclear if data on AD will be available separately.
Interventions	• Prednicarbate 0.25% (Dermatop) emulsifiable greasy ointment without water • Prednicarbate 0.25% (Dermatop) ointment • Prednicarbate 0.25% (Dermatop) cream
Outcomes	Unclear
Notes	No full text or contact information for the trial authors available

Arakawa 1990

Methods	Comparative clinical trial; otherwise unclear
Participants	Participants with AD amongst other diagnoses; unclear if data on AD will be available separately.
Interventions	Methaderm cream vs 0.1% diflucortolone valerate universal cream; otherwise unclear
Outcomes	Unclear
Notes	No abstract, full text, or contact information for the trial authors available

Atmanoglu 1989

Methods	Clinical trial; otherwise unclear
Participants	Unclear
Interventions	Diflucortolone valerate; otherwise unclear
Outcomes	Unclear
Notes	No abstract, full text, or contact information for the trial authors available

EUCTR2004-004052-39

Methods	**Trial design** Single-blind, cross-over RCT **Setting** Denmark **Duration of trial** 6 months **Inclusion criteria**

EUCTR2004-004052-39 *(Continued)*

- Children (2-17 years) with AD

Exclusion criteria

- Puberty development: Tanner stage 2-5
- Use of anti-inflammatory treatment of AD 1 week before visit 1 in period 1
- Bronchial asthma or allergic rhinoconjunctivitis requiring treatment with glucocorticoids
- Endocrinological diseases, including growth disorders, or other chronic diseases
- Major surgery within 4 weeks of, or during, the trial
- High fever (> 39.5) lasting > 3 days

Participants	20
Interventions	HC butyrate 0.1% ointment (Locoid) vs tacrolimus 0.1% (Protopic); no further information given therefore could not rule out alternating or proactive use
Outcomes	• Assessment of skin prick test data, bone collagen turnover and an inflammation parameter in urine • Mean lower leg growth rates
Notes	Information extracted from trial protocol, translated using Google Translate where required

EUCTR2007-002182-12-GB

Methods

Trial design

Single-blind, parallel-group, clinical RCT

Setting

UK

Duration of trial participation

6 months

Inclusion criteria

- Patients with mild-moderate AD (Hanifin and Rajka criteria (Hanifin 1980) and Rajka and Langeland grading of 3-7.5).
- IGA score of 2 or 3
- Male and female patients aged 2-65 years
- Sexually active female of childbearing potential must use an acceptable form of contraception

Exclusion criteria

- Severe AD requiring systemic or very-potent topical steroid treatment
- Facial AD
- Acutely infected AD, or areas where the lesions are crusted, weeping, or pustular
- Pregnancy or lactation
- Topical or systemic therapy likely to interfere with the trial within 14 days of the trial
- Participation in another research trial at any time during and within 4 weeks of the trial
- Significant concurrent illness including psoriasis, rosacea, acne vulgaris, peri-oral dermatitis and primary skin lesions caused by infection with fungi or bacteria
- History of skin disease, other than AD, or allergy, likely to interfere with the trial
- Patients unable or unlikely to attend the necessary visits

EUCTR2007-002182-12-GB *(Continued)*

	• Employees or an immediate family member of an employee of Euroderm Research or Stiefel Laboratories • Past medical history of hepatic, renal, cardiac, pulmonary, digestive, haematological, neurological, locomotor, cancer or psychiatric disease, which might affect the outcome of the trial • Known sensitivity to the test product ingredients
Participants	200
Interventions	**Run-in details** Stabilisation with betamethasone-17-valerate 0.122% cream (Betnovate) and emollient **Groups** W0153 vs emollient as maintenance therapy; unclear whether W0153 is a TCS or how it is used
Outcomes	• Time to the next AD flare (days) • IGA (6-point scale) at visits 1 to 6 inclusive • PGA of response (5-point scale) at visits 4, 5 and 6 • Change in SASSAD at weeks 4, 8 and 12 post-clearance compared to baseline
Notes	Information extracted from trial protocol; results not yet published

EUCTR2016-004542-28-NL

Methods	**Trial design** Open-label, pilot RCT **Setting** The Netherlands **Duration of trial participation** 2 years **Inclusion criteria** • Male and female children aged > 27 days to < 16 years • Diagnosis of AD (Hanifin and Rajka (Hanifin 1980)) • Moderate to severe disease (EASI > 7.1) **Exclusion criteria** • Hypersensitivity and/or intolerance to test product ingredients • Requirement for systemic therapy or higher-potency TCSs
Participants	80
Interventions	Clobetasone butyrate 0.05% ointment (Eumovate) and HC acetate 1% ointment vs Pix lihantracis 3% in zinc oxide paste and 10% coal tar cream. It is unclear if there is also a direct comparison between the 2 TCS preparations.
Outcomes	• Percentage change in EASI) at week 2 and 4 • Proportion of participants with EASI-75 at week 2 and 4 • Decrease in VAS score for pruritus • Changes in participant-reported outcome (POEM and Patient PGA)

EUCTR2016-004542-28-NL *(Continued)*

	• Changes in quality of life (CDLQI), changes in family impact (DFI) • Tolerability. • Filaggrin (FLG) genotype • Changes in Natural Moisturizing Factors (NMF) in the stratum corneum • Changes in skin microbiota
Notes	Information extracted from trial protocol; results not yet published

EUCTR2016-004687-19-NL

Methods	**Trial design** Open-label, parallel-group RCT **Setting** The Netherlands **Duration of trial participation** 2 years **Inclusion criteria** • Male and female patients aged > 16 years • Diagnosis of AD (Hanifin and Rajka (Hanifin 1980)) • Moderate-severe disease (EASI > 7.1) **Exclusion criteria** • Hypersensitivity and/or intolerance to test product ingredients • Requirement for systemic therapy or higher-potency TCSs
Participants	56
Interventions	Betamethasone valerate 0.1% ointment (Betnelan) vs HC acetate 1% ointment; also Pix lihantracis in zinc oxide paste and with or without 10% coal tar cream, it is unclear as to the exact strategies used and whether they are relevant to this review.
Outcomes	• Percentage change in (EASI) at week 2 and 4. • Proportion of participants with EASI-75 at week 2 and 4 • Decrease in NRS score for pruritus • Changes in participant-reported outcome (POEM and Patient PGA) • Changes in quality of life (CDLQI) • Tolerability • Filaggrin (FLG) genotype • Changes in Natural Moisturizing Factors (NMF) in the stratum corneum • Changes in skin microbiota
Notes	Information extracted from trial protocol; results not yet published

Gomes 1980

Methods	3-week duration clinical trial; otherwise unclear

Gomes 1980 *(Continued)*

Participants	31 participants with AD amongst other diagnoses; unclear if data on AD will be available separately
Interventions	Halcinonide; otherwise unclear
Outcomes	Unclear
Notes	No abstract, full text, or contact information for the trial authors available

GSK 1995

Methods	**Trial design** Multicentre, parallel-group, clinical, RCT **Trial registration number** GSK Report No. 135L (Protocol GL/FLT/002) **Setting** Hospital settings in the UK **Duration of trial participation** 4 weeks, with up to 3 weeks' run-in period **Inclusion criteria** • Aged 1-65 years (male and female) • Moderate-severity atopic eczema at a chosen target area (severity score ≥ 7) **Exclusion criteria** • Infected eczema requiring antibacterial treatment • Severity of disease that requires hospital admission • Very potent TCS used within 3 weeks of the trial (see run-in details) • Potent TCS used within 1 week of the trial (see run-in details) • Systemic anti-inflammatory treatment within 4 weeks of the trial • Antihistamines used within 3 days of the trial • Concomitated unstable/serious illness • History of adverse reactions to TCS or systemic corticosteroids • Involvement in another clinical trial within a month of the trial • Likely to find keeping regular attendance and records difficult • Pregnancy and lactation • Women of childbearing age not using adequate contraception
Participants	**Total number randomised** 245; 122 into the twice daily group; 123 into the once daily group **Number of withdrawals** 3 participants with unverifiable data were excluded from the analyses. 11 participants enrolled in addition to those randomised, but withdrew during the washout period.
Interventions	**Run-in details**

GSK 1995 *(Continued)*

	Participants who had applied very potent TCS within 3 weeks of the trial, or potent TCS within a week of the trial, entered a washout period of 3 weeks or 1 week, respectively, where they were given Eumovate ointment. **Groups** Fluticasone propionate 0.005% ointment (Cutivate) twice daily compared to once daily in addition to placebo ointment once daily for up to 4 weeks. **Adherence** Returned tubes were weighed. **Co-interventions** Only trial medication and emollients were permitted (no other dermatological medication).
Outcomes	• IGA of response relative to baseline (last visit; up to week 4 or sooner if eczema cleared; 7-point scale from cleared = 100% resolution to much worse = marked exacerbation). • Participant assessment of the target area (7-point scale from totally cleared to greatly worsened) • Signs and symptoms: erythema, pruritus, thickening/lichenification, scaling (scored from 0.0 = absent to 3.0 = severe). Scores were added together to give a total severity score. • Adverse events
Notes	No full text or contact information for the trial authors available. Information extracted from Green 2004.

Haque 2000

Methods	Double-blind randomised trial; otherwise unclear
Participants	45 participants with chronic eczema; otherwise unclear
Interventions	Clobetasol proprionate 0.05% vs clobetasone butyrate 0.05%; otherwise unclear
Outcomes	Unclear
Notes	No full text or contact information for the trial authors available

Jia 1998

Methods	RCT; otherwise unclear
Participants	Participants with eczema and psoriasis; unclear if data on eczema will be available separately
Interventions	0.1% Eloson vs 0.1% triamcinolone cream; otherwise unclear
Outcomes	Unclear
Notes	No abstract, full text, or contact information for the trial authors available

JPRN-UMIN000006955

Methods	**Trial design** Randomised, double-blind, parallel-group trial **Setting** Japan **Inclusion criteria** Participants with AD **Exclusion criteria** • Those discouraged to use tacrolimus or steroid ointment • Intolerance to these ointment • Pregnancy • Judged to exclude by attending physician
Participants	90 male and female participants ≥ 20 years old
Interventions	Proactive use of betamethasone butyrate vs tacrolimus and Vaseline; otherwise unclear
Outcomes	• SCORAD (severity score) • IGA • Safety (comparing between tacrolimus and steroid ointment) • Serum cortisol • Serum TARC • DLQI (quality of life) • Intensity of itch • History of usage of external medicine • Adverse/side effect • Length of remission
Notes	Information extracted from trial protocol

JPRN-UMIN000022212

Methods	**Trial design** Randomised, double-bind, parallel-group clinical trial **Setting** Japan **Duration of trial participation** 4 weeks (2 weeks of treatment; 2 weeks' post-treatment follow-up) **Inclusion criteria** • Participants with AD • Patients with mild or moderate rash on test site (both arms) **Exclusion criteria** • Severe skin disorders on test site (both arms)

JPRN-UMIN000022212 *(Continued)*

	• Complications that affect the results of this trial • Use of any external use medicines, anti-allergy drugs, or immunosuppressants • Pregnant or lactating patients • Patients deemed inappropriate to participate in this trial by the principal investigator or subinvestigators
Participants	36 male and female participants aged 16-49 years
Interventions	PVA-N11 (TCS) vs active comparator (mechanism not specified), applied twice daily for 2 weeks
Outcomes	• Severity classification (Japanese Dermatological Association) at test site (both arms) at weeks 0 and 2 • Transepidermal water loss, water content of the stratum corneum, erythema and pigmentation, and skin surface topography at test site (both arms) at weeks 0, 1, and 2 • Quality of life assessment at weeks 0, 1, 2, and 4
Notes	Information extracted from trial protocol; results not yet published

Kamimura 1976

Methods	3-week, double-blind, half-sided, multicentre clinical trial in Japan. Multiple arms; only those comparing TCS strategies are relevant to this review, i.e. vehicle controls are not considered here. It is not clear if, or how, randomisation was done.
Participants	69 participants with AD amongst other diagnoses; unclear if the AD data can be separated
Interventions	• Clobetasol propionate cream • Betamethasone valerate cream • Clobetasol propionate ointment • Betamethasone valerate ointment
Outcomes	• Skin findings, general improvement rating, and drug preference were recorded at 3 ± 1 days, 7 ± 2 days, 14 ± 3 days and 21 ± 3 days • In the cases where the lesions on both sides disappeared within the period of 3 weeks of topical treatment the relapse time was observed. • Adverse effects recorded at each visit. • Overall evaluations were made on the last day, including a general improvement rating, drug preference, relapse time, adverse effects; and comparison of global utility.
Notes	No full text or contact information for the trial authors available. Information extracted from the English abstract

Kaminsky 1962

Methods	Therapeutic trial; otherwise unclear
Participants	Unclear
Interventions	6-alpha-fluor-dexamethasone trimethylacetate ester; otherwise unclear
Outcomes	Unclear

Kaminsky 1962 *(Continued)*

Notes	No abstract, full text, or contact information for the trial authors available

Kukita 1981

Methods	Double-blind, multicentre, within-participant clinical trial conducted in Japan; otherwise unclear
Participants	508 participants were included in this trial, however some were psoriasis vulgaris, in addition to lichenified eczematous dermatitis and oozing eczematous dermatitis. It is not clear to what extent results are presented separately.
Interventions	Prednisolone valerate acetate (PVA) 0.3% cream vs HC butyrate; applied 2-3 times daily
Outcomes	Comparisons of drug efficacy, degree of improvement, improvement of itching, erythema and crusting, and adverse reactions were recorded. At end of treatment, evaluations and comparisons of clinical utility were done.
Notes	No full text or contact information for the trial authors available. Extracted from English translation of the abstract.

Miura 1977

Methods	Double-blind, multicentre, within-participant clinical trial conducted in Japan; otherwise unclear
Participants	There were 37 cases of AD alongside other diagnoses; it is not clear to what extent the data on AD would be separable.
Interventions	A number of comparisons were made, including against vehicle controls. The likely comparisons of interest are between the following. • Fluocortolone 0.25% ointment • Betamethasone valerate 0.12% ointment • Fluocortolone 0.25% ointment • Betamethasone valerate 0.12% ointment Simple application was 2-3 times daily.
Outcomes	• Each skin finding graded (4: severe, 3: moderate. 2: mild, 1: slight. 0: none) on each evaluation day • General improvement rate (++++: cure, +++: marked, ++: moderate, +: slight, O: no change, x: exacerbation) on each evaluation day • Drug preference between sides (>>, <<: big difference in efficacy, >, <: small difference in efficacy, = : no difference in efficacy) on each evaluation day • Time to recurrence up to 2 months post-treatment • Adverse reactions (+++: severe, + +: moderate, +: slight, -: none) on each evaluation day • Evaluation of clinical utility (very useful, useful, rather useful, not useful, rather harmful, harmful) at end of treatment, taking into account observations on all outcomes from all time points • Contralateral comparison of clinical utility (>>, <<: big difference, >, <: small difference, = : no difference) at end of treatment, taking into account observations on all outcomes from all time points
Notes	No full text or contact information for the trial authors available

NCT01826461

Methods	**Trial design** Randomised, parallel-group, double-blind, multicentre trial **Setting** USA **Duration of trial participation** 29 days **Inclusion criteria** • Clinical diagnosis of stable mild-moderate AD • Patient has used the same type of soap, moisturisers, lotions, creams, ointments, sunscreens or other skin products, and hair products (shampoo, etc.) for at least 2 weeks prior to trial start and agrees to continue usage with the same products and with similar frequency for the entire trial **Exclusion criteria** • Patient is pregnant, lactating or is planning to become pregnant during the trial • Patient requires any topical or systemic medications or is using topical inflammatory dermatoses therapies that could affect the course of their AD during the trial period • Patient has used systemic corticosteroids, immunomodulators including leukotriene inhibitors, or antimetabolites within 30 days prior to trial • Patient has used UV phototherapy within 30 days prior to trial • Patient has used topical therapies for the treatment of (or may affect) their AD including but not limited to corticosteroids, immunomodulators, tar, calcipotriene or other vitamin D preparations, retinoids, antihistamines, antibiotics, among others, within 14 days prior to trial • Patient desires excessive or prolonged exposure to ultraviolet light during the trial • Patient has used systemic antibiotic therapy within 7 days prior to trial • Patient is currently enrolled in another trial • Patient has used an investigational drug or investigational device treatment within 30 days prior to trial
Participants	151 participants; male and female aged 3 months-17 years
Interventions	PDI-192 0.1% vs 0.15% topical foam twice daily; unclear whether PDI-192 is a TCS
Outcomes	• Success rate, based on IGA; a measure of overall severity of AD using a 5-point scale from 0 (clear) to 4 (severe). Success defined as the percentage of participants who achieve "clear" (score = 0) or "almost clear" (score = 1) and at least a 2-grade improvement from baseline at day 29. • Change from baseline in the severity of pruritus at day 29, based on a periodic subject assessment using a 4-point scale from 0 (none) to 3 (severe) • Percent change from baseline in EASI scores at day 29 • Percent change from baseline in BSA affected by disease at days 8, 15 and 29 • Change from baseline in severity of erythema, induration/papulation, excoriation, lichenification and oozing/crusting at days 8, 15, and 29; each evaluated on a 4-point scale from 0 (none) to 3 (severe) • Change from baseline in the severity of pruritus at days 8 and 15; participant assessment using a 4-point scale from 0 (none) to 3 (severe) • PGA of improvement in AD at day 29, based on a 5-point scale from 1 (excellent improvement) to 5 (worse)
Notes	Information extracted from trial protocol; results not yet published

NCT02153762

Methods	**Trial design** Randomised, open label, within-participant, cross-over trial **Duration of trial participation** 29 days **Inclusion criteria** • Aged at least 3 months • Clinical diagnosis of stable mild-moderate AD (Hanifin and Rajka criteria (Hanifin 1980)). • Bilateral AD lesions of similar size, severity, and location • SPGA 2 or 3 and ≥ 10% BSA involvement • In good health; no disease process(es) presenting safety concerns or confounding factors • Willing to discontinue all systemic corticosteroids, immunomodulators, ultraviolet light therapy or other medication that may affect AD for 30 days prior to baseline • On a stable maintenance therapy (at least 30 days of use prior to baseline) of antihistamines and/or nasal spray containing corticosteroids for bronchial asthma or allergic rhinitis, or antibiotics for the treatment of acne. • Willing to discontinue use of topical treatments for AD including, but not limited to, corticosteroids, immunomodulators, vitamin D treatments, retinoids, topical antihistamines for at least 14 days prior to baseline • Willing to discontinue use of oral antibiotic therapy for at least 7 days prior to baseline, unless for acne as previously described • No known allergy to trial product ingredients • Women of childbearing potential must be willing to use an approved form of birth control **Exclusion criteria** • Immunocompromised patients, or those with extensive disease that cannot be controlled with topical therapy • History or evidence of other conditions that would interfere with the evaluation of the trial medication • Patients desiring excessive or prolonged exposure to ultraviolet light during the trial • Use of topical medications for AD or any other medical condition • Patients currently involved in another clinical research trial • Patients, who are pregnant, breast feeding or planning a pregnancy • Patients with clinically significant unstable medical or mental disorders • Patients who are unwilling or unable to comply with the requirements of the protocol
Participants	41 participants
Interventions	HC butyrate 0.1% lipocream (Locoid) followed by a topical skin barrier repair therapy (Hylatopic Plus lotion) vs topical skin barrier repair therapy followed by HC butyrate 0.1% lipocream
Outcomes	• Change from baseline treatment success at day 29, defined as clear or almost clear (0 or 1) on the SPGA scale based on severity of induration, scaling, and erythema • 2-point reduction of SPGA at day 29 as compared to baseline • Change from baseline pruritus at day 29
Notes	Information extracted from trial protocol; results not yet published

Odeh 1977

Methods	Clinical trials; otherwise unclear
Participants	Unclear
Interventions	Clobetasol propionate and betamethasone dipropionate; otherwise unclear
Outcomes	Unclear
Notes	No abstract, full text, or contact information for the trial authors available

Salo 1976

Methods	Double-blind comparison; otherwise unclear
Participants	Eczema; otherwise unclear
Interventions	TCSs; otherwise unclear
Outcomes	Unclear
Notes	No abstract, full text, or contact information for the trial authors available

Yasuda 1974

Methods	**Trial design** Multicentre, double-blind, within-participant comparison; it does not explicitly state it is randomised **Setting** Japan **Duration of trial participation** 2 weeks (assumed given outcomes described) **Inclusion criteria** Participants with symmetrical lesions of AD, amongst other dermatoses; it is not clear if the data will be presented separately for the AD participants.
Participants	268 cases in total; unclear how many of these are AD patients
Interventions	Betamethasone dipropionate 0.064% vs betamethasone valerate 0.12%; whilst these are both potent TCS, we cannot rule out that the strategies also compare TCS with and without occlusion.
Outcomes	Examinations at day 3, week 1 and week 2; otherwise unclear. Type and degree of response (or lack of response) to treatment. Side effects also noted. It is unclear if these data can be separated for participants with AD only.
Notes	No full text or contact information for the trial authors available. Data extracted from English Language abstract

AD: atopic dermatitis; **BSA:** body surface area; **CDLQI:** Children's Dermatology Life Quality Index; **DFI:** Dermatitis Family Impact; **DLQI:** Dermatology Life Quality Index; **EASI:** Eczema Area and Severity Index; **IGA:** Investigator Global Assessment; **NRS:** numerical rating scale; **PGA:** patient global assessment; **POEM:** Patient Oriented Eczema Measure; **RCT:** randomised controlled trial; **SASSAD:** Six Area, Six Sign Atopic Dermatitis severity score; **SCORAD:** SCORing Atopic Dermatitis; **SPGA:** Physician Global Assessment of Psoriasis scale; **TARC:** thymus and activation-regulated chemokine; **TCS:** topical corticosteroid; **VAS:** visual analogue scale

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2005-003806-27-GB

Study name	Is potent topical corticosteroid ointment covered by a plastic film dressing more effective than using potent corticosteroid ointment alone in children with atopic dermatitis?
Methods	**Trial design** Single-blinded, within-participant, phase IV, clinical RCT **Setting** UK; otherwise unclear **Duration of trial participation** 8 days (possibly with follow-up to 6 months; unclear from trial protocol) **Inclusion criteria** • Children aged 1-15 years with AD • Small active patches requiring treatment with TCSs on both sides of the body **Exclusion criteria** • Dermatitis covering an area larger than the occlusive dressing. • Known sensitivities to the trial treatments • Evidence of infected or bleeding AD, or AD is confined to the face or nappy (diaper) area • Children who had received oral steroid treatment, applied topical steroids to the trial area or used alternative remedies
Participants	Not reported
Interventions	Elocon ointment (Schering-Plough) with or without occlusive dressing for 3 days Families will be asked about compliance with instructions.
Outcomes	• 3-item severity score (TIS; evaluation of erythema, oedema/papulation and excoriation each scored 0 = absent to 3 = severe) at baseline and subsequent visits • Maximum width and length of lesion will be recorded at each visit • Parents will be asked to record any side effects and inform investigators after the final assessment • Lesions on both sides will be photographed with a scale marker. Reviews will take place on day 4 and day 8, after which participants will then be seen at routine outpatient appointments.
Starting date	Not reported
Contact information	Not reported
Notes	

JPRN-UMIN000028043

Study name	Prevention of Allergy via Cutaneous Intervention (PACI) study
Methods	**Trial design** Multicentre, investigator-blinded, parallel-group RCT **Setting** Japan **Inclusion criteria** Infants (7-13 weeks old) who develop an itchy rash within the previous 28 days and are diagnosed with AD (UK Working Party) **Exclusion criteria** • Infants born before 37 weeks of gestation • Twin or multiple births • History of side effects (heparinoid cream; Hirudoid soft ointment) and/or TCSs (alclometasone dipropionate; almeta, betamethasone valerate, Rinderon-V and/or mometasone furoate Fu-lumeta). • History of taking oral and/or IV steroids within the previous 28 days • History of taking immunosuppressive agents (ciclosporin, tacrolimus, etc) and/or biologics except immunisations and/or IV immunoglobulin within the previous 28 days • IgE-mediated hen egg allergy • Infants whose family plans to move and who may not be able to visit the trial site before 28 weeks of age • Parents unable to understand Japanese • Unwillingness or inability to comply with the trial requirements and procedures • Infants with severe congenital disease and/or a disease that affects dermatological evaluation
Participants	650 enrolled
Interventions	Early aggressive treatment with topical anti-inflammatory drug vs standard treatment (Guidelines for the Management of Atopic Dermatitis 2016)
Outcomes	• Number of participants with proven IgE-mediated hen egg allergy at 28 weeks of age • Symptom score of food challenge test at 28 weeks of age • Total IgE antibody serum titre at 28 weeks of age • Egg white, ovomucoid, milk, wheat, soy, peanut and Ara h2-specific IgE antibody serum titre at 28 weeks of age • Egg white, ovomucoid, milk, wheat, soy, peanut and Ara h2-specific IgG4 antibody serum titre at 28 weeks of age • EASI scores at 2, 4, and 8 weeks after trial entry and at 28 weeks of age • POEM scores during the trial period • Proportion of disease-free days during the trial period • Dose of rescue medication used during the trial period • IDQoL at 28 weeks of age • DFI at 28 weeks of age • Presence of IgE-mediated food allergy reaction during the trial • Presence of wheezing during the trial period
Starting date	18 July 2017; stated to be completed
Contact information	Yukihiro Ohya (ohya-y@ncchd.go.jp)

JPRN-UMIN000028043 *(Continued)*

Notes	

JPRN-UMIN000031979

Study name	Anticipate
Methods	**Trial design** Interventional clinical trial assumed to be randomised. **Setting** Japan; outpatient **Inclusion criteria** • Japanese patients diagnosed with AD (criteria of Japanese Dermatological Association) • Aged 6 to ≥15 years inclusive • Able to be treated on an outpatient basis • IGA ≥ 3 or more • Patients who have used a strong or very strong topical steroid **Exclusion criteria** • Skin infections caused by bacteria, fungi, spirochetes or viruses and patients with ectoparasitic skin diseases (scabies, pubic lice, etc.) • History of hypersensitivity to any components of the trial medications • Patients with ulcers (except for Bechet's disease) or deep burns or frostbite of second degree or higher • Active infection in the area the trial drug is to be applied • Kaposi's varicelliform eruption, scabies, molluscum contagious, psoriasis, disorders (Netherton syndrome, etc.) presenting with ichthyosiform erythroderma, collagen disease (systemic lupus erythematosus and dermatomyositis), and skin disorder on the area trial drug is to be applied to • Using the following drugs within 28 days prior to the trial: systemic adrenocortical steroid (oral, injectable, suppository, and inhaled); topical steroid (strongest); systemic immunosuppressant; live vaccine • Use of phototherapy (UVB, Narrow-band UVB, PUVA, etc.) within 28 days of the trial • Patients who participated in another clinical trial within 12 weeks of the trial • Patients determined by the investigator to be unsuitable.
Participants	Target sample size: 90
Interventions	**Group 1 (assumed from abbreviations in protocol)** Remission-induction: betamethasone butyrate propionate ointment once daily for 1-2 weeks. Intermittent treatment will be performed on trial area while maintaining remission. Even after resolution of rash, treatment will be given to the area rash was present. Phase I: betamethasone butyrate propionate ointment once daily for 1 week Phase II: betamethasone butyrate propionate ointment twice weekly for 3 weeks **Group 2 (assumed from abbreviations in protocol)** Remission-induction: betamethasone butyrate propionate ointment once daily 1-2 weeks. Dose tapering will be performed on trial area while maintaining remission. Treatment will be given to the area where rash is present.

JPRN-UMIN000031979 *(Continued)*

	Phase I: betamethasone valerate ointment once daily for 1 week Phase II: hydrocortisone butyrate (ointment once daily for 3 weeks **General** Moisturiser once daily throughout. Moisturiser should be heparinoid or petrolatum
Outcomes	• Incidence of relapse during remission-maintenance treatment • Duration of remission (number of days) prior to relapse • IGA score • Modified SCORAD score • Subjective symptom score (NRS) • Total serum IgE • Peripheral blood eosinophilia, serum LDH, serum TARC
Starting date	1st enrolment 5 November 2019, however protocol states not currently recruiting
Contact information	Mamitaro Ohtsuki (mamitaro@jichi.ac.jp)
Notes	

NCT03742414

Study name	Stopping Eczema and Allergy Study (SEAL)
Methods	**Trial design** Parallel-group, open-label, phase II RCT **Setting** USA **Duration of trial participation** 3 years **Inclusion criteria** • Early onset visible dry skin or AD ≤ 10 weeks of age • In good general health evidenced by medical history • No known adverse reaction to any of the trial medications, their components or excipients **Exclusion criteria** • Infants < 3 kg in weight • Infants with a chronic disease requiring therapy (e.g. heart disease, diabetes, serious neurological defects, immunodeficiency) • Known moderate-severe cutaneous skin disorder other than AD (e.g. cutaneous mastocytosis, bullous skin disease, pustular skin disease, neonatal herpes simplex virus, aplasia, and albinism) • Current participant or participation since birth in any interventional trial • Investigator or designee considers that the participant or parent/guardian would be unsuitable for inclusion in the trial • A course of antibiotics in infant within 7 days of enrolment
Participants	Target is to recruit 875 infants

NCT03742414 *(Continued)*

Interventions	Twice daily use of a tri-lipid skin barrier cream (Epiceram) or moisturiser and proactive use of fluticasone propionate 0.05% cream vs reactive therapy (standard care)
Outcomes	• The per-participant cumulative number of challenge-proven food allergy (1 year) • The per-participant cumulative number of challenge-proven food allergy (3 years) • Change from baseline SCORAD at 1, 2, and 3 years • Incidence of IgE and IgG4 to all specified foods and respiratory allergens (baseline and 1, 2, and 3 years • Skin prick testing to all specified foods (baseline and 1, 2, and 3 years • Skin prick testing for inhalant allergens (3 years) • Measure of environmental exposure of peanut and egg in dust (baseline and 1 year • Proportion of participants that follow current NIAID guidelines for the introduction of peanut (determined by food frequency questionnaires; 3 years) • Proportion of participants consuming allergenic foods other than peanut (determined by food frequency questionnaires; 3 years) • Occurrence and duration in months of breastfeeding and formula use (baseline, 6 months, 1 year) • Type of formula given (casein, whey, partial hydrolysate, extensive hydrolysate, amino acid/elemental, soya) at baseline, 6 months, and 1 year • Measure of epithelial function via TEWL (3 years; g/(m^2/h) • Maternal dietary consumption during pregnancy (baseline)
Starting date	Not yet recruiting
Contact information	Kari Christine Nadeau (snpcenterallergy_inquiry@stanford.edu)
Notes	

NCT04615962

Study name	Topical cream SNG100 for treatment in moderate atopic dermatitis subjects
Methods	**Trial design** Randomised, multicentre, double-blind, within-participant, phase I trial **Setting** Not reported; company based in Israel **Duration of trial participation** 14 days **Inclusion criteria** • Child age 6-18 with a diagnosis of moderate AD confirmed by a dermatologist, together with the child's parent/guardian • Capable of complying with trial requirements and trial procedure • IGA of 3 • SCORAD 26-50 and EASI 7.1-21 • Child-bearing potential women using approved contraception **Exclusion criteria** • A medical history that may interfere with trial objectives • AD lesions only on the face and scalp

NCT04615962 *(Continued)*

	• Secondary infection with bacteria, fungi, or virus • Recent or current participation in another research trial • Pregnancy and lactation • Prior wound, tattoo, pigmentation or infection in the treated area
Participants	Target enrolment: 66
Interventions	HC acetate 1% cream; mometasone furoate; SNG100; full publication is necessary to determine whether this trial is comparing included strategies of interest to this review.
Outcomes	• Safety and tolerability as measured by completion of a full prescribed treatment course, treatment interruptions, serious adverse events and adverse events (4 weeks) • Within-participant difference in response to topical product usability questionnaire items between trial treatments (4 weeks) • Change from baseline in the SCORAD index (4 weeks) • EASI Score (4 weeks) • Itch NRS. 11-point scale ranging from 0 (no itch) to 10 (worst itch imaginable); 4 weeks • IGA: static, numeric 5-point scale from 0 (clear skin) to 4 (severe disease); 4 weeks. Based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification
Starting date	January 2021
Contact information	Arik Tzour (arik@miiscience.com) and Inbal Ziv (Inbal@miiscience.com)
Notes	

Van Halewijn 2018

Study name	The Rotterdam eczema study
Methods	**Trial design** Prospective cohort trial with an embedded open-label parallel-group RCT **Setting** Primary care in The Netherlands **Duration of trial participation** 24 weeks **Inclusion criteria** • Diagnosis of AD (ICPC-code S87/S88 or prescription of topical treatment of eczema) with confirmation by the GP) • Aged between 12 weeks and 18 years • A patient that has visited the GP for AD or received repeated prescription for AD in previous 12 months • A flare-up (i.e. need to intensify topical treatment) from patients' and/or parents'-point of view • TIS-score ≥ 3 and < 6 **Exclusion criteria** • As determined by the GP (e.g. family problems) • Currently under treatment of a dermatologist

Van Halewijn 2018 *(Continued)*

	• Language barrier • No access to internet (necessary to fill in weekly online questionnaire) • Previous side effects with any of the medications • Hypersensitivity to corticosteroids • Use of TCS within 2 weeks of the trial • > 50% of body affected • Other skin disorders hampering assessment of eczema • Pregnancy or lactation • Untreated skin infections caused by a bacterium, virus, fungal, or parasite • Incurable wounds or ulcerative skin disorders • Ichthyoses, acne vulgaris, rosacea, juvenile plantar dermatosis, skin atrophy, skin lesions • Nappy (diaper) rash • Perianal and genital itching • AD on eyelid(s)
Participants	Target size 150
Interventions	Intervention group will start with fluticasone propionate cream 0.05% or ointment 0.005% at a flare-up of the AD. Control group will receive treatment according to the Dutch GP-guideline (start with HC 1% cream). If not improved with mild TCS within 1–2 weeks, triamcinolone acetonide 0.1% cream once daily will be prescribed. If in turn there is no improvement within 1–2 weeks, fluticasone propionate cream 0.05% cream will be prescribed once daily. Children aged > 2 years will follow a predefined weaning-off scheme when symptoms have improved. Children < 2 years will be reassessed after 1–2 weeks. All children will be advised to use emollients daily. Children (or their parents/carers) will receive an email reminder if questionnaires are not completed after 3 days. If still not filled in at key time points, participants will receive a telephone reminder. If patients are ≥ 16 years, they will complete the questionnaires themselves. Children under 16 may choose to complete the questionnaire themselves or together with/by a parent/carer
Outcomes	• Changes in subjective disease severity after 1, 4, and 24 weeks (POEM). A treatment effect of 3.0 POEM-points is considered clinically relevant. • Changes in objective disease severity relative to baseline after 1 week, 4 weeks and 24 weeks (EASI) • Quality of life with IDQOL or CDLQI depending on age • Compliance (determined as a POEM > 8 and use of TCS during that week) • Local side-effects (painful application, telangiectasia, atrophy, hypopigmentation and striae) • Systemic side-effects • Time to recovery. • Frequency of flare-ups. • Medication use. • Healthcare use • PGA and IGA (both on a 6-point scale; clear, almost clear, mild, moderate, severe, very severe) • Itch intensity score (NRS-11 from 0, no itch to 10, worst itch imaginable) • All (serious) adverse events and suspected unexpected serious adverse reactions reported spontaneously by the participant or observed by the investigator or the staff will be recorded
Starting date	Stated to be ongoing
Contact information	G. Elshout (g.elshout@erasmusmc.nl)
Notes	

AD: atopic dermatitis; **CDLQI:** Children's Dermatology Life Quality Index; **DFI:** Dermatitis Family Impact; **EASI:** Eczema Area and Severity Index; **GP:** general practitioner**; HC:** hydrocortisone; **IDQOL:** Infants Dermatology Quality of Life Index; **IGA: I**nvestigator Global Assessment; I**gE:** immunoglobulin E; **IV:** intravenous; **IgG4:** immunoglobulin G4; **LDH:** lactate dehydrogenase; **NIAID:** National Institute of Allergy and Infectious Diseases; **NRS:** numerical rating scale; **POEM:** Patient Oriented Eczema Measure; **PUVA:** psoralen + ultraviolet light A; **RCT:** randomised controlled trial; **SCORAD:** SCORing Atopic Dermatitis; **TARC:** thymus and activation-regulated chemokine; **TCS:** topical corticosteroids; **TEWL:** transepidermal water loss; **TIS:** Three-Item Severity score; **UVB:** ultraviolet light B

DATA AND ANALYSES

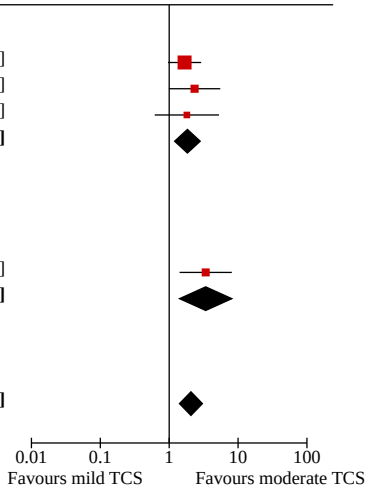
Comparison 1. Moderate-potency versus mild-potency topical corticosteroid (TCS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Cleared or marked improvement on IGA (short term); all ages; all severities	4	449	Odds Ratio (IV, Random, 95% CI)	2.07 [1.41, 3.04]
1.1.1 Moderate TCS versus mild TCS; parallel-group studies	3	391	Odds Ratio (IV, Random, 95% CI)	1.84 [1.20, 2.82]
1.1.2 Moderate TCS versus mild TCS; within-participant study	1	58	Odds Ratio (IV, Random, 95% CI)	3.39 [1.42, 8.11]
1.2 Cleared or marked improvement on IGA (short-term); children; all severities	2	169	Odds Ratio (IV, Random, 95% CI)	2.11 [1.08, 4.13]
1.3 Cleared or marked improvement on IGA (end of treatment); all ages; all severities	4	456	Odds Ratio (IV, Random, 95% CI)	2.74 [1.47, 5.11]
1.3.1 Moderate TCS versus mild TCS; parallel-group studies	3	398	Odds Ratio (IV, Random, 95% CI)	2.68 [1.16, 6.18]
1.3.2 Moderate TCS versus mild TCS; within-participant study	1	58	Odds Ratio (IV, Random, 95% CI)	3.39 [1.41, 8.11]
1.4 Cleared or marked improvement on IGA (end of treatment); children; all severities	2	169	Odds Ratio (IV, Random, 95% CI)	3.90 [1.84, 8.25]
1.5 SMD in investigator assessment of clinical signs (short term); children; moderate to severe eczema	2	51	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.27, 0.56]
1.5.1 Moderate TCS versus mild TCS; parallel-group study	1	9	Std. Mean Difference (IV, Random, 95% CI)	0.32 [-1.26, 1.90]
1.5.2 Moderate TCS versus mild TCS; within-participant study	1	42	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.29, 0.56]
1.6 SMD in investigator assessment of clinical signs (end of treatment); children; moderate to severe eczema	2	51	Std. Mean Difference (IV, Random, 95% CI)	0.43 [0.00, 0.86]
1.6.1 Moderate TCS versus mild TCS; parallel-group study	1	9	Std. Mean Difference (IV, Random, 95% CI)	0.32 [-1.26, 1.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.2 Moderate TCS versus mild TCS; within-participant study	1	42	Std. Mean Difference (IV, Random, 95% CI)	0.44 [-0.01, 0.89]
1.7 Number of participants with a greater IGA/PGA compared to the other group; short term and end of treatment	3	944	Odds Ratio (IV, Random, 95% CI)	3.14 [1.39, 7.13]
1.7.1 Children; unspecified severity eczema	1	50	Odds Ratio (IV, Random, 95% CI)	479.40 [42.38, 5422.40]
1.7.2 Unspecified age; unspecified severity eczema	2	894	Odds Ratio (IV, Random, 95% CI)	2.02 [1.05, 3.88]
1.8 Included studies with no poolable clinician-reported signs data	2		Other data	No numeric data
1.9 Included studies with no poolable patient-reported symptoms data	3		Other data	No numeric data
1.10 Number of participants with local site reactions; end of treatment	4		Other data	No numeric data
1.10.1 Burning	1		Other data	No numeric data
1.10.2 Stinging	1		Other data	No numeric data
1.10.3 Burning or stinging	1		Other data	No numeric data
1.10.4 Pruritus	1		Other data	No numeric data
1.10.5 Sensitisation	1		Other data	No numeric data
1.10.6 Urticarial rash	1		Other data	No numeric data
1.10.7 Unspecified	1		Other data	No numeric data

Analysis 1.1. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 1: Cleared or marked improvement on IGA (short term); all ages; all severities

Study or Subgroup	log[OR]	SE	Moderate TCS Total	Mild TCS Total	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 Moderate TCS versus mild TCS; parallel-group studies						
Bagatell 1983 (1)	0.5145	0.283	111	111	47.9%	1.67 [0.96 , 2.91]
Jorizzo 1995 (1)	0.8492	0.438	55	56	20.0%	2.34 [0.99 , 5.52]
Mobacken 1986 (2)	0.5909	0.5482	29	29	12.8%	1.81 [0.62 , 5.29]
Subtotal (95% CI)			**195**	**196**	**80.7%**	**1.84 [1.20 , 2.82]**
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.80 (P = 0.005)						
1.1.2 Moderate TCS versus mild TCS; within-participant study						
Roth 1978a (3)	1.220309	0.44550382	29	29	19.3%	3.39 [1.42 , 8.11]
Subtotal (95% CI)			**29**	**29**	**19.3%**	**3.39 [1.42 , 8.11]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.74 (P = 0.006)						
Total (95% CI)			**224**	**225**	**100.0%**	**2.07 [1.41 , 3.04]**
Heterogeneity: Tau² = 0.00; Chi² = 1.93, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.71 (P = 0.0002)						
Test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.0%						

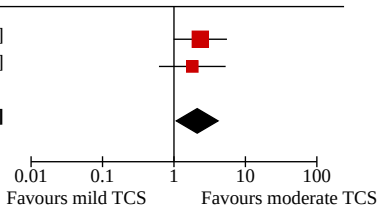


Footnotes

(1) Week 1.
(2) Day 7-10.
(3) Day 26-35. Unit of analysis is side; variance is corrected.

Analysis 1.2. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 2: Cleared or marked improvement on IGA (short-term); children; all severities

Study or Subgroup	log[OR]	SE	Moderate TCS Total	Mild TCS Total	Weight	Odds Ratio IV, Random, 95% CI
Jorizzo 1995 (1)	0.8492	0.438	55	56	61.0%	2.34 [0.99 , 5.52]
Mobacken 1986 (2)	0.5909	0.5482	29	29	39.0%	1.81 [0.62 , 5.29]
Total (95% CI)			**84**	**85**	**100.0%**	**2.11 [1.08 , 4.13]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.19 (P = 0.03)						
Test for subgroup differences: Not applicable						

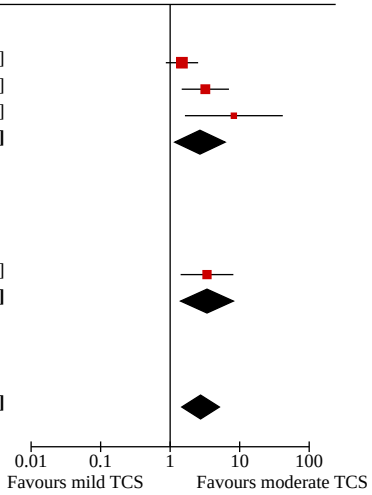


Footnotes

(1) Week 1.
(2) Day 7-10.

Analysis 1.3. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 3: Cleared or marked improvement on IGA (end of treatment); all ages; all severities

Study or Subgroup	log[OR]	SE	Moderate TCS Total	Mild TCS Total	Weight	Odds Ratio IV, Random, 95% CI
1.3.1 Moderate TCS versus mild TCS; parallel-group studies						
Bagatell 1983 (1)	0.3916	0.273	114	115	36.0%	1.48 [0.87 , 2.53]
Jorizzo 1995 (2)	1.1654	0.399	55	56	27.7%	3.21 [1.47 , 7.01]
Mobacken 1986 (3)	2.1102	0.8267	29	29	11.4%	8.25 [1.63 , 41.70]
Subtotal (95% CI)			**198**	**200**	**75.0%**	**2.68 [1.16 , 6.18]**
Heterogeneity: Tau² = 0.33; Chi² = 5.51, df = 2 (P = 0.06); I² = 64%						
Test for overall effect: Z = 2.32 (P = 0.02)						
1.3.2 Moderate TCS versus mild TCS; within-participant study						
Roth 1978a (4)	1.2203	0.44550382	29	29	25.0%	3.39 [1.41 , 8.11]
Subtotal (95% CI)			**29**	**29**	**25.0%**	**3.39 [1.41 , 8.11]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.74 (P = 0.006)						
Total (95% CI)			**227**	**229**	**100.0%**	**2.74 [1.47 , 5.11]**
Heterogeneity: Tau² = 0.21; Chi² = 6.45, df = 3 (P = 0.09); I² = 53%						
Test for overall effect: Z = 3.17 (P = 0.002)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.70), I² = 0%						

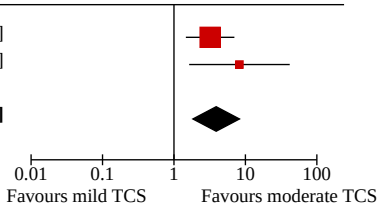


Footnotes

(1) Week 3.
(2) Week 5.
(3) Day 19-25.
(4) Day 26-35. Unit of analysis is side; variance is corrected.

Analysis 1.4. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 4: Cleared or marked improvement on IGA (end of treatment); children; all severities

Study or Subgroup	log[OR]	SE	Moderate TCS Total	Mild TCS Total	Weight	Odds Ratio IV, Random, 95% CI
Jorizzo 1995 (1)	1.1654	0.399	55	56	79.4%	3.21 [1.47 , 7.01]
Mobacken 1986 (2)	2.1102	0.8267	29	29	20.6%	8.25 [1.63 , 41.70]
Total (95% CI)			**84**	**85**	**100.0%**	**3.90 [1.84 , 8.25]**
Heterogeneity: Tau² = 0.03; Chi² = 1.06, df = 1 (P = 0.30); I² = 6%						
Test for overall effect: Z = 3.56 (P = 0.0004)						
Test for subgroup differences: Not applicable						

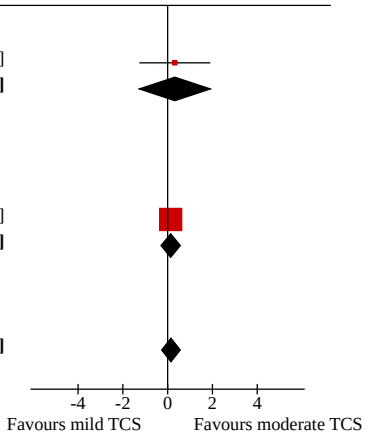


Footnotes

(1) Week 5.
(2) Day 19-25.

Analysis 1.5. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 5: SMD in investigator assessment of clinical signs (short term); children; moderate to severe eczema

Study or Subgroup	SMD	SE	Moderate TCS Total	Mild TCS Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.5.1 Moderate TCS versus mild TCS; parallel-group study						
Queille 1984 (1)	0.3207	0.8081	2	7	6.9%	0.32 [-1.26 , 1.90]
Subtotal (95% CI)			**2**	**7**	**6.9%**	**0.32 [-1.26 , 1.90]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
1.5.2 Moderate TCS versus mild TCS; within-participant study						
Haribhakti 1982 (2)	0.1349189	0.2192087	21	21	93.1%	0.13 [-0.29 , 0.56]
Subtotal (95% CI)			**21**	**21**	**93.1%**	**0.13 [-0.29 , 0.56]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
Total (95% CI)			**23**	**28**	**100.0%**	**0.15 [-0.27 , 0.56]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.49)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%						



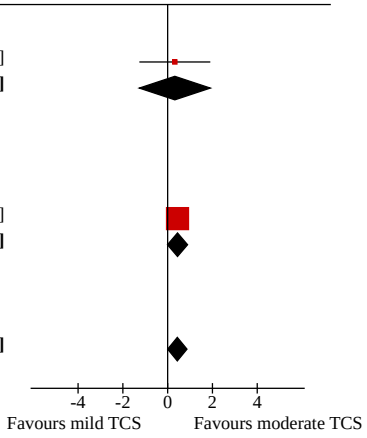
Footnotes

(1) Group C versus groups A+B. Day 6. Decrease in unnamed scale from baseline.

(2) Week 1. Decrease in unnamed scale from baseline. Unit of analysis is side; variance is corrected.

Analysis 1.6. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 6: SMD in investigator assessment of clinical signs (end of treatment); children; moderate to severe eczema

Study or Subgroup	SMD	SE	Moderate TCS Total	Mild TCS Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.6.1 Moderate TCS versus mild TCS; parallel-group study						
Queille 1984 (1)	0.3207	0.8081	2	7	7.4%	0.32 [-1.26 , 1.90]
Subtotal (95% CI)			**2**	**7**	**7.4%**	**0.32 [-1.26 , 1.90]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
1.6.2 Moderate TCS versus mild TCS; within-participant study						
Haribhakti 1982 (2)	0.4402934	0.2285492	21	21	92.6%	0.44 [-0.01 , 0.89]
Subtotal (95% CI)			**21**	**21**	**92.6%**	**0.44 [-0.01 , 0.89]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.93 (P = 0.05)						
Total (95% CI)			**23**	**28**	**100.0%**	**0.43 [0.00 , 0.86]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.96 (P = 0.05)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%						

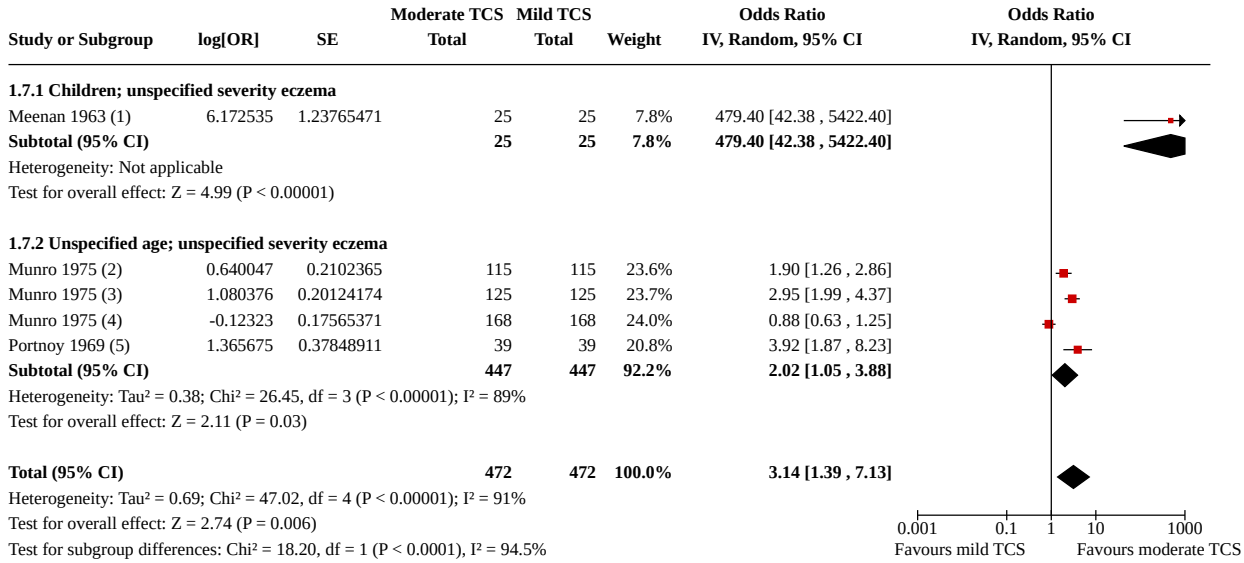


Footnotes

(1) Group C versus groups A+B. Day 6. Decrease in unnamed scale from baseline.

(2) Up to week 3. Decrease in unnamed scale from baseline. Unit of analysis is side; variance is corrected.

Analysis 1.7. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 7: Number of participants with a greater IGA/PGA compared to the other group; short term and end of treatment



Footnotes

(1) Week 2. Clinician and patient preference. Unit of analysis is side; variance is corrected.
(2) C versus B. Duration of treatment unclear. Clinician preference only. Unit of analysis is side; variance is corrected.
(3) D versus B. Duration of treatment unclear. Clinician preference only. Unit of analysis is side; variance is corrected.
(4) A versus B. Duration of treatment unclear. Clinician preference only. Unit of analysis is side; variance is corrected.
(5) Day 7. Clinician and patient preference. Unit of analysis is side; variance is corrected.

Analysis 1.8. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 8: Included studies with no poolable clinician-reported signs data

Included studies with no poolable clinician-reported signs data

Study	Intervention and comparison	Comments
Kuokkanen 1987	Moderate TCS versus mild TCS	Within-participant study. Children with moderate to severe eczema. Average percentage improvement in unnamed scale. 54% improvement on sides treated with moderate TCS compared to 49% treated with mild TCS at week 1 (n = 32). 88% improvement on sides treated with moderate TCS and 86% treated with mild TCS at end of treatment (week 3; n = 32)
Rossi 2002	Moderate TCS versus mild TCS	Parallel-group; unspecified age and severity of eczema. Unnamed scale. Quote: "the two groups were not significantly different, except for pruritus (p=0.046) and excoriation (p=0.01)"; n = 152. It was not clear whether pruritus was assessed by clinician or patient, however pruritus was not listed in the details of the investigator assessment.

Analysis 1.9. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 9: Included studies with no poolable patient-reported symptoms data

Included studies with no poolable patient-reported symptoms data

Study	Intervention and comparison	Comments
Jorizzo 1995	Moderate TCS versus mild TCS	Parallel-group; children; mild to moderate eczema. Number of participants without pruritus. 32 in the moderate TCS group (n = 55) compared to 22 in the mild TCS group (n = 56) at the end of treatment (last observation assumed up to week 5)

Rossi 2002	Moderate TCS versus mild TCS	Parallel-group; unspecified age and severity of eczema. Unnamed scale at 3 weeks (assumed). Quote: "the two groups were not significantly different, except for pruritus (p=0.046) and excoriation (p=0.01)"; n = 152. It was not clear whether pruritus was assessed by clinician or patient, however pruritus was not listed in the details of the investigator assessment
Roth 1978a	Moderate TCS versus mild TCS	Within-participant; unspecified age and severity of eczema. Pruritus scored on a 10-point scale. In 29 participants, there was a greater improvement in pruritus score on the side treated with moderate TCS ($P < 0.05$ at day 5-9; $P < 0.005$ at days 26-35)

Analysis 1.10. Comparison 1: Moderate-potency versus mild-potency topical corticosteroid (TCS), Outcome 10: Number of participants with local site reactions; end of treatment

Number of participants with local site reactions; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Burning								
Roth 1978a	Within- participant	Moderate TCS	Mild TCS	Unspecified	Day 26-35	1/29	0/29	Quotes: "brief"; "no significant side effects were seen with either medication."
Stinging								
Roth 1978a	Within- participant	Moderate TCS	Mild TCS	Unspecified	Day 26-35	0/29	0/29	
Burning or stinging								
Jorizzo 1995	Parallel- group.	Moderate TCS	Mild TCS	Children; mild to moderate eczema.	Up to week 25.	?/57	?/56	Quote: “any stinging or burning sensation that occurred was slight." 36 patients remained after week 5.
Pruritus								
Roth 1978a	Within- participant	Moderate TCS	Mild TCS	Unspecified	Day 26-35	1/29	0/29	Quotes: "increased pruritus"; "no significant side effects were seen with either medication."
Sensitisation								
Bagatell 1983	Parallel- group	Moderate TCS	Mild TCS	Adults and children; moderate to severe eczema	Up to week 3	0/127	0/122	
Urticarial rash								
Kuokkanen 1987	Within- participant	Moderate TCS	Mild TCS	Children; moderate to severe eczema	Up to week 1	1/34	1/34	Same individual affected in both arms
Unspecified								
Bagatell 1983	Parallel- group	Moderate TCS	Mild TCS	Adults and children; moderate to severe eczema	Up to week 3	4/127	3/122	Included skin dryness, irritation, burning and erythema with moderate TCS. Included pruritus, fissuring of the skin and an "appli-

				cation site reaction" judged unrelated to the study medication with mild TCS

Comparison 2. Potent versus mild-potency topical corticosteroid (TCS)

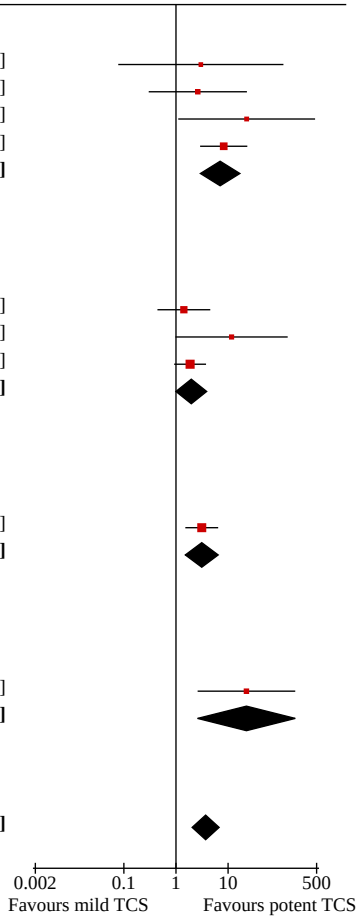
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Cleared or marked improvement on IGA (short-term); all ages; all severities	9	458	Odds Ratio (IV, Random, 95% CI)	3.71 [2.04, 6.72]
2.1.1 Potent TCS versus mild TCS; parallel-group studies	4	176	Odds Ratio (IV, Random, 95% CI)	7.04 [2.94, 16.83]
2.1.2 Potent TCS versus mild TCS; within-participant studies	3	132	Odds Ratio (IV, Random, 95% CI)	1.97 [1.00, 3.88]
2.1.3 Second-generation potent TCS versus mild TCS; parallel-group study	1	127	Odds Ratio (IV, Random, 95% CI)	3.12 [1.51, 6.45]
2.1.4 Once daily second-generation potent TCS versus twice daily mild TCS; parallel-group study	1	23	Odds Ratio (IV, Random, 95% CI)	22.50 [2.60, 194.50]
2.2 Cleared or marked improvement on IGA (short term); children; all severities	3	245	Odds Ratio (IV, Random, 95% CI)	2.21 [1.39, 3.51]
2.3 Cleared or marked improvement on IGA (short term); all ages; split by severity	5		Odds Ratio (IV, Random, 95% CI)	Subtotals only
2.3.1 Moderate to severe eczema	3	232	Odds Ratio (IV, Random, 95% CI)	2.69 [1.34, 5.39]
2.3.2 Mild- to moderate-severity eczema	2	63	Odds Ratio (IV, Random, 95% CI)	4.84 [0.33, 71.44]
2.4 SMD in investigator assessment of clinical signs (short term); children; severe eczema; parallel-group studies	2	46	Std. Mean Difference (IV, Random, 95% CI)	0.63 [-0.95, 2.21]
2.5 Number of participants with a greater IGA compared to the other group; short term	3	134	Odds Ratio (IV, Random, 95% CI)	11.70 [5.67, 24.15]
2.6 Included studies with no poolable clinician-reported signs data	9		Other data	No numeric data
2.7 Included studies with no poolable patient-reported symptoms data	5		Other data	No numeric data
2.7.1 Itch	4		Other data	No numeric data
2.7.2 Sleep	2		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.3 Number of participants with a greater PGA compared to the other group	1		Other data	No numeric data
2.8 Number of participants with skin thinning and related signs; end of treatment	5		Other data	No numeric data
2.8.1 Skin thinning	5		Other data	No numeric data
2.8.2 Striae	1		Other data	No numeric data
2.8.3 Telangiectasia	1		Other data	No numeric data
2.8.4 Loss of elasticity	1		Other data	No numeric data
2.8.5 Loss of normal skin markings	1		Other data	No numeric data
2.8.6 Gloss or shine	1		Other data	No numeric data
2.8.7 Pigmentation change	1		Other data	No numeric data
2.9 Number of participants with local site reactions; end of treatment	8		Other data	No numeric data
2.9.1 Burning	2		Other data	No numeric data
2.9.2 Stinging	1		Other data	No numeric data
2.9.3 Burning or stinging	1		Other data	No numeric data
2.9.4 Irritation	1		Other data	No numeric data
2.9.5 Spots or rashes	3		Other data	No numeric data
2.9.6 Itching	1		Other data	No numeric data
2.10 Number of participants with skin infection; end of treatment	4		Other data	No numeric data
2.10.1 Folliculitis	1		Other data	No numeric data
2.10.2 Ringworm and folliculitis	1		Other data	No numeric data
2.10.3 Acne	1		Other data	No numeric data
2.10.4 Secondary infection	1		Other data	No numeric data
2.10.5 Eczema herpeticum	1		Other data	No numeric data
2.10.6 Staphylococcus aureus infection (scalp)	1		Other data	No numeric data
2.10.7 Skin infection	1		Other data	No numeric data
2.10.8 Impetigo contagiosa	1		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.10.9 Boil	1		Other data	No numeric data
2.10.10 Pustules	1		Other data	No numeric data
2.11 Number of participants with abnormal cortisol; end of treatment	4		Other data	No numeric data
2.12 Included studies with unspecified adverse event data	7		Other data	No numeric data

Analysis 2.1. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 1: Cleared or marked improvement on IGA (short-term); all ages; all severities

Study or Subgroup	log[OR]	SE	Potent TCS Total	Mild TCS Total	Weight	Odds Ratio IV, Random, 95% CI
2.1.1 Potent TCS versus mild TCS; parallel-group studies						
Gentry 1973 (1)	1.0986	1.8619	3	2	2.5%	3.00 [0.08 , 115.34]
Mali 1976 (2)	0.965	1.107	7	9	6.2%	2.62 [0.30 , 22.98]
Savin 1976 (3)	3.1238	1.5426	15	12	3.5%	22.73 [1.11 , 467.43]
Wortzel 1975 (4)	2.1094	0.532	66	62	16.6%	8.24 [2.91 , 23.39]
Subtotal (95% CI)			**91**	**85**	**28.7%**	**7.04 [2.94 , 16.83]**
Heterogeneity: Tau² = 0.00; Chi² = 1.67, df = 3 (P = 0.64); I² = 0%						
Test for overall effect: Z = 4.39 (P < 0.0001)						
2.1.2 Potent TCS versus mild TCS; within-participant studies						
Giannetti 1981 (5)	0.348307	0.59547195	20	20	14.7%	1.42 [0.44 , 4.55]
Handa 1985 (6)	2.456736	1.2650335	7	7	4.9%	11.67 [0.98 , 139.23]
Veien 1984 (7)	0.624154	0.35917406	39	39	23.0%	1.87 [0.92 , 3.77]
Subtotal (95% CI)			**66**	**66**	**42.6%**	**1.97 [1.00 , 3.88]**
Heterogeneity: Tau² = 0.06; Chi² = 2.30, df = 2 (P = 0.32); I² = 13%						
Test for overall effect: Z = 1.95 (P = 0.05)						
2.1.3 Second-generation potent TCS versus mild TCS; parallel-group study						
Kirkup 2003a (8)	1.1391	0.3701	62	65	22.5%	3.12 [1.51 , 6.45]
Subtotal (95% CI)			**62**	**65**	**22.5%**	**3.12 [1.51 , 6.45]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.08 (P = 0.002)						
2.1.4 Once daily second-generation potent TCS versus twice daily mild TCS; parallel-group study						
Ryu 1997 (9)	3.1135	1.1005	12	11	6.2%	22.50 [2.60 , 194.50]
Subtotal (95% CI)			**12**	**11**	**6.2%**	**22.50 [2.60 , 194.50]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.83 (P = 0.005)						
Total (95% CI)			**231**	**227**	**100.0%**	**3.71 [2.04 , 6.72]**
Heterogeneity: Tau² = 0.27; Chi² = 13.13, df = 8 (P = 0.11); I² = 39%						
Test for overall effect: Z = 4.32 (P < 0.0001)						
Test for subgroup differences: Chi² = 8.17, df = 3 (P = 0.04), I² = 63.3%						



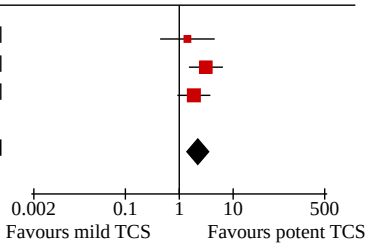
Footnotes

(1) Week 4 (assumed). Patients not assessed after rated "cleared".
(2) Week 3 (assumed). Number "much better".
(3) Week 1. Number "excellent" or "good".
(4) Day 22.
(5) Week 1. Number with complete healing. Unit of analysis is side; variance is corrected.
(6) Week 3 (assumed). Unit of analysis is side; variance is corrected.
(7) Week 2. Number of patients cleared. Unit of analysis is side; variance is corrected.
(8) Week 2-4.
(9) Day 14 (assumed).

Analysis 2.2. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 2: Cleared or marked improvement on IGA (short term); children; all severities

Study or Subgroup	log[OR]	SE	Potent TCS Total	Mild TCS Total	Weight	Odds Ratio IV, Random, 95% CI
Giannetti 1981 (1)	0.3483	0.595472	20	20	15.8%	1.42 [0.44 , 4.55]
Kirkup 2003a (2)	1.1391	0.3701	62	65	40.8%	3.12 [1.51 , 6.45]
Veien 1984 (3)	0.6242	0.359174	39	39	43.4%	1.87 [0.92 , 3.77]
Total (95% CI)			**121**	**124**	**100.0%**	**2.21 [1.39 , 3.51]**

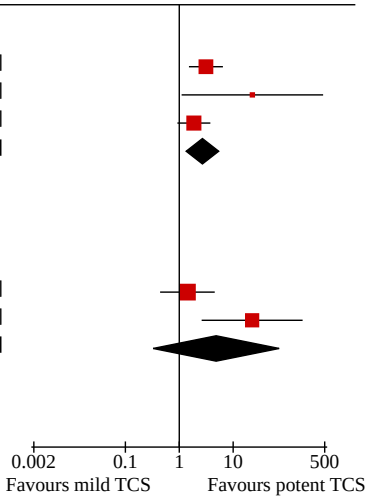
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 3.34 (P = 0.0008)
Test for subgroup differences: Not applicable



Footnotes
(1) Week 1. Number with complete healing. Unit of analysis is side; variance is corrected.
(2) Week 2-4.
(3) Week 2. Number of patients cleared. Unit of analysis is side; variance is corrected.

Analysis 2.3. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 3: Cleared or marked improvement on IGA (short term); all ages; split by severity

Study or Subgroup	log[OR]	SE	Potent TCS Total	Mild TCS Total	Weight	Odds Ratio IV, Random, 95% CI
2.3.1 Moderate to severe eczema						
Kirkup 2003a (1)	1.1391	0.3701	62	65	46.8%	3.12 [1.51 , 6.45]
Savin 1976 (2)	3.1238	1.5426	15	12	5.0%	22.73 [1.11 , 467.43]
Veien 1984 (3)	0.6242	0.359174	39	39	48.2%	1.87 [0.92 , 3.77]
Subtotal (95% CI)			**116**	**116**	**100.0%**	**2.69 [1.34 , 5.39]**
Heterogeneity: Tau² = 0.13; Chi² = 3.07, df = 2 (P = 0.22); I² = 35%						
Test for overall effect: Z = 2.80 (P = 0.005)						
2.3.2 Mild- to moderate-severity eczema						
Giannetti 1981 (4)	0.3483	0.595472	20	20	55.6%	1.42 [0.44 , 4.55]
Ryu 1997 (5)	3.1135	1.1005	12	11	44.4%	22.50 [2.60 , 194.50]
Subtotal (95% CI)			**32**	**31**	**100.0%**	**4.84 [0.33 , 71.44]**
Heterogeneity: Tau² = 3.04; Chi² = 4.88, df = 1 (P = 0.03); I² = 80%						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						

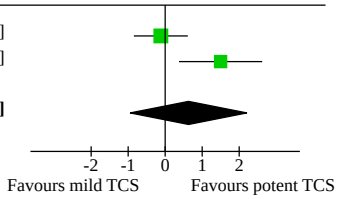


Footnotes
(1) Week 2-4.
(2) Week 1. Number "excellent" or "good".
(3) Week 2. Number of patients cleared. Unit of analysis is side; variance is corrected.
(4) Week 1. Number with complete healing. Unit of analysis is side; variance is corrected.
(5) Day 14 (assumed).

Analysis 2.4. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 4: SMD in investigator assessment of clinical signs (short term); children; severe eczema; parallel-group studies

Study or Subgroup	Potent TCS Mean	Potent TCS SD	Potent TCS Total	Mild TCS Mean	Mild TCS SD	Mild TCS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Lebrun-Vignes 2000 (1)	4.71	1.89	14	5	2.82	15	53.7%	-0.12 [-0.85 , 0.61]
Queille 1984 (2)	22.5	9.43	10	9.14	6.77	7	46.3%	1.50 [0.37 , 2.62]
Total (95% CI)			**24**			**22**	**100.0%**	**0.63 [-0.95 , 2.21]**

Heterogeneity: Tau² = 1.07; Chi² = 5.58, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.78 (P = 0.43)
Test for subgroup differences: Not applicable

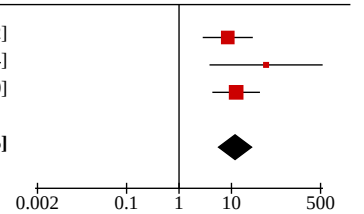


Footnotes
(1) Day 5. Decrease in unnamed scale from baseline.
(2) Groups D+E+F versus groups A+B. Day 6. Decrease in unnamed scale from baseline.

Analysis 2.5. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 5: Number of participants with a greater IGA compared to the other group; short term

Study or Subgroup	log[OR]	SE	Potent TCS Total	Mild TCS Total	Weight	Odds Ratio IV, Random, 95% CI
Cahn 1961 (1)	2.140066	0.56094494	20	20	43.4%	8.50 [2.83 , 25.52]
Roth 1973 (2)	3.822227	1.26715015	18	18	8.5%	45.71 [3.81 , 547.74]
Yasuda 1976 (3)	2.507791	0.53296671	29	29	48.1%	12.28 [4.32 , 34.90]
Total (95% CI)			**67**	**67**	**100.0%**	**11.70 [5.67 , 24.15]**

Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 6.66 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Week 1. Three times daily application. Unspecified age and severity.
(2) Week 1. Adults and children; moderate to severe eczema.
(3) Week 1. Unspecified age and severity.

Analysis 2.6. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 6: Included studies with no poolable clinician-reported signs data

Included studies with no poolable clinician-reported signs data

Study	Intervention and comparison	Comments
Fadrhoncova 1982	Potent TCS versus mild TCS	Within-participant study; adults and children; unclear severity. Percentage decrease in unnamed scale; no dispersion. 45.1% on sides treated with potent TCS compared to 44.3% for sides treated with mild TCS at week 1. 85.6% on sides treated with potent TCS compared to 84.1% for the sides treated with mild TCS at end of treatment (week 4; n = 24 assumed as all reported data is from 24 participants, however 26 were randomised). Extracted using WebPlotDigitizer
Kaplan 1978	Potent TCS cream versus mild TCS ointment	Parallel-group; unspecified age and severity eczema. Mean IGA; no dispersion. 55.9% reduction in potent TCS group compared to 31.4% in mild TCS group at week 3 (n = 58; P < 0.05)
Kirkup 2003a	Second-generation potent TCS versus mild TCS	Parallel-group; children; moderate to severe eczema. Mean IGA. Mean difference between groups was −1.88 (−3.20, 0.56) in favour of potent TCS at end of treatment (week 16; P = 0.006; n = 107)
Marten 1980	Potent TCS versus mild TCS (group B versus group A)	Parallel-group; children; moderate severity eczema. Unnamed scale. Quote: "numerical indications of improvements in signs and symptoms were observed in

		all four treatment groups. However, the number of observations was too small to obtain statistical significance"; week 4; n = 10
Marten 1980	Potent TCS versus mild TCS (group D versus group C)	Parallel-group; children; severe eczema. Unnamed scale. Quote: "numerical indications of improvements in signs and symptoms were observed in all four treatment groups. However, the number of observations was too small to obtain statistical significance"; week 4; n = 10
Noren 1989	Potent TCS (stepped down to mild after 2 weeks) versus mild TCS (group B versus group A)	Parallel-group; adults; moderate to severe eczema. Mean decrease in unnamed scale from baseline; no dispersion. 1.07 in the potent TCS group (n = 11) compared to 0.55 with mild TCS (n = 11) at week 2. 0.85 in the potent TCS group (n = 11) compared to 0.76 with mild TCS (n = 11) at end of treatment (week 4). Extracted using WebPlotDigitizer
Noren 1989	Potent TCS (stepped down to mild after 2 weeks) versus mild TCS (group D versus group C)	Parallel-group; adults; moderate to severe eczema. Mean decrease in unnamed scale from baseline; no dispersion. 1.54 in the potent TCS group (n = 10) compared to 1.16 with mild TCS (n = 13) at week 2. 1.66 in the potent TCS group (n = 10) compared to 1.42 with mild TCS (n = 13) at end of treatment (week 4). Extracted using WebPlotDigitizer
Prado de Oliveira 2002	Second-generation potent TCS versus mild TCS	Parallel-group; children; moderate to severe eczema. Investigator global assessment; 10 of 13 participants receiving potent TCS had complete disappearance of lesions at day 42 compared to 8 of 11 receiving mild TCS; OR = 1.25 (95% CI 0.20 to 7.96)
Sanabria-Silva 1991	Potent TCS versus mild TCS	Parallel group; children; unspecified severity. Percentage improvement on unnamed scale; dispersion type unclear. Average percentage improvement 28 [26, 30] (unclear dispersion type) in potent group (n = 15 assumed) compared to 21 [18, 23] (unclear dispersion type) in the mild group (n = 15 assumed) at end of treatment (week 4; P < 0.01). Participants were followed up for at least 10 days after the end of treatment to identify those that had a "rebound" defined as "reactivation of lesions with greater intensity than their pre-treatment state". No participants in either group were reported to have experienced rebound. Extracted using WebPlotDigitizer
Thomas 2002	3-day 'pulse' of potent TCS versus 7 days of mild TCS	Parallel-group; children; mild to moderate eczema; community patients only. Number of participants with > 20% improvement in SASSAD. Odds ratio at end of treatment was 1.05 [0.58, 1.91]; week 18; n = 87 in both groups
Vernon 1991	Once daily, second-generation potent TCS versus twice daily mild TCS	Parallel-group; children; moderate to severe eczema. Mean decrease in unnamed scale from baseline; no dispersion. At end of treatment (week 6 or sooner if AD clearance was achieved), mean difference was 10.7 in the once daily potent group; n = 23 (assumed). In the twice daily mild group mean difference was 8.7; n = 24 (assumed). Extracted using WebPlotDigitizer

Analysis 2.7. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 7: Included studies with no poolable patient-reported symptoms data

Included studies with no poolable patient-reported symptoms data

Study	Intervention and comparison	Comments
Itch		
Giannetti 1981	Potent TCS versus mild TCS	Within-participant; children; mild to moderate severity eczema. Mean decrease in itch NRS relative to baseline. Mean (assumed) difference was 0.60 [95% CI 0.28, 0.92] in the short term (week 1; n = 20) in favour of potent TCS and 0.50 [95% CI 0.20, 0.80] at end of treatment (week 3; n = 20)
Kirkup 2003a	Second-generation potent TCS versus mild TCS	Parallel-group; children; moderate to severe eczema. Number judging itch to be better. Odds ratio at 2-4 weeks was 1.95 [0.84, 4.53]; n = 120. Odds ratio at 14-16 weeks was 1.20 [0.49, 2.90]; n = 107. N assumed

Noren 1989	Potent TCS (stepped down to mild after 2 weeks) versus mild TCS (group B versus group A)	Parallel-group; adults; moderate to severe eczema. Percentage decrease in frequency of scratching using a counter. 74% in the potent TCS group at end of treatment (week 4) compared to 65% in the group treated with mild TCS (n = 11 in both groups). Two participants withdrew; unclear why and to which group they belonged.
Noren 1989	Potent TCS (stepped down to mild after 2 weeks) versus mild TCS (group D versus group C)	Parallel-group; adults; moderate to severe eczema. Percentage decrease in frequency of scratching using a counter. 90% in the potent TCS group (n = 10) at end of treatment (week 4) compared to 88% in the group treated with mild TCS (n = 13). Two participants withdrew; unclear why and to which group they belonged.
Thomas 2002	3-day 'pulse' of potent TCS versus seven days of mild TCS	Parallel-group; children; mild to moderate eczema. Median number of scratch-free days. 117.5 (IQR 99.3-125.0; n = 100) in the 'pulse' group compared to 118 (IQR 99.8-124.0; n = 98) in the daily mild TCS group. Difference between groups was 0.5 days (95% CI -3.0 to 2.0, P = 0.68) at end of treatment (week 18)
Sleep		
Kirkup 2003a	Second-generation potent TCS versus mild TCS	Parallel-group; children; moderate to severe eczema. Number judging sleep to be better. Odds ratio at 2-4 weeks was 2.35 [0.99, 5.56]; n = 120. Odds ratio at 14-16 weeks was 1.71 [0.67, 4.38]; n = 107. N assumed
Thomas 2002	3-day 'pulse' of potent TCS versus 7 days of mild TCS	Parallel-group; children; mild to moderate eczema; community patients only. Median number of undisturbed nights. 121 (IQR 101.3-126.0; n = 84) in the 'pulse' group compared to 123 (IQR 109.5-126.0; n = 81) in the daily mild TCS group. Difference between groups was 2 days (95% CI 0.0 to 2.0, P = 0.53) at end of treatment (week 18)
Number of participants with a greater PGA compared to the other group		
Veien 1984	Potent TCS versus mild TCS	Within-participant; children; moderate to severe eczema. Number of participants judging potent to be better or very much better. 19 in the short term (week 2; n = 39); 17 at end of treatment (week 4; n = 40). Manually calculated

Analysis 2.8. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 8: Number of participants with skin thinning and related signs; end of treatment

Number of participants with skin thinning and related signs; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Skin thinning								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/70	0/67	Assumed number randomised
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	4/13	2/12	
Ryu 1997	Parallel- group	Once daily second-generation potent TCS	Twice daily mild TCS	Adults and children; mild to moderate eczema	Up to day 14	0/12	0/12	
Thomas 2002	Parallel- group	3-day 'pulse' of potent TCS	7 days of mild TCS	Children; mild to moderate eczema	Up to week 18	0/103	0/104	Assumed number randomised. Not used continuously
Vernon 1991	Parallel- group	Once daily second-generation potent	Twice daily mild	Children; moderate to severe eczema	Up to week 6	0/23	0/24	N assumed
Striae								

Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Telangiectasia								
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Loss of elasticity								
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Loss of normal skin markings								
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Gloss or shine								
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Pigmentation change								
Ryu 1997	Parallel- group	Once daily second-generation potent TCS	Twice daily mild TCS	Adults and children; mild to moderate eczema	Up to day 14	0/12	0/12	

Analysis 2.9. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 9: Number of participants with local site reactions; end of treatment

Number of participants with local site reactions; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Burning								
Kaplan 1978	Parallel- group	Potent TCS cream	Mild TCS ointment	Unspecified	Up to week 3	0/30	1/30	"Burning with immediate drying"; resulted in discontinuation
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	3/13	1/12	Strategy A: "ardor on 1st application" in one participant and "ardor on application of product" in 2 participants Strategy B: "ardor days 1 and 2 after application."
Stinging								
Vernon 1991	Parallel- group	Once daily Second-generation potent	Twice daily mild	Children; moderate to severe eczema	Up to week 6	3/23	0/24	N assumed
Burning or stinging								
Fadrhoncova 1982	Within- participant	Potent TCS	Mild TCS	Adults and children; severity of eczema unclear	Up to week 4	1/24	1/24	Both events in the same participant who completed treatment. The mild TCS-treated side was worse than the potent TCS side. N assumed as all reported data are from 24 partic-

								ipants, however 26 were randomised.
Irritation								
Cahn 1961	Within-participant	Potent TCS	Mild TCS	Unspecified	Up to week 1	0/20	0/20	The narrative was suggestive of zero events on the side treated with mild TCS, however this was not explicitly reported.
Spots or rashes								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised
Ryu 1997	Parallel- group	Once daily second-generation potent TCS	Twice daily mild TCS	All ages; mild to moderate eczema	Up to day 14	0/12	0/12	Maculopapular rash
Thomas 2002	Parallel- group	3-day 'pulse' of potent TCS	7 days of mild TCS	Children; mild to moderate eczema	Up to week 18	2/103	0/104	Assumed number randomised
Itching								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised

Analysis 2.10. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 10: Number of participants with skin infection; end of treatment

Number of participants with skin infection; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Folliculitis								
Ryu 1997	Parallel- group	Once daily Second-generation potent TCS	Twice daily mild TCS	Adults and children; mild- to moderate-severity eczema	Up to day 14.	1/12	0/12	
Ringworm and folliculitis								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	mild TCS	Children; moderate to severe eczema.	Up to week 16 (includes 4 weeks acute treatment phase)	1/70	0/67	Assumed number randomised.
Acne								
Ryu 1997	Parallel- group	Once daily Second-generation potent TCS	Twice daily mild TCS	Adults and children; mild- to moderate-severity eczema	Up to day 14.	0/12	0/12	
Secondary infection								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	mild TCS	Children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/70	1/67	Assumed number randomised
Eczema herpeticum								
Marten 1980	Parallel- group	Potent TCS (group D)	Mild TCS (group C)	Children; severe eczema	Up to week 4	0/5	0/5	
Marten 1980	Parallel- group	Potent TCS (group B)	Mild TCS (group A)	Children; moderate-severity eczema	Up to week 4	1/5	0/5	On face
Staphylococcus aureus infection (scalp)								

Vernon 1991	Parallel- group	Once daily second-generation potent	Twice daily mild	Children; moderate to severe eczema	Up to 6 weeks	1/23	0/24	N assumed. Occurred at 36 days and resulted in discontinuation
Skin infection								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised
Impetigo contagiosa								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised
Boil								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised
Pustules								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised

Analysis 2.11. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 11: Number of participants with abnormal cortisol; end of treatment

Number of participants with abnormal cortisol; end of treatment

Study	Intervention and comparison	Cases/N A	Cases/N B	Additional information
Lebrun-Vignes 2000	Potent TCS versus mild TCS (both twice daily until day 5, then once daily until day 7, then alternate days until day 15)	?/13	?/14	Parallel-group; children; severe eczema. Morning plasma cortisol (mg/mL) at baseline and days 5, 20, and 30. Mean change from baseline was reported with no indication of how many people were outside of the normal range.
Marten 1980	Potent TCS versus mild TCS (group B versus group A)	2/4	2/3	Parallel-group; children; moderate-severity eczema. Plasma cortisol response to Synacthen at baseline and end of treatment (week 4); event defined as below 140 at baseline, and 500 nmol/L after 30-minutes. 3 children failed to attend for the final assessment and were replaced; unclear which group. Participants with an abnormal result at baseline were excluded from this review.
Marten 1980	Potent TCS versus mild TCS (group D versus group C)	0/3	1/4	Parallel-group; children; severe eczema. Plasma cortisol response to Synacthen at baseline and end of treatment (week 4); event defined as below 140 at baseline, and 500 nmol/L after 30-minutes. 3 children failed to attend for the final assessment and were replaced; unclear which group. Participants with an abnormal result at baseline were excluded from this review.
Queille 1984	Potent TCS versus mild TCS (groups D+E+F versus groups A+B)	9/13	0/8	Parallel-group; children; severe eczema. Individual plasma cortisol measurements converted to number of participants with levels outside a reference range (6-23 µg/dL or 170-635 nmol/L; Royal College, Canada) at any visit up to day 6. 8/9 participants were retest-

				ed at 30-180 days and 5 had returned to normal levels.
Vernon 1991	Once daily second-generation potent TCS versus twice daily mild TCS	0/23	1/24	Parallel-group; children; moderate to severe eczema. Morning plasma cortisol at baseline, week 1 and end of treatment (up to week 6). Event detected at week 1 (< 5.0 µg/dL) and was transient. N assumed

Analysis 2.12. Comparison 2: Potent versus mild-potency topical corticosteroid (TCS), Outcome 12: Included studies with unspecified adverse event data

Included studies with unspecified adverse event data

Study	Intervention and comparison	Comments
Gentry 1973	Potent TCS versus mild TCS	Parallel-group; unspecified age and severity. No adverse events were reported (up to week 4; n = 5)
Giannetti 1981	Potent TCS versus mild TCS	Within-participant; children; mild to moderate eczema. Implied both treatments were "optimally tolerated" (up to week 3; n = 20)
Sanabria-Silva 1991	Potent TCS versus mild TCS	Parallel-group; children; unknown severity; "adverse events were not observed after 4 weeks of treatment" (n = 30)
Savin 1976	Potent TCS versus mild TCS	Parallel-group; age unspecified; moderate-severity eczema (one was "very severe"). No adverse events were reported (up to week 3; n = 23)
Veien 1984	Potent TCS versus mild TCS	Within-participant; children; moderate to severe eczema. No serious side effects were reported (up to week 4; n = 40)
Wortzel 1975	Potent TCS versus mild TCS	Parallel-group; unspecified age or severity of eczema. Stated that "Serious side effects did not occur with [the potent] preparation. One patient among 207 tested with betamethasone dipropionate ointment manifested itching as a side effect." However it was unclear if this occurred in the trial we have included (n = 128; up to day 22)
Yasuda 1976	Potent TCS versus mild TCS	Within-participant; unspecified age and severity. Adverse events stated to be looked for in the methods, but nothing was reported (n = 29 (assumed)); up to 7 days)

Comparison 3. Potent versus moderate-potency topical corticosteroid (TCS)

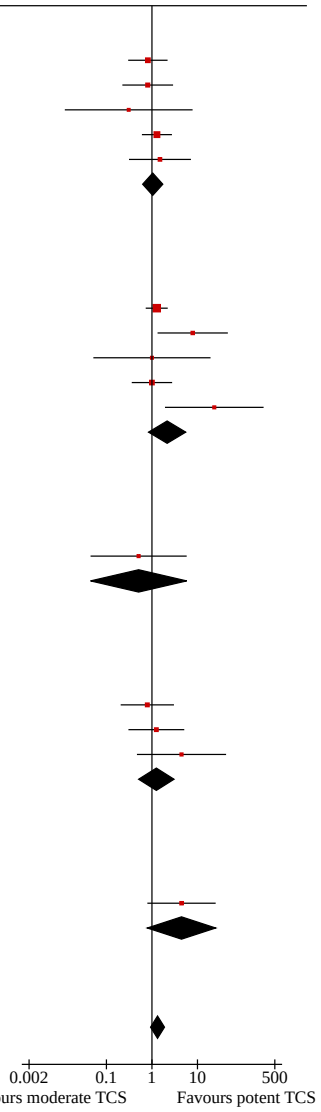
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Cleared or marked improvement on IGA (short term); all ages; all severities	15	1173	Odds Ratio (IV, Random, 95% CI)	1.33 [0.93, 1.89]
3.1.1 Potent TCS versus moderate TCS; parallel-group studies	5	510	Odds Ratio (IV, Random, 95% CI)	1.04 [0.63, 1.73]
3.1.2 Potent TCS versus moderate TCS; within-participant studies	5	180	Odds Ratio (IV, Random, 95% CI)	2.16 [0.84, 5.52]
3.1.3 Once daily potent TCS versus twice daily moderate TCS; parallel-group study	1	108	Odds Ratio (IV, Random, 95% CI)	0.51 [0.04, 5.79]
3.1.4 Once daily second-generation potent TCS versus twice daily moderate TCS; parallel-group studies	3	315	Odds Ratio (IV, Random, 95% CI)	1.25 [0.51, 3.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.5 Potent lipocream versus moderate-potency ointment; within-participant study	1	60	Odds Ratio (IV, Random, 95% CI)	4.46 [0.79, 25.10]
3.2 Cleared or marked improvement on IGA (short term); split by age; all severities	8		Odds Ratio (IV, Random, 95% CI)	Subtotals only
3.2.1 Adults	3	131	Odds Ratio (IV, Random, 95% CI)	3.43 [0.79, 14.86]
3.2.2 Children	6	482	Odds Ratio (IV, Random, 95% CI)	1.12 [0.50, 2.51]
3.3 Cleared or marked improvement on IGA (short term); all ages; moderate to severe eczema	9	770	Odds Ratio (IV, Random, 95% CI)	1.39 [0.86, 2.23]
3.4 SMD in investigator assessment of clinical signs (short term); all ages; all severities	3	39	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.70, 0.72]
3.4.1 Potent TCS versus moderate-potency TCS; children; parallel-group studies	2	33	Std. Mean Difference (IV, Random, 95% CI)	0.23 [-1.14, 1.60]
3.4.2 Potent TCS versus moderate-potency TCS; unspecified age; within-participant study	1	6	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-1.22, 1.05]
3.5 SMD in investigator assessment of clinical signs (end of treatment); all ages; all severities	3	21	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.62, 1.20]
3.5.1 Potent TCS versus moderate-potency TCS; children; parallel-group studies	2	17	Std. Mean Difference (IV, Random, 95% CI)	0.49 [-0.87, 1.85]
3.5.2 Potent TCS versus moderate-potency TCS; unspecified age; within-participant study	1	4	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-1.39, 1.39]
3.6 Number of participants with a greater IGA compared to the other group (short term); unspecified age; unspecified severity	2	200	Odds Ratio (IV, Random, 95% CI)	3.86 [2.42, 6.14]
3.7 Included studies with no poolable clinician-reported signs data	5		Other data	No numeric data
3.8 Included studies with no poolable patient-reported symptoms data	2		Other data	No numeric data
3.9 Number of participants with skin thinning or related signs; end of treatment	10		Other data	No numeric data
3.9.1 Skin thinning	6		Other data	No numeric data
3.9.2 Striae	1		Other data	No numeric data
3.9.3 Pigmentation change	4		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9.4 Increased capillary fragility	1		Other data	No numeric data
3.10 Number of participants with local site reactions; end of treatment	13		Other data	No numeric data
3.10.1 Burning	8		Other data	No numeric data
3.10.2 Stinging	2		Other data	No numeric data
3.10.3 Irritation	2		Other data	No numeric data
3.10.4 Sensitisation	1		Other data	No numeric data
3.10.5 Itching	5		Other data	No numeric data
3.10.6 Eruption	3		Other data	No numeric data
3.10.7 Papular eruption	3		Other data	No numeric data
3.10.8 Unspecified	1		Other data	No numeric data
3.11 Number of participants with skin infection; end of treatment	7		Other data	No numeric data
3.11.1 Folliculitis	2		Other data	No numeric data
3.11.2 Secondary infection	3		Other data	No numeric data
3.11.3 Impetigo contagiosa	2		Other data	No numeric data
3.12 Number of participants with abnormal cortisol	3		Other data	No numeric data

Analysis 3.1. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 1: Cleared or marked improvement on IGA (short term); all ages; all severities

Study or Subgroup	log[OR]	SE	Potent TCS Total	Moderate potency TCS Total	Weight	Odds Ratio IV, Random, 95% CI
3.1.1 Potent TCS versus moderate TCS; parallel-group studies						
Bluefarb 1976 (1)	-0.2058	0.508	103	96	10.4%	0.81 [0.30 , 2.20]
Lassus 1983 (2)	-0.2136	0.6543	20	20	6.7%	0.81 [0.22 , 2.91]
Rampini 1992b (3)	-1.1756	1.6486	38	40	1.2%	0.31 [0.01 , 7.81]
Ulrich 1991 (4)	0.2517	0.3871	81	84	15.9%	1.29 [0.60 , 2.75]
Van Del Rey 1983 (1)	0.4055	0.799	13	15	4.7%	1.50 [0.31 , 7.18]
Subtotal (95% CI)			**255**	**255**	**38.8%**	**1.04 [0.63 , 1.73]**
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 4 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
3.1.2 Potent TCS versus moderate TCS; within-participant studies						
Craps 1973 (5)	0.241162	0.283877676	50	50	24.2%	1.27 [0.73 , 2.22]
Cullen 1971 (6)	2.061423	0.906746714	12	12	3.7%	7.86 [1.33 , 46.46]
Innocenti 1977 (7)	0	1.511857892	3	3	1.4%	1.00 [0.05 , 19.36]
Roth 1978b (8)	0	0.520988072	19	19	9.9%	1.00 [0.36 , 2.78]
Ruiz 1976 (9)	3.152736	1.272167777	6	6	1.9%	23.40 [1.93 , 283.20]
Subtotal (95% CI)			**90**	**90**	**41.2%**	**2.16 [0.84 , 5.52]**
Heterogeneity: Tau² = 0.55; Chi² = 9.01, df = 4 (P = 0.06); I² = 56%						
Test for overall effect: Z = 1.60 (P = 0.11)						
3.1.3 Once daily potent TCS versus twice daily moderate TCS; parallel-group study						
Rampini 1992a (3)	-0.6741	1.2402	55	53	2.0%	0.51 [0.04 , 5.79]
Subtotal (95% CI)			**55**	**53**	**2.0%**	**0.51 [0.04 , 5.79]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
3.1.4 Once daily second-generation potent TCS versus twice daily moderate TCS; parallel-group studies						
Lebwohl 1999 (10)	-0.2343	0.6873	94	94	6.1%	0.79 [0.21 , 3.04]
Nolting 1991 (11)	0.2231	0.7204	33	34	5.6%	1.25 [0.30 , 5.13]
Rafanelli 1993 (12)	1.4955	1.1502	30	30	2.3%	4.46 [0.47 , 42.51]
Subtotal (95% CI)			**157**	**158**	**14.1%**	**1.25 [0.51 , 3.05]**
Heterogeneity: Tau² = 0.00; Chi² = 1.67, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.63)						
3.1.5 Potent lipocream versus moderate-potency ointment; within-participant study						
Rajka 1986 (13)	1.495494	0.881292526	30	30	3.9%	4.46 [0.79 , 25.10]
Subtotal (95% CI)			**30**	**30**	**3.9%**	**4.46 [0.79 , 25.10]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
Total (95% CI)			**587**	**586**	**100.0%**	**1.33 [0.93 , 1.89]**
Heterogeneity: Tau² = 0.05; Chi² = 15.76, df = 14 (P = 0.33); I² = 11%						
Test for overall effect: Z = 1.57 (P = 0.12)						
Test for subgroup differences: Chi² = 4.38, df = 4 (P = 0.36), I² = 8.7%						

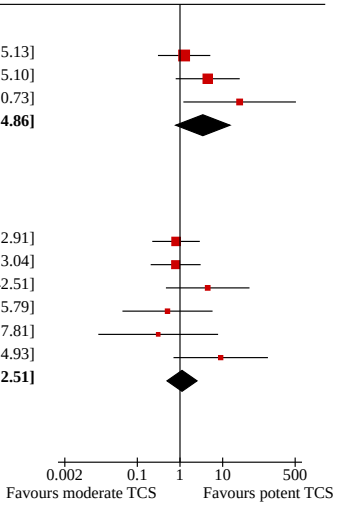


Footnotes

(1) Week 1.
(2) Week 2.
(3) Day 21.
(4) Week 2 (assumed).
(5) Day 14. Unit of analysis is side; variance is corrected.
(6) Week 2 (assumed). Unit of analysis is side; variance is corrected.
(7) Week 1. Unit of analysis is side; variance is corrected.
(8) Week 4 (assumed). Unit of analysis is side; variance is corrected.
(9) Up to week 4. Patients were consulted when judging the IGA. Unit of analysis is side; variance is corrected.
(10) Day 8. Number 100% cleared.
(11) Day 21. Unit of analysis is side; variance is corrected.
(12) Day 7.
(13) Up to week 4. Unit of analysis is side; variance is corrected.

Analysis 3.2. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 2: Cleared or marked improvement on IGA (short term); split by age; all severities

Study or Subgroup	log[OR]	SE	Favours moderate TCS Total	Moderate potency TCS Total	Weight	Odds Ratio IV, Random, 95% CI
3.2.1 Adults						
Nolting 1991 (1)	0.2231	0.7204	33	34	44.9%	1.25 [0.30 , 5.13]
Rajka 1986 (2)	1.495494	0.88129253	30	30	37.2%	4.46 [0.79 , 25.10]
Ruiz 1976 (3)	3.218876	1.54919334	2	2	17.9%	25.00 [1.20 , 520.73]
Subtotal (95% CI)			**65**	**66**	**100.0%**	**3.43 [0.79 , 14.86]**
Heterogeneity: Tau² = 0.73; Chi² = 3.53, df = 2 (P = 0.17); I² = 43%						
Test for overall effect: Z = 1.65 (P = 0.10)						
3.2.2 Children						
Lassus 1983 (4)	-0.2136	0.6543	20	20	32.2%	0.81 [0.22 , 2.91]
Lebwohl 1999 (5)	-0.2343	0.6873	94	94	29.7%	0.79 [0.21 , 3.04]
Rafanelli 1993 (6)	1.4955	1.1502	30	30	12.0%	4.46 [0.47 , 42.51]
Rampini 1992a (7)	-0.6741	1.2402	55	53	10.4%	0.51 [0.04 , 5.79]
Rampini 1992b (7)	-1.1756	1.6486	38	40	6.1%	0.31 [0.01 , 7.81]
Ruiz 1976 (8)	2.197225	1.29957258	4	4	9.5%	9.00 [0.70 , 114.93]
Subtotal (95% CI)			**241**	**241**	**100.0%**	**1.12 [0.50 , 2.51]**
Heterogeneity: Tau² = 0.10; Chi² = 5.53, df = 5 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Test for subgroup differences: Chi² = 1.73, df = 1 (P = 0.19), I² = 42.1%						

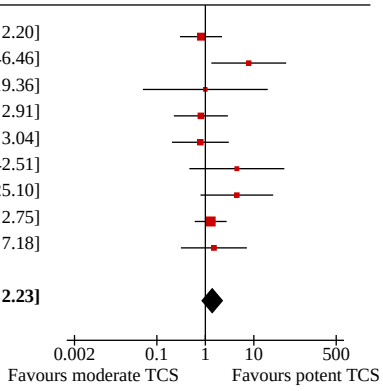


Footnotes

(1) Day 21. Unit of analysis is side; variance is corrected.
(2) Up to week 4. Unit of analysis is side; variance is corrected.
(3) Up to week 4. Patients were consulted when judging the IGA. Unit of analysis is side; variance is corrected.
(4) Week 2.
(5) Day 8. Number 100% cleared.
(6) Day 7.
(7) Day 21.
(8) As above.

Analysis 3.3. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 3: Cleared or marked improvement on IGA (short term); all ages; moderate to severe eczema

Study or Subgroup	log[OR]	SE	Potent TCS Total	Moderate TCS Total	Weight	Odds Ratio IV, Random, 95% CI
Bluefarb 1976 (1)	-0.2058	0.508	103	96	18.8%	0.81 [0.30 , 2.20]
Cullen 1971 (2)	2.0614	0.90674671	12	12	6.8%	7.86 [1.33 , 46.46]
Innocenti 1977 (3)	0	1.51185789	3	3	2.5%	1.00 [0.05 , 19.36]
Lassus 1983 (4)	-0.2136	0.6543	20	20	12.2%	0.81 [0.22 , 2.91]
Lebwohl 1999 (5)	-0.2343	0.6873	94	94	11.2%	0.79 [0.21 , 3.04]
Rafanelli 1993 (6)	1.4955	1.1502	30	30	4.3%	4.46 [0.47 , 42.51]
Rajka 1986 (7)	1.495494	0.88129253	30	30	7.1%	4.46 [0.79 , 25.10]
Ulrich 1991 (8)	0.2517	0.3871	81	84	28.5%	1.29 [0.60 , 2.75]
Van Del Rey 1983 (1)	0.4055	0.799	13	15	8.5%	1.50 [0.31 , 7.18]
Total (95% CI)			**386**	**384**	**100.0%**	**1.39 [0.86 , 2.23]**
Heterogeneity: Tau² = 0.06; Chi² = 8.98, df = 8 (P = 0.34); I² = 11%						
Test for overall effect: Z = 1.33 (P = 0.18)						
Test for subgroup differences: Not applicable						

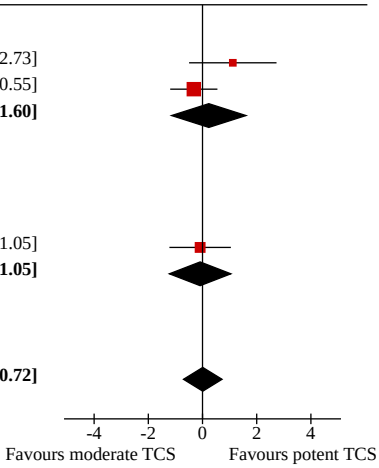


Footnotes

(1) Week 1.
(2) Week 2 (assumed). Unit of analysis is side; variance is corrected.
(3) Week 1. Unit of analysis is side; variance is corrected.
(4) Week 2.
(5) Day 8. Number 100% cleared.
(6) Day 7.
(7) Up to week 4. Unit of analysis is side; variance is corrected.
(8) Week 2 (assumed).

Analysis 3.4. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 4: SMD in investigator assessment of clinical signs (short term); all ages; all severities

Study or Subgroup	SMD	SE	Potent TCS Total	Moderate TCS Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.4.1 Potent TCS versus moderate-potency TCS; children; parallel-group studies						
Queille 1984 (1)	1.118	0.8231	10	2	17.7%	1.12 [-0.50 , 2.73]
Wolkerstorfer 1998 (2)	-0.321	0.4444	12	9	49.6%	-0.32 [-1.19 , 0.55]
Subtotal (95% CI)			**22**	**11**	**67.3%**	**0.23 [-1.14 , 1.60]**
Heterogeneity: Tau² = 0.60; Chi² = 2.37, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 0.33 (P = 0.74)						
3.4.2 Potent TCS versus moderate-potency TCS; unspecified age; within-participant study						
Henrijean 1983 (3)	-0.087791	0.5784616	3	3	32.7%	-0.09 [-1.22 , 1.05]
Subtotal (95% CI)			**3**	**3**	**32.7%**	**-0.09 [-1.22 , 1.05]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
Total (95% CI)			**25**	**14**	**100.0%**	**0.01 [-0.70 , 0.72]**
Heterogeneity: Tau² = 0.07; Chi² = 2.38, df = 2 (P = 0.30); I² = 16%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.72), I² = 0%						



Footnotes

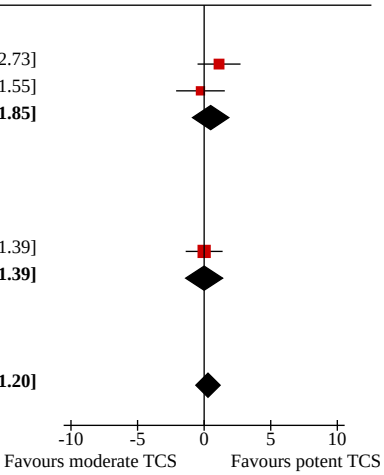
(1) Groups D+E+F versus group C. Day 6. Decrease in unnamed scale from baseline. Severe eczema

(2) Week 1. Decrease in ObjSCORAD from baseline. Once daily potent TCS versus twice daily moderate TCS. Moderate severity eczema.

(3) Day 7. Decrease in unnamed scale from baseline. Unspecified severity eczema. Unit of analysis is side; variance is corrected.

Analysis 3.5. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 5: SMD in investigator assessment of clinical signs (end of treatment); all ages; all severities

Study or Subgroup	SMD	SE	Potent TCS Total	Moderate TCS Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.5.1 Potent TCS versus moderate-potency TCS; children; parallel-group studies						
Queille 1984 (1)	1.118	0.8231	10	2	31.9%	1.12 [-0.50 , 2.73]
Wolkerstorfer 1998 (2)	-0.2766	0.9324	3	2	24.9%	-0.28 [-2.10 , 1.55]
Subtotal (95% CI)			**13**	**4**	**56.8%**	**0.49 [-0.87 , 1.85]**
Heterogeneity: Tau² = 0.20; Chi² = 1.26, df = 1 (P = 0.26); I² = 20%						
Test for overall effect: Z = 0.71 (P = 0.48)						
3.5.2 Potent TCS versus moderate-potency TCS; unspecified age; within-participant study						
Henrijean 1983 (3)	0	0.7071068	2	2	43.2%	0.00 [-1.39 , 1.39]
Subtotal (95% CI)			**2**	**2**	**43.2%**	**0.00 [-1.39 , 1.39]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)			**15**	**6**	**100.0%**	**0.29 [-0.62 , 1.20]**
Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 2 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.62 (P = 0.54)						
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%						



Footnotes

(1) Groups D+E+F versus group C. Day 6. Decrease in unnamed scale from baseline. Severe eczema

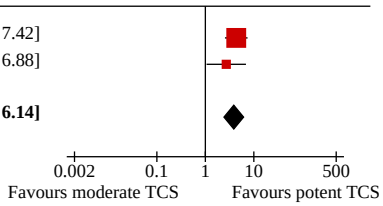
(2) Week 4. Decrease in ObjSCORAD from baseline. Once daily potent TCS versus twice daily moderate TCS. Moderate severity eczema.

(3) Day 14. Decrease in unnamed scale from baseline. Unspecified severity. Unit of analysis is side; variance is corrected.

Analysis 3.6. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 6: Number of participants with a greater IGA compared to the other group (short term); unspecified age; unspecified severity

Study or Subgroup	log[OR]	SE	Potent TCS Total	Moderate TCS Total	Weight	Odds Ratio IV, Random, 95% CI
Munro 1967 (1)	1.467398	0.27374626	66	66	75.2%	4.34 [2.54 , 7.42]
Stewart 1973 (2)	0.993252	0.47699794	34	34	24.8%	2.70 [1.06 , 6.88]
Total (95% CI)			**100**	**100**	**100.0%**	**3.86 [2.42 , 6.14]**

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 5.69 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Day 7. Manually calculated. Unit of analysis is side; variance is corrected.
(2) Week 1. Unit of analysis is side; variance is corrected.

Analysis 3.7. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 7: Included studies with no poolable clinician-reported signs data

Included studies with no poolable clinician-reported signs data

Study	Intervention and comparison	Comments
Allenby 1981	Potent TCS versus moderate TCS	Within-participant; unspecified age and severity of eczema. Both local steroids were stated to be effective and no differences between them were demonstrated at around day 7 (n = 33)
Sefton 1984a	Potent TCS (triamcinolone acetonide) versus moderate TCS (hydrocortisone valerate)	Within-participant; unspecified age; mild- to moderate-severity eczema. Mean decrease in IGA (scale of 0-100) from baseline; no dispersion. 22.5 using potent TCS compared to 26.4 using moderate TCS at day 7 (n = 37). 33.4 using potent TCS compared to 30.8 using moderate TCS at day 14 (n = 36)
Sefton 1984b	Potent TCS (triamcinolone acetonide) versus moderate TCS (betamethasone valerate)	Within-participant; unspecified age; mild - to moderate-severity eczema. Mean decrease in IGA (scale of 0-100) from baseline; no dispersion. 28.9 using potent TCS compared to 28.6 using moderate TCS at day 7 (n = 62). 32.7 using potent TCS compared to 31.5 using moderate TCS at day 14 (n = 65)
Sefton 1984c	Potent TCS (fluocinolone acetonide) versus moderate TCS (hydrocortisone valerate)	Within-participant; unspecified age; mild- to moderate-severity eczema. Mean decrease in IGA (scale of 0-100) from baseline; no dispersion. 19.1 using potent TCS compared to 17.9 using moderate TCS at day 7 (n = 26). 22.3 using potent TCS compared to 22.4 using moderate TCS at day 14 (n = 25)
Wolkerstorfer 1998	Once daily second-generation potent TCS versus twice daily moderate-potency TCS	Parallel-group; children; moderate-severity eczema. Short-term and end of treatment values are included in Analysis 3.4 and Analysis 3.5, respectively. At end of follow-up (week 6; 2 weeks post-treatment follow-up) mean decrease in ObjSCORAD was 6 ± 7.98 in the once daily potent group compared to 11 ± 6.42 in the twice daily moderate group; MD = −5.00 (95% CI −17.67 to 7.67; n = 5). Some discrepancies were noted where data were presented in both tables and figures

Analysis 3.8. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 8: Included studies with no poolable patient-reported symptoms data

Included studies with no poolable patient-reported symptoms data

Study	Intervention and comparison	Comments
Munro 1967	Potent TCS versus moderate TCS	Within-participant; unspecified age and severity. Number judging potent TCS to be superior was 35 of 66 participants at around day 7. Manually calculated

Rafanelli 1993	Once daily second-generation potent TCS versus older moderate TCS	Parallel-group; children; moderate to severe eczema. Patient global assessment was stated to be consistent with the investigator global assessment (Analysis 3.1)

Analysis 3.9. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 9: Number of participants with skin thinning or related signs; end of treatment

Number of participants with skin thinning or related signs; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Skin thinning								
Cullen 1971	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; moderate to severe eczema	Up to week 2	0/12	0/12	
Innocenti 1977	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; moderate to severe eczema	Up to week 1	0/3	0/3	
Lebwohl 1999	Parallel- group	Once daily second-generation potent	Twice daily moderate	Children; moderate to severe eczema	Up to day 22	0/109	0/110	
Nolting 1991	Parallel- group	Once daily second-generation potent	Twice daily moderate	Adults; unspecified severity eczema	Up to week 3	2/33	2/34	
Rafanelli 1993	Parallel- group	Once daily second-generation potent	Twice daily moderate	Children; moderate to severe eczema	Up to week 3	0/30	0/30	
Ulrich 1991	Parallel- group	Potent TCS	Moderate TCS	All ages; moderate to severe eczema	Up to week 2 (assumed).	0/81	0/84	
Striae								
Van Del Rey 1983	Parallel- group	Potent TCS	Moderate TCS	Adults and children; moderate to severe eczema	Up to week 3	0/14	0/15	
Pigmentation change								
Cullen 1971	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; moderate to severe eczema	Up to week 2	0/12	0/12	
Sefton 1984a	Within- participant	Potent TCS	Moderate TCS	Unspecified; mild to moderate eczem	Up to week 2	0/39	0/39	Hypopigmentation
Sefton 1984b	Within- participant	Potent TCS	Moderate TCS	Unspecified; mild to moderate eczema	Up to week 2	0/75	0/75	Hypopigmentation
Sefton 1984c	Within- participant	Potent TCS	Moderate TCS	Unspecified; mild to moderate eczema	Up to week 2	1/31	1/31	Hypopigmentation
Increased capillary fragility								
Cullen 1971	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; moderate to severe eczema	Up to week 2	0/12	0/12	

Analysis 3.10. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 10: Number of participants with local site reactions; end of treatment

Number of participants with local site reactions; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Burning								

Busch-Heidger 1993	Parallel- group	Potent TCS	Moderate TCS	Adults; unspecified severity eczema	Up to 5 weeks	1/38	0/37	Potent event was mild
Cullen 1971	Within- participant	Potent TCS	Moderate TCS	Unspecified age; moderate to severe eczema	Up to week 2	0/12	0/12	
Rampini 1992a	Parallel- group	Once daily potent TCS	Twice daily moderate TCS	Children; unspecified severity eczema	Up to day 21	0/55	0/53	
Rampini 1992b	Parallel- group	Potent TCS	Moderate TCS	Children; unspecified severity eczema	Up to day 21	5/38	3/40	Mild; did not cause discontinuation
Roth 1978b	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; unspecified severity eczema	Up to 4 weeks	2/19	1/19	One participant reported brief burning on both sides, the other only with betamethasone
Sefton 1984a	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	0/39	1/39	
Sefton 1984b	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	0/75	1/75	
Sefton 1984c	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	1/31	0/31	
Stinging								
Lassus 1983	Parallel- group	Potent TCS	Moderate TCS	Children; moderate to severe eczema	Up to week 2	1/20	2/20	Judged treatment-related by the investigator. Mild; < 15 minutes
Roth 1978b	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; unspecified severity eczema	Up to 4 weeks	0/19	1/19	
Irritation								
Bluefarb 1976	Parallel- group	Potent TCS	Moderate TCS	Mostly adults; moderate to severe eczema	Up to week 3 (check)	0/103	1/98	Quote: "Could be construed as idiosyncratic reactions in sensitive patients."
Van Del Rey 1983	Parallel- group	Potent TCS	Moderate TCS	Adults and children; moderate to severe eczema	Up to week 3	0/14	0/15	
Sensitisation								
Van Del Rey 1983	Parallel- group	Potent TCS	Moderate TCS	Adults and children; moderate to severe eczema	Up to week 3	0/14	0/15	
Itching								
Rajka 1986	Within- participant	Potent lipocream	Moderate ointment	Adults; moderate to severe eczema	Up to week 4	2/30	2/30	One participant had "slight itching mainly on the side treated with desonide ointment" the other slight itching immediately after application of

								both preparations
Roth 1978b	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; unspecified severity eczema	Up to 4 weeks	0/19	0/19	
Sefton 1984a	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	1/39	2/39	
Sefton 1984b	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	3/75	1/75	
Sefton 1984c	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	2/31	2/31	
Eruption								
Sefton 1984a	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	1/39	1/39	
Sefton 1984b	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	0/75	0/75	
Sefton 1984c	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	0/31	0/31	
Papular eruption								
Sefton 1984a	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	1/39	1/39	
Sefton 1984b	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	0/75	0/75	
Sefton 1984c	Within- participant	Potent TCS	Moderate TCS	Unspecified ages; mild to moderate eczema	Up to week 2	0/31	0/31	
Unspecified								
Lebwohl 1999	Parallel- group	Once daily second-generation potent TCS	Twice daily moderate TCS	Children; moderate to severe eczema	Up to day 22	4/109	2/110	

Analysis 3.11. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 11: Number of participants with skin infection; end of treatment

Number of participants with skin infection; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Folliculitis								
Cullen 1971	Within- participant	Potent TCS	Moderate TCS	Unspecified age; moderate to severe eczema	Up to week 2	0/12	0/12	
Van Del Rey 1983	Parallel- group	Potent TCS	Moderate TCS	Adults and children; moderate to severe eczema	Up to week 3	0/14	0/15	
Secondary infection								

Sefton 1984a	Within- participant	Potent TCS	Moderate TCS	Unspecified age; mild to moderate eczema	Up to week 2	0/39	0/39
Sefton 1984b	Within- participant	Potent TCS	Moderate TCS	Unspecified age; mild to moderate eczema	Up to week 2	0/75	0/75
Sefton 1984c	Within- participant	Potent TCS	Moderate TCS	Unspecified age; mild to moderate eczema	Up to week 2	1/31	1/31
Impetigo contagiosa							
Rampini 1992a	Parallel- group	Once daily potent TCS	Twice daily moderate TCS	Children; unspecified severity eczema	Up to day 21	1/55	0/53
Rampini 1992b	Parallel- group	Potent TCS	Moderate TCS	Children; unspecified severity eczema	Up to day 21	0/38	0/40

Analysis 3.12. Comparison 3: Potent versus moderate-potency topical corticosteroid (TCS), Outcome 12: Number of participants with abnormal cortisol

Number of participants with abnormal cortisol

Study	Intervention and comparison	Cases/N A	Cases/N B	Additional information
Queille 1984	Potent TCS versus moderate TCS (groups D+E+F versus group C)	9/13	0/5	Children; severe eczema. Individual plasma cortisol measurements converted to number of participants with levels outside a reference range (6-23 µg/dL or 170-635 nmol/L; Royal College, Canada) at any visit up to day 6. 8/9 participants were retested at 30-180 days and 5 had returned to normal levels.
Rafanelli 1993	Once daily second-generation potent versus twice daily moderate TCS	0/30	0/30	Children; moderate to severe eczema. Blood cortisol at baseline and week 3
Wolkerstorfer 1998	Once daily second-generation potent TCS versus twice daily moderate TCS	0/12	1/9	Children; moderate to severe eczema. Urinary cortisol excretion at baseline and end of treatment (week 4). One participant decreased from 162.8 nmol/24 h at baseline to 67 nmol/24 h at end of treatment, and returned to normal by two weeks' post-treatment follow-up. N assumed

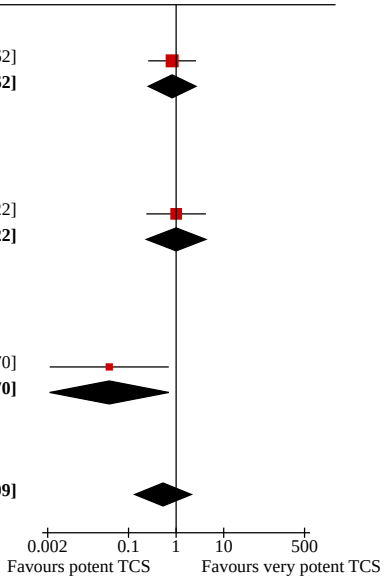
Comparison 4. Very potent versus potent topical corticosteroid (TCS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Cleared or marked improvement on IGA (short term); all ages; all severities	3	243	Odds Ratio (IV, Random, 95% CI)	0.53 [0.13, 2.09]
4.1.1 Very potent TCS versus potent TCS; parallel-group study	1	117	Odds Ratio (IV, Random, 95% CI)	0.82 [0.26, 2.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.2 Very potent TCS versus potent TCS; within-participant study	1	54	Odds Ratio (IV, Random, 95% CI)	1.00 [0.24, 4.22]
4.1.3 Once daily very potent TCS versus three times daily potent TCS; parallel-group study	1	72	Odds Ratio (IV, Random, 95% CI)	0.04 [0.00, 0.70]
4.2 Number of participants with a greater IGA compared to the other group (short term); unspecified age and severity	1	796	Odds Ratio (IV, Random, 95% CI)	1.68 [1.00, 2.83]
4.3 Included studies with no poolable clinician-reported signs data	2		Other data	No numeric data
4.4 Included studies with no poolable patient-reported symptoms data	1		Other data	No numeric data
4.5 Number of participants with skin thinning and related signs; end of treatment	2		Other data	No numeric data
4.6 Number of participants with local site reactions; end of treatment	2		Other data	No numeric data
4.7 Number of participants with systemic adverse effects	1		Other data	No numeric data

Analysis 4.1. Comparison 4: Very potent versus potent topical corticosteroid (TCS), Outcome 1: Cleared or marked improvement on IGA (short term); all ages; all severities

Study or Subgroup	log[OR]	SE	Very potent TCS Total	Potent TCS Total	Weight	Odds Ratio IV, Random, 95% CI
4.1.1 Very potent TCS versus potent TCS; parallel-group study						
Yawalkar 1991 (1)	-0.1926	0.59	58	59	44.9%	0.82 [0.26 , 2.62]
Subtotal (95% CI)			**58**	**59**	**44.9%**	**0.82 [0.26 , 2.62]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
4.1.2 Very potent TCS versus potent TCS; within-participant study						
Bleeker 1975 (2)	0	0.73484692	27	27	38.2%	1.00 [0.24 , 4.22]
Subtotal (95% CI)			**27**	**27**	**38.2%**	**1.00 [0.24 , 4.22]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
4.1.3 Once daily very potent TCS versus three times daily potent TCS; parallel-group study						
Harder 1983 (3)	-3.2356	1.4695	38	34	16.9%	0.04 [0.00 , 0.70]
Subtotal (95% CI)			**38**	**34**	**16.9%**	**0.04 [0.00 , 0.70]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						
Total (95% CI)			**123**	**120**	**100.0%**	**0.53 [0.13 , 2.09]**
Heterogeneity: Tau² = 0.74; Chi² = 4.14, df = 2 (P = 0.13); I² = 52%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Test for subgroup differences: Chi² = 4.14, df = 2 (P = 0.13), I² = 51.7%						

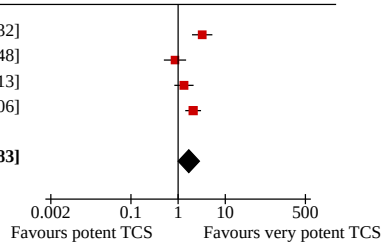


Footnotes

(1) Authors suggest day 11, however visits were between 12 and 17 days.
(2) Week 2. Unit of analysis is side; variance is corrected.
(3) Week 1.

Analysis 4.2. Comparison 4: Very potent versus potent topical corticosteroid (TCS), Outcome 2: Number of participants with a greater IGA compared to the other group (short term); unspecified age and severity

Study or Subgroup	log[OR]	SE	Very potent TCS Total	Potent TCS Total	Weight	Odds Ratio IV, Random, 95% CI
Sparkes 1974 (1)	1.175573	0.25337232	96	96	24.5%	3.24 [1.97 , 5.32]
Sparkes 1974 (2)	-0.15287	0.27684372	74	74	23.5%	0.86 [0.50 , 1.48]
Sparkes 1974 (3)	0.284837	0.23954679	87	87	25.1%	1.33 [0.83 , 2.13]
Sparkes 1974 (4)	0.733785	0.1965501	141	141	26.9%	2.08 [1.42 , 3.06]
Total (95% CI)			**398**	**398**	**100.0%**	**1.68 [1.00 , 2.83]**
Heterogeneity: Tau² = 0.22; Chi² = 14.63, df = 3 (P = 0.002); I² = 80%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Not applicable						



Footnotes

(1) As above. Treatment D versus E or F.
(2) As above. Treatment A versus G.
(3) As above. Treatment D versus G.
(4) Around 7 days. Visual approximation (figure too poor for digital extraction). Unit of analysis is side; variance is corrected. Treatment A versus B or C.

Analysis 4.3. Comparison 4: Very potent versus potent topical corticosteroid (TCS), Outcome 3: Included studies with no poolable clinician-reported signs data

Included studies with no poolable clinician-reported signs data

Study	Intervention and comparison	Comments
Goh 1999	Very potent TCS twice daily versus potent second-generation TCS once daily	Within-participant study, not included in the meta-analysis as thought to be **clinically incomparable** owing to the use of the more potent TCS more fre-

		quently than the less potent TCS. Adults with moderate and severe eczema (n = 58). At day 8 the number achieving cleared or marked improvement on IGA was 9 on the side treated with twice daily very potent TCS compared to 5 on the side treated with once daily second-generation potent TCS; OR 1.95 (95% CI 0.85 to 4.48). At day 22, number achieving cleared or marked improvement was 41 on the side treated with twice daily very potent TCS compared to 16 on the side treated with once daily second-generation potent TCS; OR 6.33 (95% CI 3.58 to 11.20)
Guttman-Yassky 2017	Very potent TCS once daily versus potent TCS once daily	Within-participant study, not included in the meta-analyses because it reported IGA data as a continuous instead of a dichotomous outcome. Adults with mild to moderate eczema (n = 29). At day 8, the mean change was −0.967 (95% CI (assumed) −1.275 to −0.659) on lesions treated with very potent TCS compared to −0.932 (−1.240 to −0.625) on lesions treated with potent TCS; MD −0.04 (95% CI −0.33 to 0.26). At end of treatment (day 15) mean change in IGA was −1.656 (−1.964 to −1.349) on lesions treated with very potent TCS compared to −1.588 (−1.895 to −1.280) on lesions treated with potent TCS; MD −0.07 (95% CI −0.36 to 0.23)

Analysis 4.4. Comparison 4: Very potent versus potent topical corticosteroid (TCS), Outcome 4: Included studies with no poolable patient-reported symptoms data

Included studies with no poolable patient-reported symptoms data

Study	Intervention and comparison	Comment
Goh 1999	Very potent TCS twice daily versus potent second-generation TCS once daily	Within-participant study. Adults with moderate to severe eczema (n = 58). At day 8, the number of participants reporting an excellent response on the side treated with very potent TCS was 9 compared to 3 for the side treated with potent TCS; OR 3.37 (95% CI 1.22 to 9.29; n = 58). At day 22, 25 participants reported an excellent response on the side treated with very potent TCS compared to 6 treated with potent TCS; OR 6.57 (95% CI 3.14 to 13.74; n = 58)

Analysis 4.5. Comparison 4: Very potent versus potent topical corticosteroid (TCS), Outcome 5: Number of participants with skin thinning and related signs; end of treatment

Number of participants with skin thinning and related signs; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Goh 1999	Within- participant	Very potent TCS twice daily	Potent second-generation TCS once daily	Adults; moderate to severe eczema	Up to day 22	0/58	0/58	
Yawalkar 1991	Parallel-group	Very potent TCS twice daily	Potent TCS twice daily	Adults; moderate to severe eczema	Up to week 2	0/58	0/59	

Analysis 4.6. Comparison 4: Very potent versus potent topical corticosteroid (TCS), Outcome 6: Number of participants with local site reactions; end of treatment

Number of participants with local site reactions; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Goh 1999	Within-participant	Very potent TCS twice daily	Second generation-potent TCS once daily	Adults; moderate to severe eczema	Up to day 22	0/58	0/58	"No side effects were observed on any

								of the treated sites"
Yawalkar 1991	Parallel group	Very potent TCS twice daily	Potent TCS twice daily	Adults; moderate to severe eczema	Up to week 2	5/58	2/59	Included dryness and itching. One participant per group discontinued due to severe dryness

Analysis 4.7. Comparison 4: Very potent versus potent topical corticosteroid (TCS), Outcome 7: Number of participants with systemic adverse effects

Number of participants with systemic adverse effects

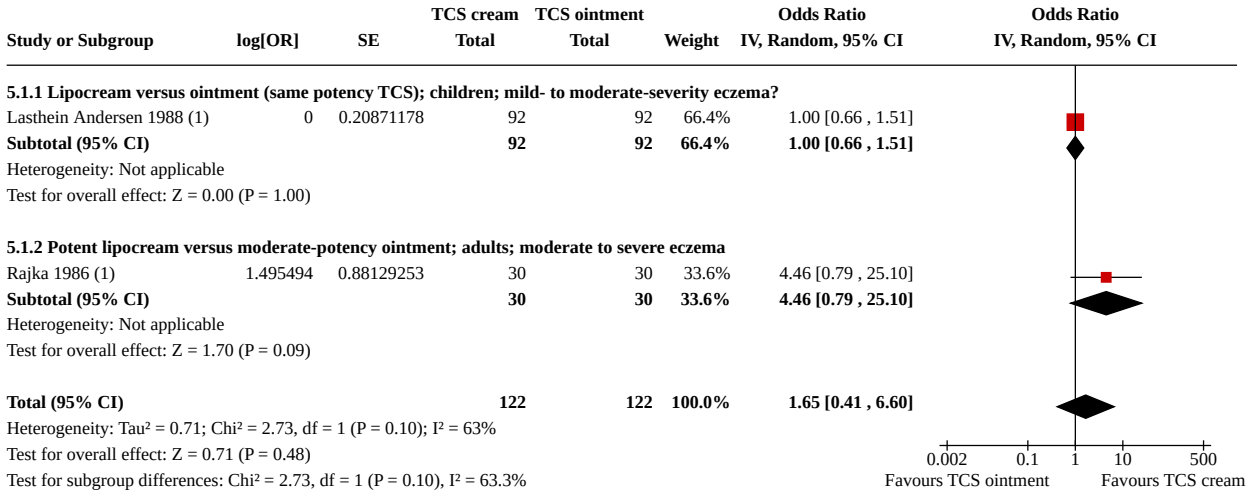
Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Yawalkar 1991	Parallel-group	Very potent TCS twice daily	Potent TCS twice daily	Adults; moderate to severe eczema	Up to week 2	0/58	0/59	None

Comparison 5. Topical corticosteroid (TCS) cream versus TCS ointment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Cleared or marked improvement on IGA (short term and end of treatment); within-participant studies	2	244	Odds Ratio (IV, Random, 95% CI)	1.65 [0.41, 6.60]
5.1.1 Lipocream versus ointment (same potency TCS); children; mild- to moderate-severity eczema?	1	184	Odds Ratio (IV, Random, 95% CI)	1.00 [0.66, 1.51]
5.1.2 Potent lipocream versus moderate-potency ointment; adults; moderate to severe eczema	1	60	Odds Ratio (IV, Random, 95% CI)	4.46 [0.79, 25.10]
5.2 Included studies with no poolable clinician-reported signs data	5		Other data	No numeric data
5.3 Number of participants with skin thinning or related signs; end of treatment	2		Other data	No numeric data
5.3.1 Skin thinning	1		Other data	No numeric data
5.3.2 Telangiectasia	1		Other data	No numeric data
5.3.3 Striae	1		Other data	No numeric data
5.4 Number of participants with local site reactions; end of treatment	4		Other data	No numeric data
5.4.1 Burning	2		Other data	No numeric data
5.4.2 Itching	1		Other data	No numeric data
5.4.3 Stinging	1		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4.4 Other	1		Other data	No numeric data
5.5 Number of participants with skin infection	3		Other data	No numeric data
5.5.1 Folliculitis	2		Other data	No numeric data
5.5.2 Skin infection	2		Other data	No numeric data
5.5.3 Pustules	1		Other data	No numeric data

Analysis 5.1. Comparison 5: Topical corticosteroid (TCS) cream versus TCS ointment, Outcome 1: Cleared or marked improvement on IGA (short term and end of treatment); within-participant studies



Footnotes

(1) Up to week 4. Unit of analysis is side; variance is corrected.

Analysis 5.2. Comparison 5: Topical corticosteroid (TCS) cream versus TCS ointment, Outcome 2: Included studies with no poolable clinician-reported signs data

Included studies with no poolable clinician-reported signs data

Study	Intervention and comparison	Comments
Berth-Jones 2003	Twice daily TCS cream versus twice daily TCS ointment (group B versus group D)	Parallel-group; adults and children; moderate to severe eczema. Number of participants with TIS ≤ 1. After 4-week stabilisation phase 76 of 91 participants achieved remission using 0.05% fluticasone cream compared to 94 of 90 using 0.005% fluticasone ointment; OR 2.06 (95% CI 1.00 to 4.22; n = 181)
Berth-Jones 2003	Once daily TCS cream versus once daily TCS ointment (group A versus group C)	Parallel-group; adults and children; moderate to severe eczema. Number of participants with TIS ≤ 1. After the 4-week stabilisation phase 76 of 95 participants achieved remission using 0.05% fluticasone cream compared to 77 of 100 using 0.005% fluticasone ointment; OR 1.19 (95% CI 0.60 to 2.37; n = 195)
Cadmus 2019	TCS cream versus TCS ointment (both under wet wraps)	Within-participant; children; all eczema severities. Mean difference in IGA at day 3-5 was 0.13 (95% CI −0.07 to 0.33; n = 39)

EUCTR2009-012028-98-DE	TCS cream versus TCS ointment	Parallel-group; adults; all severities (modified EASI > 6). Decrease in modified EASI from baseline. Mean difference at day 21 was 0.40 (95% CI −4.79 to 5.59; n = 50 assumed)
Kaplan 1978	TCS cream versus TCS ointment	Parallel-group; unspecified age and severity eczema. Mean IGA; no dispersion. 55.9% reduction in cream group compared to 31.4% in ointment group at week 3 (n = 58; P < 0.05)
Wilson 2009	TCS ointment versus TCS lipocream versus TCS cream	Parallel-group; adults; mild to moderate eczema. No significant difference in EASI at week 2 (Kruskal-Wallis P < 0.05; n = 20)

Analysis 5.3. Comparison 5: Topical corticosteroid (TCS) cream versus TCS ointment, Outcome 3: Number of participants with skin thinning or related signs; end of treatment

Number of participants with skin thinning or related signs; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Skin thinning								
EUCTR2009-012028-98-DE	Parallel-group	TCS cream	TCS ointment	Adults; mild to severe eczema	Up to day 21	0/25	0/25	N assumed
Telangiectasia								
Berth-Jones 2003	Parallel-group	Twice daily TCS cream (group B)	Twice daily TCS ointment (group D)	Adults and children; moderate to severe eczema	Up to 4 weeks (acute phase)	1/91	0/90	
Berth-Jones 2003	Parallel-group	Once daily TCS cream (group A)	Once daily TCS ointment (group C)	Adults and children; moderate to severe eczema	Up to 4 weeks (acute phase)	0/95	1/100	
Striae								
Berth-Jones 2003	Parallel-group	Twice daily TCS cream (group B)	Twice daily TCS ointment (group D)	Adults and children; moderate to severe eczema	Up to 4 weeks (acute phase)	0/91	0/90	
Berth-Jones 2003	Parallel-group	Once daily TCS cream (group A)	Once daily TCS ointment (group C)	Adults and children; moderate to severe eczema	Up to 4 weeks (acute phase)	0/95	1/100	

Analysis 5.4. Comparison 5: Topical corticosteroid (TCS) cream versus TCS ointment, Outcome 4: Number of participants with local site reactions; end of treatment

Number of participants with local site reactions; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Burning								
Cadmus 2019	Within-participant	TCS cream	TCS ointment	Children; unspecified severity eczema	Up to day 5	5/39	2/39	
Kaplan 1978	Parallel-group	Potent TCS cream	Mild TCS ointment	Unspecified	Up to week 3	0/30	1/30	Burning with immediate drying; resulted in discontinuation
Itching								
Rajka 1986	Within- participant	Potent lipocream	Moderate ointment	Adults; moderate to severe eczema	Up to week 4	2/30	2/30	One participant had "slight itching mainly on the side treated with desonide ointment" the

								other slight itching immediately after application of both preparations.
Stinging								
Cadmus 2019	Within-participant	TCS cream	TCS ointment	Children; unspecified severity eczema	Up to day 5	4/39	0/39	
Other								
EUC-TR2009-012028-98-DE	Parallel-group	TCS cream	TCS ointment	Adults; mild to severe eczema	Up to day 21	2/25	0/25	N assumed. Quote: "subjective ('application site pruritus' and 'skin tightness') symptoms, showed no objective signs and were resolved after one day or in one case after 14-day duration, with no AE related alterations of the use of study medication."

Analysis 5.5. Comparison 5: Topical corticosteroid (TCS) cream versus TCS ointment, Outcome 5: Number of participants with skin infection

Number of participants with skin infection

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Folliculitis								
Cadmus 2019	Within-participant	TCS cream	TCS ointment	Children; unspecified severity eczema	Up to day 5	0/39	0/39	
EUC-TR2009-012028-98-DE	Parallel-group	TCS cream	TCS ointment	Adults; mild to severe eczema	Up to day 21	0/25	0/25	N assumed
Skin infection								
Cadmus 2019	Within-participant	TCS cream	TCS ointment	Children; unspecified severity eczema	Up to day 5	0/39	0/39	
EUC-TR2009-012028-98-DE	Parallel-group	TCS cream	TCS ointment	Adults; mild to severe eczema	Up to day 21	0/25	0/25	N assumed
Pustules								
Lasthein Andersen 1988	Within-participant	Mild TCS cream	Mild TCS ointment	Children; mild- to moderate-severity eczema	Up to week 4	0/92	1/92	

Comparison 6. Second-generation versus older topical corticosteroid (TCS)

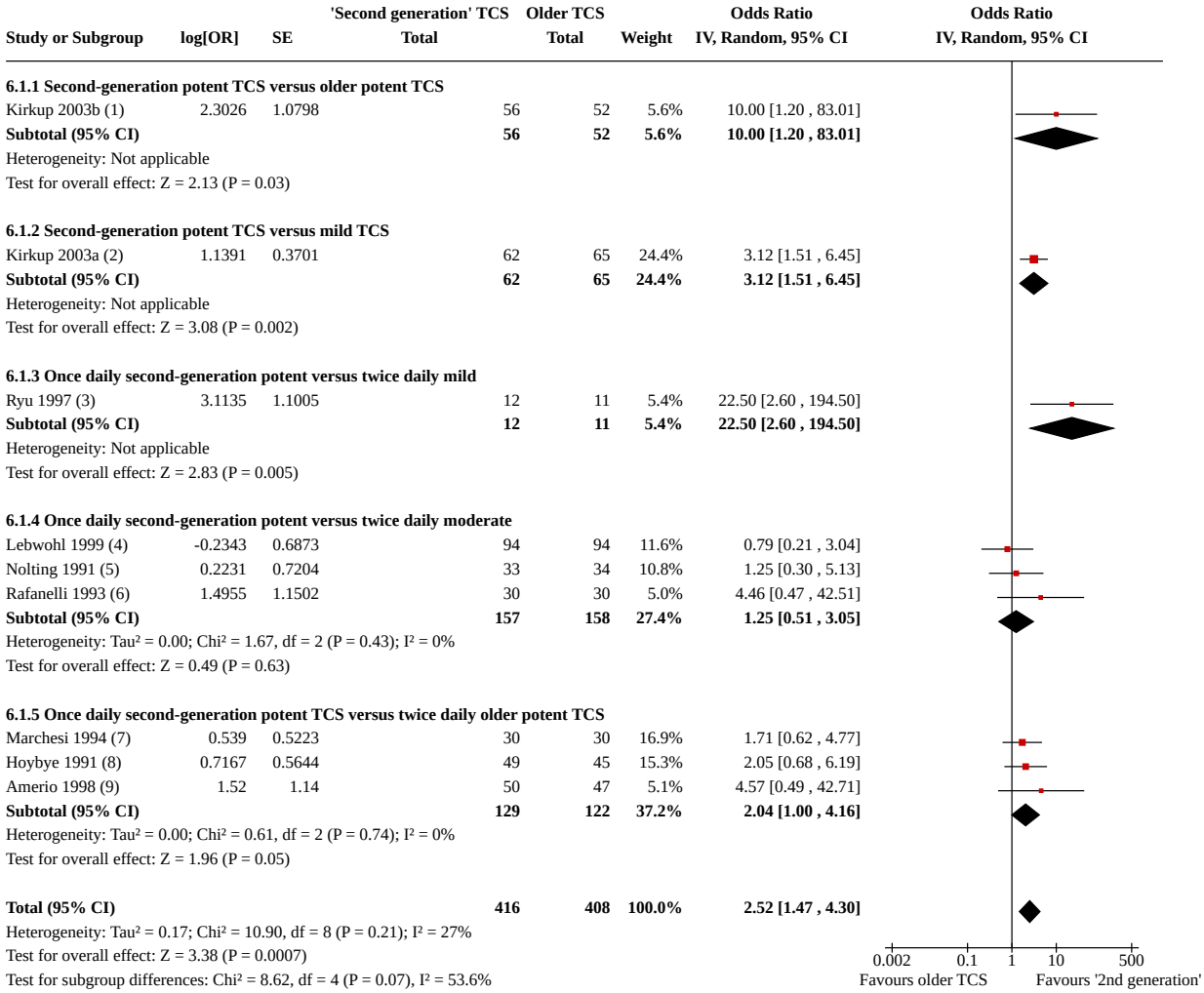
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Cleared or marked improvement on IGA (short term); all ages; all severities; parallel-group studies	9	824	Odds Ratio (IV, Random, 95% CI)	2.52 [1.47, 4.30]
6.1.1 Second-generation potent TCS versus older potent TCS	1	108	Odds Ratio (IV, Random, 95% CI)	10.00 [1.20, 83.01]
6.1.2 Second-generation potent TCS versus mild TCS	1	127	Odds Ratio (IV, Random, 95% CI)	3.12 [1.51, 6.45]
6.1.3 Once daily second-generation potent versus twice daily mild	1	23	Odds Ratio (IV, Random, 95% CI)	22.50 [2.60, 194.50]
6.1.4 Once daily second-generation potent versus twice daily moderate	3	315	Odds Ratio (IV, Random, 95% CI)	1.25 [0.51, 3.05]
6.1.5 Once daily second-generation potent TCS versus twice daily older potent TCS	3	251	Odds Ratio (IV, Random, 95% CI)	2.04 [1.00, 4.16]
6.2 Cleared or marked improvement on IGA (short term); split by age; all severities	7	704	Odds Ratio (IV, Random, 95% CI)	2.18 [1.38, 3.45]
6.2.1 Adults	3	221	Odds Ratio (IV, Random, 95% CI)	1.70 [0.88, 3.31]
6.2.2 Children	4	483	Odds Ratio (IV, Random, 95% CI)	2.68 [1.07, 6.76]
6.3 Cleared or marked improvement on IGA (short term); all ages; moderate to severe eczema	7	734	Odds Ratio (IV, Random, 95% CI)	2.40 [1.53, 3.79]
6.4 Cleared or marked improvement on IGA (end of treatment); all ages; all severities; parallel-group studies	8	580	Odds Ratio (IV, Random, 95% CI)	2.79 [1.71, 4.56]
6.4.1 Second-generation potent TCS versus mild TCS	1	24	Odds Ratio (IV, Random, 95% CI)	1.25 [0.20, 7.96]
6.4.2 Once daily second-generation potent versus twice daily mild	1	23	Odds Ratio (IV, Random, 95% CI)	22.50 [2.60, 194.50]
6.4.3 Once daily second-generation potent versus twice daily moderate	3	290	Odds Ratio (IV, Random, 95% CI)	2.67 [1.36, 5.24]
6.4.4 Once daily second-generation versus twice daily older TCS	3	243	Odds Ratio (IV, Random, 95% CI)	2.55 [1.00, 6.48]
6.5 Cleared or marked improvement on IGA (end of treatment); split by age; all severities	6	460	Odds Ratio (IV, Random, 95% CI)	2.43 [1.49, 3.98]
6.5.1 Adults	3	213	Odds Ratio (IV, Random, 95% CI)	1.84 [0.80, 4.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.5.2 Children	3	247	Odds Ratio (IV, Random, 95% CI)	2.83 [1.54, 5.22]
6.6 Cleared or marked improvement on IGA (end of treatment); all ages; moderate to severe eczema	6	490	Odds Ratio (IV, Random, 95% CI)	2.74 [1.64, 4.58]
6.7 Mean difference in IGA (end of treatment); parallel-group; children; moderate to severe eczema	2	193	Mean Difference (IV, Random, 95% CI)	-1.63 [-2.57, -0.69]
6.7.1 Second-generation potent TCS versus older mild TCS	1	107	Mean Difference (IV, Random, 95% CI)	-1.88 [-3.20, -0.56]
6.7.2 Second-generation potent TCS versus older potent TCS	1	86	Mean Difference (IV, Random, 95% CI)	-1.38 [-2.72, -0.04]
6.8 SMD in investigator assessment of clinical signs (end of treatment); all ages; moderate to severe eczema	2	339	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.45, 0.77]
6.8.1 Once daily second-generation potent TCS versus twice daily moderate TCS; children; parallel-group study	1	21	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-1.19, 0.55]
6.8.2 Second-generation TCS versus older TCS; all ages; within-participant study	1	318	Std. Mean Difference (IV, Random, 95% CI)	0.36 [0.20, 0.52]
6.9 Included studies with no poolable clinician-reported signs data	4		Other data	No numeric data
6.10 Number of participants judging itch to be better (short term); parallel-group; children; moderate to severe eczema)	2	243	Odds Ratio (M-H, Random, 95% CI)	2.26 [1.24, 4.14]
6.10.1 Second-generation potent TCS versus older mild TCS	1	120	Odds Ratio (M-H, Random, 95% CI)	1.95 [0.84, 4.53]
6.10.2 Second-generation potent TCS versus older potent TCS	1	123	Odds Ratio (M-H, Random, 95% CI)	2.65 [1.12, 6.28]
6.11 Number of participants judging itch to be better (end of treatment); parallel-group; children; moderate to severe eczema)	2	193	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.60, 2.25]
6.11.1 Second-generation potent TCS versus older mild TCS	1	107	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.49, 2.90]
6.11.2 Second-generation potent TCS versus older potent TCS	1	86	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.41, 3.04]
6.12 Number of participants judging sleep disturbance to be better (short term); parallel-group; children; moderate to severe eczema)	2	242	Odds Ratio (M-H, Random, 95% CI)	2.09 [1.15, 3.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.12.1 Second-generation potent TCS versus older mild TCS	1	120	Odds Ratio (M-H, Random, 95% CI)	2.35 [0.99, 5.56]
6.12.2 Second-generation potent TCS versus older potent TCS	1	122	Odds Ratio (M-H, Random, 95% CI)	1.87 [0.81, 4.31]
6.13 Number of participants judging sleep disturbance to be better (end of treatment); parallel-group; children; moderate to severe eczema)	2	193	Odds Ratio (M-H, Random, 95% CI)	2.41 [1.03, 5.65]
6.13.1 Second-generation potent TCS versus older mild TCS	1	107	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.67, 4.38]
6.13.2 Second-generation potent TCS versus older potent TCS	1	86	Odds Ratio (M-H, Random, 95% CI)	4.17 [1.19, 14.60]
6.14 Included studies with no poolable patient-reported symptoms data	6		Other data	No numeric data
6.14.1 Itch	3		Other data	No numeric data
6.14.2 Patient global assessment	3		Other data	No numeric data
6.15 Number of participants with skin thinning and related signs	11		Other data	No numeric data
6.15.1 Skin thinning	11		Other data	No numeric data
6.15.2 Striae	1		Other data	No numeric data
6.15.3 Telangiectasia	1		Other data	No numeric data
6.15.4 Loss of elasticity	1		Other data	No numeric data
6.15.5 Loss of normal skin markings	1		Other data	No numeric data
6.15.6 Gloss or shine	1		Other data	No numeric data
6.15.7 Pigmentation change	1		Other data	No numeric data
6.16 Number of participants with local site reactions	8		Other data	No numeric data
6.16.1 Burning	1		Other data	No numeric data
6.16.2 Itching	3		Other data	No numeric data
6.16.3 Stinging	1		Other data	No numeric data
6.16.4 Spots or rashes	3		Other data	No numeric data
6.16.5 Unspecified	2		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.17 Number of participants with skin infection	4		Other data	No numeric data
6.17.1 Folliculitis	1		Other data	No numeric data
6.17.2 Ringworm and folliculitis	2		Other data	No numeric data
6.17.3 Acne	1		Other data	No numeric data
6.17.4 Secondary infection	2		Other data	No numeric data
6.17.5 Skin infection	2		Other data	No numeric data
6.17.6 Impetigo contagiosa	2		Other data	No numeric data
6.17.7 Boil	2		Other data	No numeric data
6.17.8 Papules	1		Other data	No numeric data
6.17.9 Pustules	2		Other data	No numeric data
6.17.10 Staphylococcus aureus infection (scalp)	1		Other data	No numeric data
6.18 Number of participants with abnormal cortisol	4		Other data	No numeric data

Analysis 6.1. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 1: Cleared or marked improvement on IGA (short term); all ages; all severities; parallel-group studies

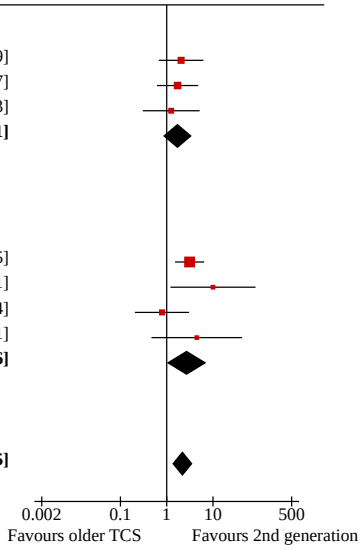


Footnotes

(1) Week 2 or week 4. Number much improved/improved.
(2) Week 2.
(3) Day 14 (assumed).
(4) Day 8. Number 100% cleared.
(5) Day 21.
(6) Day 7.
(7) Week 1.
(8) Week 3.
(9) Day 8-15.

Analysis 6.2. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 2: Cleared or marked improvement on IGA (short term); split by age; all severities

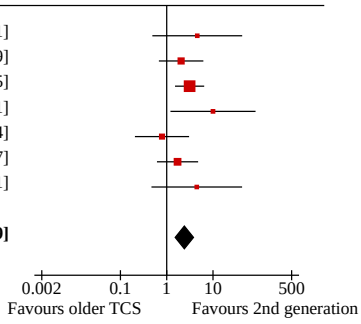
Study or Subgroup	log[OR]	SE	Second-generation TCS Total	Older TCS Total	Weight	Odds Ratio IV, Random, 95% CI
6.2.1 Adults						
Hoybye 1991 (1)	0.7167	0.5644	49	45	16.2%	2.05 [0.68 , 6.19]
Marchesi 1994 (2)	0.539	0.5223	30	30	18.8%	1.71 [0.62 , 4.77]
Nolting 1991 (3)	0.2231	0.7204	33	34	10.2%	1.25 [0.30 , 5.13]
Subtotal (95% CI)			**112**	**109**	**45.2%**	**1.70 [0.88 , 3.31]**
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.12)						
6.2.2 Children						
Kirkup 2003a (4)	1.1391	0.3701	62	65	34.9%	3.12 [1.51 , 6.45]
Kirkup 2003b (5)	2.3026	1.0798	56	52	4.6%	10.00 [1.20 , 83.01]
Lebwohl 1999 (6)	-0.2343	0.6873	94	94	11.2%	0.79 [0.21 , 3.04]
Rafanelli 1993 (7)	1.4955	1.1502	30	30	4.1%	4.46 [0.47 , 42.51]
Subtotal (95% CI)			**242**	**241**	**54.8%**	**2.68 [1.07 , 6.76]**
Heterogeneity: Tau² = 0.35; Chi² = 5.01, df = 3 (P = 0.17); I² = 40%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Total (95% CI)			**354**	**350**	**100.0%**	**2.18 [1.38 , 3.45]**
Heterogeneity: Tau² = 0.02; Chi² = 6.32, df = 6 (P = 0.39); I² = 5%						
Test for overall effect: Z = 3.32 (P = 0.0009)						
Test for subgroup differences: Chi² = 0.61, df = 1 (P = 0.43), I² = 0%						



Footnotes
(1) Week 3.
(2) Week 1.
(3) Day 21.
(4) Week 2.
(5) Week 2 or week 4. Number much improved/improved.
(6) Day 8. Number 100% cleared.
(7) Day 7.

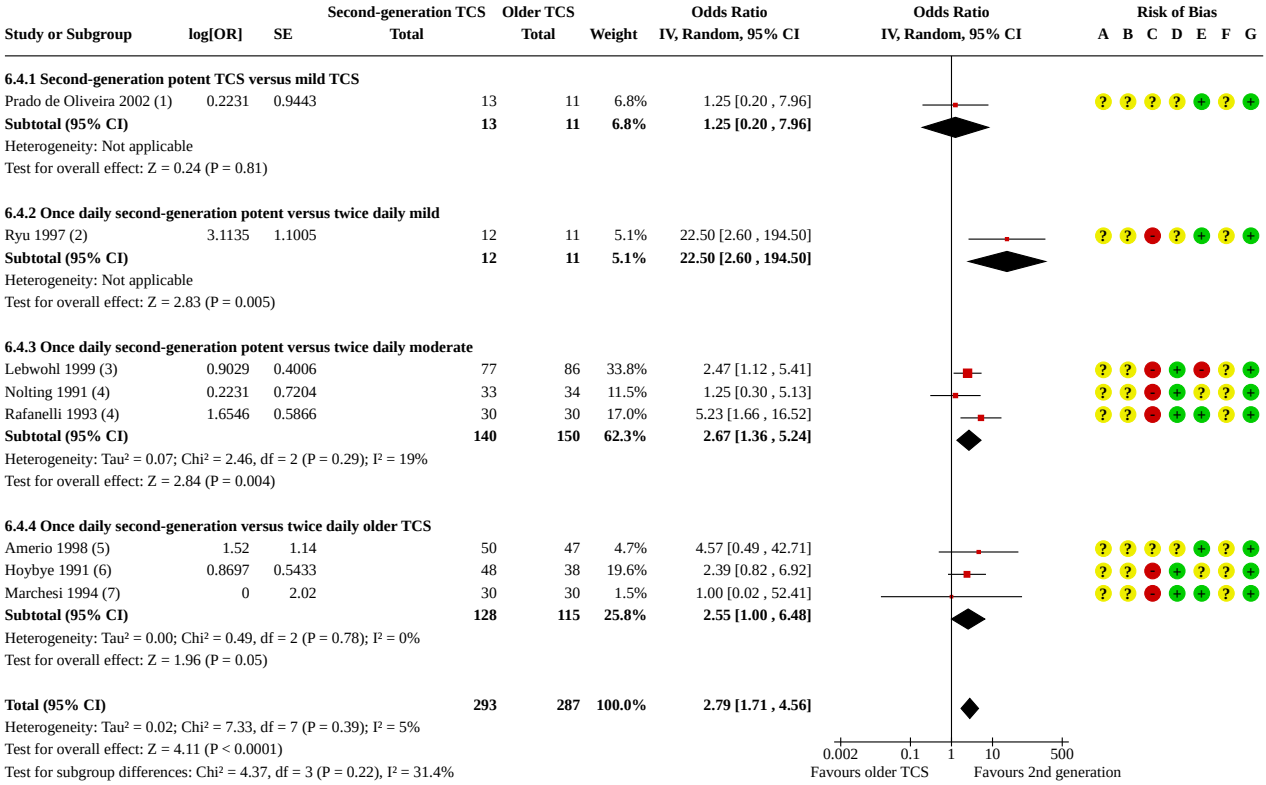
Analysis 6.3. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 3: Cleared or marked improvement on IGA (short term); all ages; moderate to severe eczema

Study or Subgroup	log[OR]	SE	Second-generation TCS Total	Older TCS Total	Weight	Odds Ratio IV, Random, 95% CI
Amerio 1998 (1)	1.52	1.14	50	47	4.1%	4.57 [0.49 , 42.71]
Hoybye 1991 (2)	0.7167	0.5644	49	45	16.9%	2.05 [0.68 , 6.19]
Kirkup 2003a (3)	1.1391	0.3701	62	65	39.2%	3.12 [1.51 , 6.45]
Kirkup 2003b (4)	2.3026	1.0798	56	52	4.6%	10.00 [1.20 , 83.01]
Lebwohl 1999 (5)	-0.2343	0.6873	94	94	11.4%	0.79 [0.21 , 3.04]
Marchesi 1994 (6)	0.539	0.5223	30	30	19.7%	1.71 [0.62 , 4.77]
Rafanelli 1993 (7)	1.4955	1.1502	30	30	4.1%	4.46 [0.47 , 42.51]
Total (95% CI)			**371**	**363**	**100.0%**	**2.40 [1.53 , 3.79]**
Heterogeneity: Tau² = 0.00; Chi² = 5.97, df = 6 (P = 0.43); I² = 0%						
Test for overall effect: Z = 3.78 (P = 0.0002)						
Test for subgroup differences: Not applicable						



Footnotes
(1) Day 8-15.
(2) Week 3.
(3) Week 2.
(4) Week 2 or week 4. Number much improved/improved.
(5) Day 8. Number 100% cleared.
(6) Week 1.
(7) Day 7.

Analysis 6.4. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 4: Cleared or marked improvement on IGA (end of treatment); all ages; all severities; parallel-group studies



Footnotes

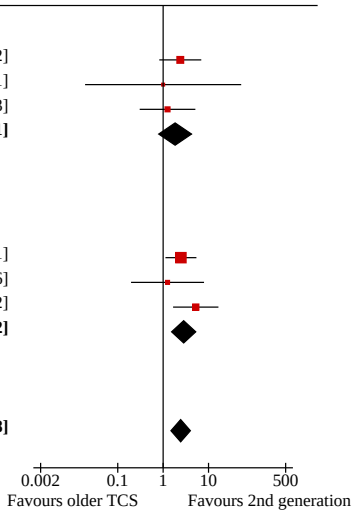
(1) Day 42.
(2) Day 14 (assumed).
(3) Day 21. Number 100% cleared.
(4) Day 21.
(5) Day 8-15.
(6) Week 6. Treatment was stepped down after week 3.
(7) Week 3.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.5. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 5: Cleared or marked improvement on IGA (end of treatment); split by age; all severities

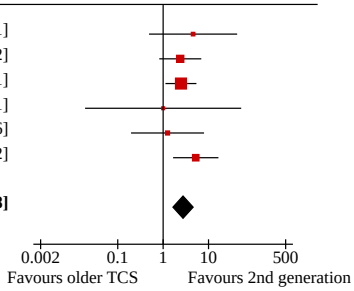
Study or Subgroup	log[OR]	SE	Second-generation TCS Total	Older TCS Total	Weight	Odds Ratio IV, Random, 95% CI
6.5.1 Adults						
Hoybye 1991 (1)	0.8697	0.5433	48	38	21.4%	2.39 [0.82 , 6.92]
Marchesi 1994 (2)	0	2.02	30	30	1.5%	1.00 [0.02 , 52.41]
Nolting 1991 (3)	0.2231	0.7204	33	34	12.2%	1.25 [0.30 , 5.13]
Subtotal (95% CI)			**111**	**102**	**35.1%**	**1.84 [0.80 , 4.21]**
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
6.5.2 Children						
Lebwohl 1999 (4)	0.9029	0.4006	77	86	39.4%	2.47 [1.12 , 5.41]
Prado de Oliveira 2002 (5)	0.2231	0.9443	13	11	7.1%	1.25 [0.20 , 7.96]
Rafanelli 1993 (3)	1.6546	0.5866	30	30	18.4%	5.23 [1.66 , 16.52]
Subtotal (95% CI)			**120**	**127**	**64.9%**	**2.83 [1.54 , 5.22]**
Heterogeneity: Tau² = 0.00; Chi² = 1.96, df = 2 (P = 0.37); I² = 0%						
Test for overall effect: Z = 3.34 (P = 0.0009)						
Total (95% CI)			**231**	**229**	**100.0%**	**2.43 [1.49 , 3.98]**
Heterogeneity: Tau² = 0.00; Chi² = 3.25, df = 5 (P = 0.66); I² = 0%						
Test for overall effect: Z = 3.54 (P = 0.0004)						
Test for subgroup differences: Chi² = 0.68, df = 1 (P = 0.41), I² = 0%						



Footnotes
(1) Week 6. Treatment was stepped down after week 3.
(2) Week 3.
(3) Day 21.
(4) Day 21. Number 100% cleared.
(5) Day 42.

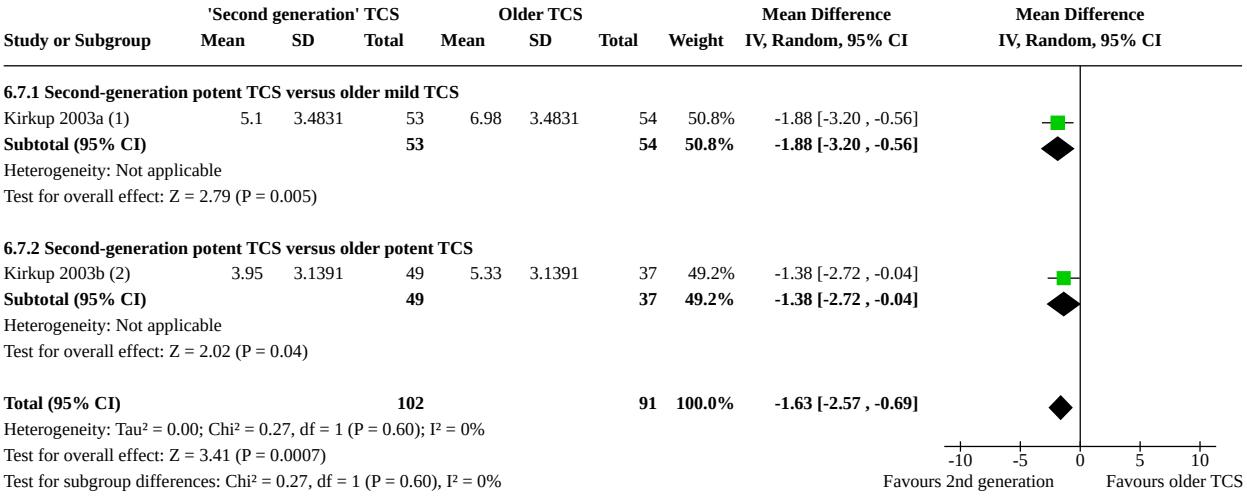
Analysis 6.6. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 6: Cleared or marked improvement on IGA (end of treatment); all ages; moderate to severe eczema

Study or Subgroup	log[OR]	SE	Second-generation TCS Total	Older TCS Total	Weight	Odds Ratio IV, Random, 95% CI
Amerio 1998 (1)	1.52	1.14	50	47	5.2%	4.57 [0.49 , 42.71]
Hoybye 1991 (2)	0.8697	0.5433	48	38	23.1%	2.39 [0.82 , 6.92]
Lebwohl 1999 (3)	0.9029	0.4006	77	86	42.5%	2.47 [1.12 , 5.41]
Marchesi 1994 (4)	0	2.02	30	30	1.7%	1.00 [0.02 , 52.41]
Prado de Oliveira 2002 (5)	0.2231	0.9443	13	11	7.6%	1.25 [0.20 , 7.96]
Rafanelli 1993 (6)	1.6546	0.5866	30	30	19.8%	5.23 [1.66 , 16.52]
Total (95% CI)			**248**	**242**	**100.0%**	**2.74 [1.64 , 4.58]**
Heterogeneity: Tau² = 0.00; Chi² = 2.49, df = 5 (P = 0.78); I² = 0%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
Test for subgroup differences: Not applicable						



Footnotes
(1) Day 8-15.
(2) Week 6. Treatment was stepped down after week 3.
(3) Day 21. Number 100% cleared.
(4) Week 3.
(5) Day 42.
(6) Day 21.

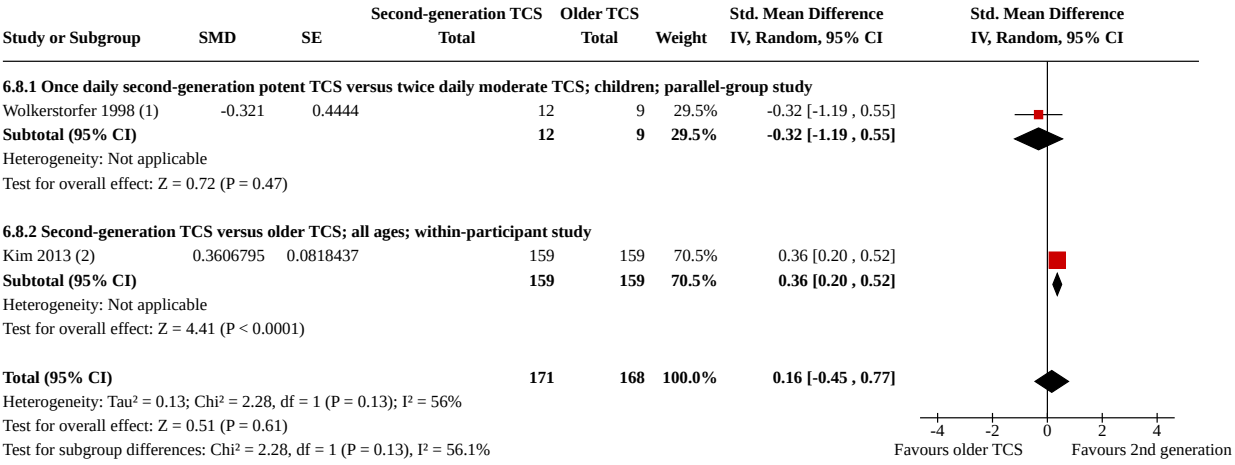
Analysis 6.7. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 7: Mean difference in IGA (end of treatment); parallel-group; children; moderate to severe eczema



Footnotes

(1) Week 14-16 (including 2-4 week acute phase).
(2) As above.

Analysis 6.8. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 8: SMD in investigator assessment of clinical signs (end of treatment); all ages; moderate to severe eczema



Footnotes

(1) Week 1. Decrease in ObjSCORAD from baseline.
(2) Day 15 (day 8 unable to be pooled). Decrease in unnamed scale from baseline. Unit of analysis is side; variance is corrected.

Analysis 6.9. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 9: Included studies with no poolable clinician-reported signs data

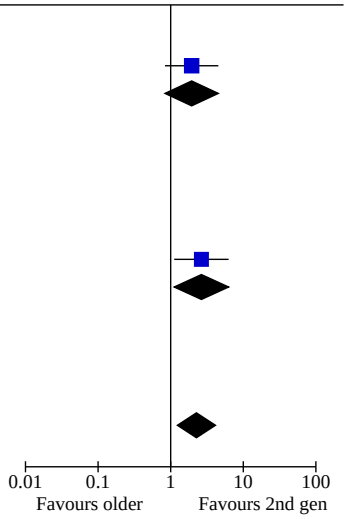
Included studies with no poolable clinician-reported signs data

Study	Intervention and comparison	Comments
Goh 1999	Twice daily very potent TCS versus once daily second-generation potent TCS	Within-participant; adults; moderate to severe eczema. At day 8, the number achieving cleared or marked improvement on IGA was 5 on the side treated with once daily second-generation potent TCS compared to 9 on the side treated with twice daily very potent TCS; OR 0.51 (95% CI 0.22 to 1.18). At day 22, num-

		ber achieving cleared or marked improvement was 16 on the side treated with once daily second-generation potent TCS compared to 41 on the side treated with twice daily very potent TCS; OR 0.16 (95% CI 0.09 to 0.28).
Reidhav 1996	Second-generation potent TCS versus older potent TCS	Within-participant; adults; unclear severity eczema. Quote: "no significant differences were found for any of the symptoms scored following 1 and 4 weeks of treatment"; n = 30
Vernon 1991	Once daily second-generation potent TCS versus twice daily mild TCS	Parallel-group; children; moderate to severe eczema. Mean decrease in unnamed scale from baseline; no dispersion. At end of treatment (week 6 or sooner if AD clearance was achieved), mean difference was 10.7 in the once daily potent group; n = 23 (assumed). In the twice daily mild group mean difference was 8.7; n = 24 (assumed). Extracted using WebPlotDigitizer
Wolkerstorfer 1998	Once daily second-generation potent TCS versus twice daily moderate potency TCS	Parallel-group; children; moderate-severity eczema. Short-term values are included in Analysis 6.8. At end of follow-up (week 6; 2 weeks post-treatment follow-up) mean ObjSCORAD was 23 ± 9 in the once daily group compared to 21 ± 7 in the twice daily group; MD −5.00 (95% CI −17.67 to 7.67; n = 5)

Analysis 6.10. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 10: Number of participants judging itch to be better (short term); parallel-group; children; moderate to severe eczema)

Study or Subgroup	'Second generation' TCS Events	Total	Older TCS Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
6.10.1 Second-generation potent TCS versus older mild TCS						
Kirkup 2003a (1)	46	57	43	63	51.0%	1.95 [0.84 , 4.53]
Subtotal (95% CI)		**57**		**63**	**51.0%**	**1.95 [0.84 , 4.53]**
Total events:	46		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
6.10.2 Second-generation potent TCS versus older potent TCS						
Kirkup 2003b (2)	53	63	40	60	49.0%	2.65 [1.12 , 6.28]
Subtotal (95% CI)		**63**		**60**	**49.0%**	**2.65 [1.12 , 6.28]**
Total events:	53		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.21 (P = 0.03)						
Total (95% CI)		**120**		**123**	**100.0%**	**2.26 [1.24 , 4.14]**
Total events:	99		83			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 2.65 (P = 0.008)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						



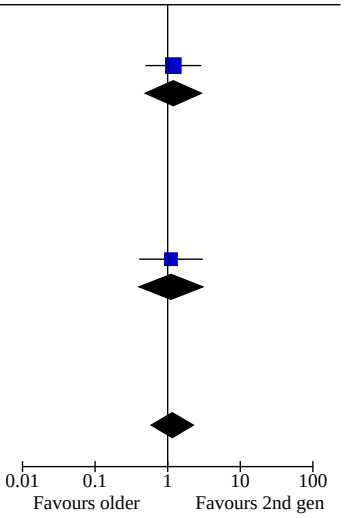
Footnotes

(1) Week 2-4 (acute phase).

(2) As above.

Analysis 6.11. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 11: Number of participants judging itch to be better (end of treatment); parallel-group; children; moderate to severe eczema)

Study or Subgroup	'Second generation' TCS Events	Total	Older TCS Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
6.11.1 Second-generation potent TCS versus older mild TCS						
Kirkup 2003a (1)	41	53	40	54	56.4%	1.20 [0.49 , 2.90]
Subtotal (95% CI)		**53**		**54**	**56.4%**	**1.20 [0.49 , 2.90]**
Total events:	41		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
6.11.2 Second-generation potent TCS versus older potent TCS						
Kirkup 2003b (2)	38	49	28	37	43.6%	1.11 [0.41 , 3.04]
Subtotal (95% CI)		**49**		**37**	**43.6%**	**1.11 [0.41 , 3.04]**
Total events:	38		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
Total (95% CI)		**102**		**91**	**100.0%**	**1.16 [0.60 , 2.25]**
Total events:	79		68			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.67)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						



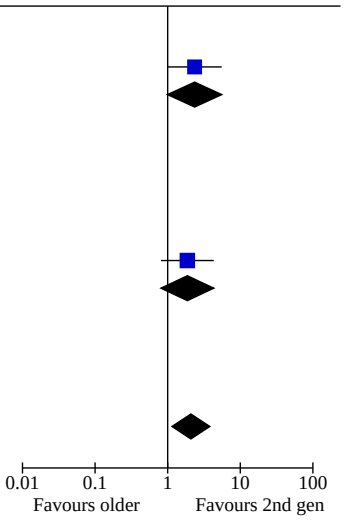
Footnotes

(1) Week 14-16 (including 2-4 week acute phase).

(2) As above.

Analysis 6.12. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 12: Number of participants judging sleep disturbance to be better (short term); parallel-group; children; moderate to severe eczema)

Study or Subgroup	'Second generation' TCS Events	Total	Older TCS Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
6.12.1 Second-generation potent TCS versus older mild TCS						
Kirkup 2003a (1)	47	57	42	63	48.7%	2.35 [0.99 , 5.56]
Subtotal (95% CI)		**57**		**63**	**48.7%**	**2.35 [0.99 , 5.56]**
Total events:	47		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						
6.12.2 Second-generation potent TCS versus older potent TCS						
Kirkup 2003b (2)	51	63	41	59	51.3%	1.87 [0.81 , 4.31]
Subtotal (95% CI)		**63**		**59**	**51.3%**	**1.87 [0.81 , 4.31]**
Total events:	51		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
Total (95% CI)		**120**		**122**	**100.0%**	**2.09 [1.15 , 3.81]**
Total events:	98		83			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.40 (P = 0.02)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%						



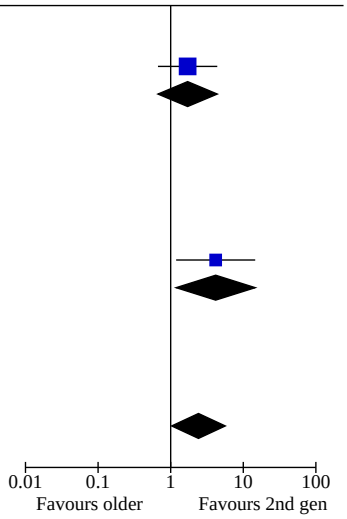
Footnotes

(1) Week 2-4 (acute phase).

(2) As above.

Analysis 6.13. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 13: Number of participants judging sleep disturbance to be better (end of treatment); parallel-group; children; moderate to severe eczema)

Study or Subgroup	'Second generation' TCS Events	Total	Older TCS Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
6.13.1 Second-generation potent TCS versus older mild TCS						
Kirkup 2003a (1)	44	53	40	54	61.3%	1.71 [0.67 , 4.38]
Subtotal (95% CI)		**53**		**54**	**61.3%**	**1.71 [0.67 , 4.38]**
Total events:	44		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
6.13.2 Second-generation potent TCS versus older potent TCS						
Kirkup 2003b (2)	45	49	27	37	38.7%	4.17 [1.19 , 14.60]
Subtotal (95% CI)		**49**		**37**	**38.7%**	**4.17 [1.19 , 14.60]**
Total events:	45		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.23 (P = 0.03)						
Total (95% CI)		**102**		**91**	**100.0%**	**2.41 [1.03 , 5.65]**
Total events:	89		67			
Heterogeneity: Tau² = 0.08; Chi² = 1.24, df = 1 (P = 0.27); I² = 19%						
Test for overall effect: Z = 2.03 (P = 0.04)						
Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.3%						



Footnotes

(1) Week 14-16 (including 2-4 week acute phase).

(2) As above.

Analysis 6.14. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 14: Included studies with no poolable patient-reported symptoms data

Included studies with no poolable patient-reported symptoms data

Study	Intervention and comparison	Comments
Itch		
Amerio 1998	Twice daily older potent TCS versus once daily second-generation potent TCS	Parallel-group; adults and children; moderate-severity eczema. Percentage reduction in patient-assessed itch (assumed; could be a more general symptoms assessment). 55.9% in both the second-generation TCS group and the older TCS group at day 7. 85.5% in the second-generation group and 77.7% in the older TCS group at end of treatment (day 8-15). 75.4% in the second-generation group and 65.9% in the older TCS group at end of follow-up (day 23-30). Throughout, n = 47 (assumed) in the second-generation TCS group and 50 in the older TCS group. Extracted using WebPlot-Digitizer
Kim 2013	Second-generation potent TCS versus older potent TCS	Within-participant study; adults and children; moderate to severe eczema. Decrease in itch VAS relative to baseline. Mean difference was 0.34 [95% CI 0.02, 0.66] at day 15; n = 159
Reidhav 1996	second-generation potent TCS versus older potent TCS.	Within-participant; adults; unclear severity eczema. Quote: "At each visit, the patient was asked to score the severity of pruritus and smarting pain on a scale from 0 to 3. [...] No significant differences were found for any of the symptoms scored following 1 and 4 weeks of treatment with betamethasone valerate or mometasone furoate cream."
Patient global assessment		
Goh 1999	Once daily application of a second-generation potent TCS versus twice daily application of a very potent TCS	Within participant; adults; moderate to severe eczema. Number of participants reporting an excellent response. Odds ratio at day 8 was 0.30 [95% CI

		0.11, 0.82]; n = 58. Odds ratio at day 22 was 0.15 [95% CI 0.07, 0.32]; n = 58
Hoybye 1991	Once daily second-generation potent TCS versus twice daily older potent TCS	Parallel-group; adults; at least moderate-severity eczema. There was no difference in efficacy between groups at weeks 3 and 6 (VAS; P = 0.30)
Rafanelli 1993	Once daily second-generation potent TCS versus older moderate TCS	Parallel-group; children; moderate to severe eczema. Patient global assessment was stated to be consistent with the investigator global assessment (Analysis 6.1 and Analysis 6.4)

Analysis 6.15. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 15: Number of participants with skin thinning and related signs

Number of participants with skin thinning and related signs

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Skin thinning								
Amerio 1998	Parallel- group	Once daily second-generation potent	Twice daily potent	All ages; ≥ moderate-severity eczema	Up to day 15	0/50	0/47	
Goh 1999	Within- participant	Once daily second-generation potent	Twice daily very potent	Adults; moderate to severe eczema	Up to day 22	0/58	0/58	
Hoybye 1991	Parallel- group	Once daily second-generation potent	Twice daily potent	Adults; ≥ moderate-severity eczema	Up to week 6	0/49	0/45	
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/70	0/67	Assumed number randomised
Kirkup 2003b	Parallel- group	Second-generation potent TCS	Older potent TCS	Children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/66	0/62	Assumed number randomised
Lebwohl 1999	Parallel- group	Once daily second-generation potent	Twice daily moderate	Children; moderate to severe eczema	Up to day 22	0/109	0/110	
Nolting 1991	Parallel- group	Once daily second-generation potent	Twice daily moderate	Adults; unspecified severity eczema	Up to week 3	2/33	2/34	
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	4/13	2/12	
Rafanelli 1993	Parallel- group	Once daily second-generation potent	Twice daily moderate	Children; moderate to severe eczema	up to week 3	0/30	0/30	
Ryu 1997	Parallel- group	Once daily second-generation potent TCS	Twice daily mild TCS	All ages; mild to moderate eczema	Up to day 14	0/12	0/12	
Vernon 1991	Parallel- group	Once daily second-generation potent	Twice daily mild	Children; moderate to severe eczema	up to week 6	0/23	0/24	N assumed
Striae								
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Telangiectasia								
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Loss of elasticity								

Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Loss of normal skin markings								
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Gloss or shine								
Prado de Oliveira 2002	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to day 42	0/13	0/12	
Pigmentation change								
Ryu 1997	Parallel- group	Once daily second-generation potent TCS	Twice daily mild TCS	All ages; mild to moderate eczema	Up to day 14	0/12	0/12	

Analysis 6.16. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 16: Number of participants with local site reactions

Number of participants with local site reactions

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Burning								
Prado de Oliveira 2002	Parallel- group	second-generation potent TCS	Mild TCS	Children; moderate to severe eczema.	Up to day 42.	3/13	1/12	Events in A: "ardor on 1st application" in one patient, and "ardor on application of product" in 2 patients Events in B: "ardor days 1 and 2 after application."
Itching								
Kim 2013	Within- participant	second-generation potent TCS	Older TCS	Adults and children; moderate to severe eczema.	Up to day 15.	2/174	4/174	
Kirkup 2003a	Parallel- group	second-generation potent TCS	mild TCS	Children; moderate to severe eczema.	Up to week 16.	0/70	0/67	Assumed number randomised.
Kirkup 2003b	Parallel- group	second-generation potent TCS	Older TCS	Children; moderate to severe eczema.	Up to week 16 (includes 4 weeks acute treatment phase).	0/66	2/62	On application. Assumed number randomised.
Stinging								
Vernon 1991	Parallel- group	Once daily second-generation potent	Twice daily mild	Children; moderate to severe	Up to week 6	0/23	3/24	N assumed
Spots or rashes								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised
Kirkup 2003b	Parallel- group	Second-generation potent TCS	Older TCS	Children; moderate to severe eczema	Up to week 16 (acute and maintenance)	1/66	0/62	Red papules on right leg. Assumed number randomised
Ryu 1997	Parallel- group	Once daily second-generation potent TCS	Twice daily mild TCS	Adults and children; mild- to moderate-severity eczema	Up to day 14	0/12	0/12	Maculopapular rash
Unspecified								

Lebwohl 1999	Parallel- group	Once daily second-generation potent	Twice daily moderate	Children; moderate to severe eczema	up to day 22	4/109	2/110	
Marchesi 1994	Parallel- group	Once daily second-generation potent TCS	Twice daily older TCS	Adults; moderate to severe eczema	up to week 3	0/30	0/30	

Analysis 6.17. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 17: Number of participants with skin infection

Number of participants with skin infection

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Folliculitis								
Ryu 1997	Parallel- group	Once daily second-generation potent TCS	Twice daily mild TCS	Adults and children; mild- to moderate-severity eczema	Up to day 14	1/12	0/12	
Ringworm and folliculitis								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	1/70	0/67	Assumed number randomised
Kirkup 2003b	Parallel- group	Second-generation potent TCS	Older TCS	Children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/66	0/62	Assumed number randomised
Acne								
Ryu 1997	Parallel- group	Once daily second-generation potent TCS	Twice daily mild TCS	Adults and children; mild- to moderate-severity eczema	Up to day 14	0/12	0/12	
Secondary infection								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/70	1/67	Assumed number randomised
Kirkup 2003b	Parallel- group	Second-generation potent TCS	Older TCS	Children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/66	0/62	Assumed number randomised
Skin infection								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised
Kirkup 2003b	Parallel- group	second-generation potent TCS	Older TCS	Children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/66	1/62	Assumed number randomised
Impetigo contagiosa								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised
Kirkup 2003b	Parallel- group	second-generation potent TCS	Older TCS	Children; moderate to severe eczema	Up to week 16 (acute and maintenance)	0/66	1/62	On face. Assumed number randomised
Boil								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised

Kirkup 2003b	Parallel- group	Second-generation potent TCS	Older TCS	Children; moderate to severe eczema	Up to week 16 (acute and maintenance)	1/66	0/62	On lower left leg
Papules								
Ryu 1997	Parallel- group	Twice daily mild	Once daily second-generation potent	Adults and children; mild- to moderate-severity eczema	Day 14 (assumed).	0/12	0/12	Maculopapular rash.
Pustules								
Kirkup 2003a	Parallel- group	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema	Up to week 16	0/70	0/67	Assumed number randomised
Kirkup 2003b	Parallel- group	Second-generation potent TCS	Older TCS	Children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/66	1/62	On lower legs. Assumed number randomised
Staphylococcus aureus infection (scalp)								
Vernon 1991	Parallel- group	Once daily second-generation potent	Twice daily mild	Children; moderate to severe eczema	Up to 6 weeks	1/23	0/24	N assumed. Occurred at 36 days and resulted in discontinuation

Analysis 6.18. Comparison 6: Second-generation versus older topical corticosteroid (TCS), Outcome 18: Number of participants with abnormal cortisol

Number of participants with abnormal cortisol

Study	Intervention and comparison	Cases/N A	Cases/N B	Additional information
Hoybye 1991	Once daily second-generation potent TCS versus twice daily older potent TCS	?/9	?/9	Adults; ≥ moderate-severity eczema. Morning plasma cortisol at baseline, week 3 and week 6. It was stated that there was no significant difference in plasma cortisol between the two groups; median (range) was reported with no indication of how many people were outside of the normal range. Second-generation TCS group: 430 (330 to 920; n = 9) at baseline; 450 (273 to 710; n = 9) at week 3; 460 (167 to 1020; n = 9) at week 6 Older TCS group: 470 (183 to 720; n = 10) at baseline; 420 (183 to 910; n = 9) at week 3; 485 (168 to 1240; n = 6) at week 6 Normal range was stated to be 190 to 600 nmol/L
Rafanelli 1993	Once daily second-generation potent TCS versus twice daily moderate TCS	0/30	0/30	Children; moderate to severe eczema. Blood cortisol at baseline and week 3
Vernon 1991	Once daily second-generation potent TCS versus twice daily mild TCS	0/23	1/24	Children; moderate to severe eczema. Morning plasma cortisol at baseline, week 1 and end of treatment (up to week 6). Event detected at week 1 (< 5.0 µg/dL) and was transient. N assumed
Wolkerstorfer 1998	Once daily second-generation potent TCS versus twice daily moderate TCS	0/12	1/9	Children; moderate to severe eczema. Urinary cortisol excretion at baseline and end of treatment (week 4). One participant decreased from 162.8 nmol/24 h at baseline to 67 nmol/24 h at end of treat-

ment, and returned to normal by two weeks' post-treatment follow-up. N assumed

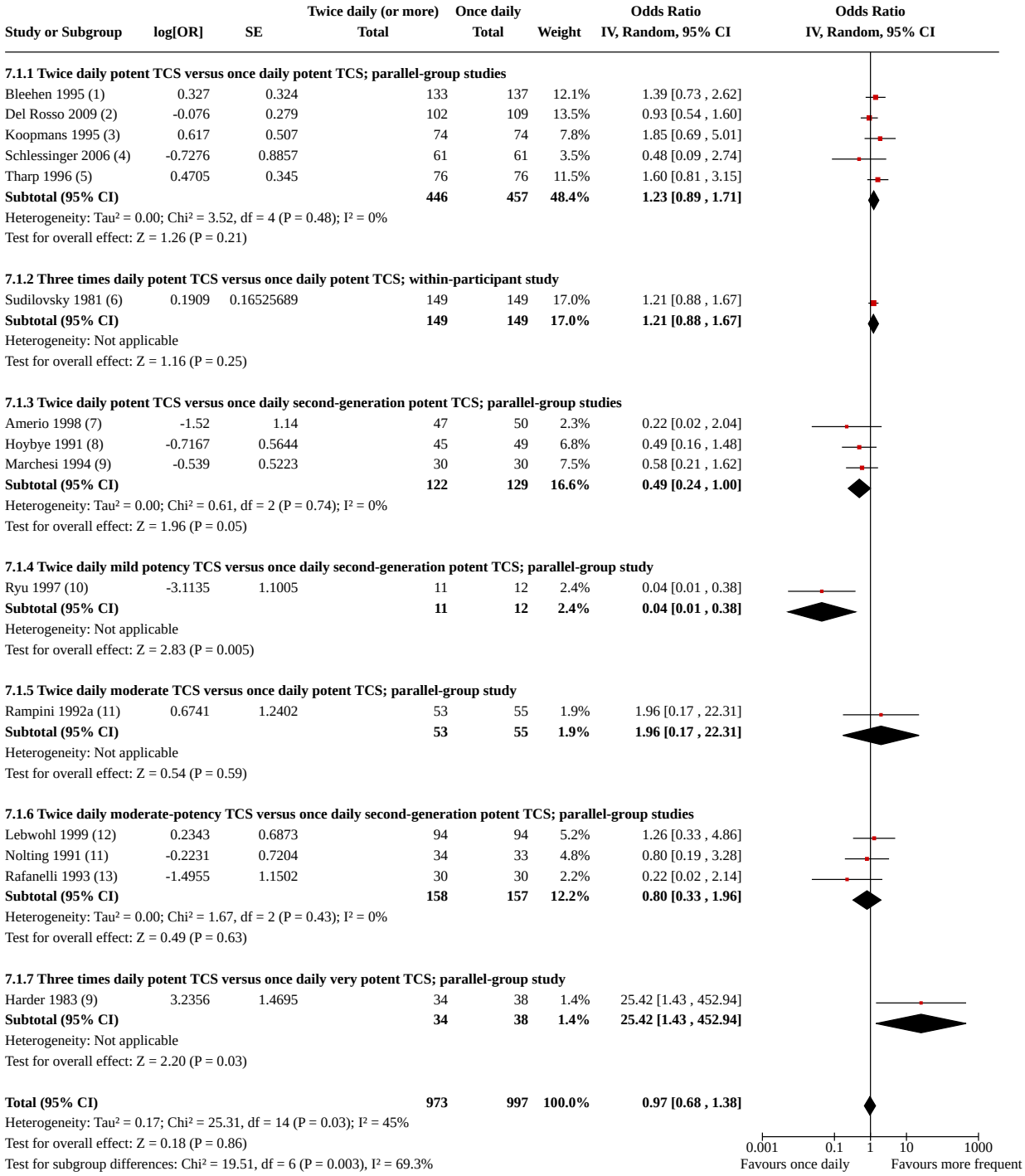
Comparison 7. Twice or more versus once daily topical corticosteroid (TCS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Cleared or marked improvement (unless stated) on IGA (short term); all ages; all severities	15	1970	Odds Ratio (IV, Random, 95% CI)	0.97 [0.68, 1.38]
7.1.1 Twice daily potent TCS versus once daily potent TCS; parallel-group studies	5	903	Odds Ratio (IV, Random, 95% CI)	1.23 [0.89, 1.71]
7.1.2 Three times daily potent TCS versus once daily potent TCS; within-participant study	1	298	Odds Ratio (IV, Random, 95% CI)	1.21 [0.88, 1.67]
7.1.3 Twice daily potent TCS versus once daily second-generation potent TCS; parallel-group studies	3	251	Odds Ratio (IV, Random, 95% CI)	0.49 [0.24, 1.00]
7.1.4 Twice daily mild potency TCS versus once daily second-generation potent TCS; parallel-group study	1	23	Odds Ratio (IV, Random, 95% CI)	0.04 [0.01, 0.38]
7.1.5 Twice daily moderate TCS versus once daily potent TCS; parallel-group study	1	108	Odds Ratio (IV, Random, 95% CI)	1.96 [0.17, 22.31]
7.1.6 Twice daily moderate-potency TCS versus once daily second-generation potent TCS; parallel-group studies	3	315	Odds Ratio (IV, Random, 95% CI)	0.80 [0.33, 1.96]
7.1.7 Three times daily potent TCS versus once daily very potent TCS; parallel-group study	1	72	Odds Ratio (IV, Random, 95% CI)	25.42 [1.43, 452.94]
7.2 Cleared or marked improvement (unless stated) on IGA (short term); split by age; all severities	8		Odds Ratio (IV, Random, 95% CI)	Subtotals only
7.2.1 Adults	4	432	Odds Ratio (IV, Random, 95% CI)	0.77 [0.51, 1.17]
7.2.2 Children	4	478	Odds Ratio (IV, Random, 95% CI)	0.79 [0.32, 1.94]
7.3 Cleared or marked improvement (unless stated) on IGA (short term); all ages; moderate to severe eczema	9	1254	Odds Ratio (IV, Random, 95% CI)	0.93 [0.65, 1.34]
7.4 Cleared or marked improvement on IGA (end of follow-up); parallel-group; all ages; all severities	2	333	Odds Ratio (M-H, Random, 95% CI)	1.58 [0.80, 3.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.5 SMD in investigator assessment of clinical signs (short term); children; moderate-severity eczema	2	40	Std. Mean Difference (IV, Random, 95% CI)	0.40 [-0.23, 1.03]
7.5.1 Twice daily moderate-potency TCS versus once daily second-generation potent TCS; parallel-group study	1	21	Std. Mean Difference (IV, Random, 95% CI)	0.32 [-0.55, 1.19]
7.5.2 Twice daily mild TCS versus once daily mild TCS under wet wrap; parallel-group study	1	19	Std. Mean Difference (IV, Random, 95% CI)	0.49 [-0.43, 1.41]
7.6 SMD in investigator assessment of clinical signs (end of treatment); children; moderate-severity eczema	2	24	Std. Mean Difference (IV, Random, 95% CI)	0.51 [-0.32, 1.33]
7.6.1 Twice daily moderate-potency TCS versus once daily second-generation potent TCS; parallel-group study	1	5	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-1.55, 2.10]
7.6.2 Twice daily mild TCS versus once daily mild TCS under wet wrap; parallel-group study	1	19	Std. Mean Difference (IV, Random, 95% CI)	0.56 [-0.36, 1.49]
7.7 Included studies with no poolable clinician-reported signs data	10		Other data	No numeric data
7.8 Cleared or marked improvement on PGA (short term); parallel-group; all ages; all severities	2	300	Odds Ratio (M-H, Random, 95% CI)	1.91 [0.62, 5.83]
7.9 Included studies with no poolable patient-reported symptoms data	8		Other data	No numeric data
7.9.1 Itch	3		Other data	No numeric data
7.9.2 Sleep	2		Other data	No numeric data
7.9.3 Patient global assessment	4		Other data	No numeric data
7.9.4 Unnamed scale	1		Other data	No numeric data
7.10 Number of participants with skin thinning or related signs; end of treatment	12		Other data	No numeric data
7.10.1 Skin thinning	11		Other data	No numeric data
7.10.2 Striae	3		Other data	No numeric data
7.10.3 Telangiectasia	3		Other data	No numeric data
7.10.4 Transparency	1		Other data	No numeric data
7.10.5 Loss of elasticity	1		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.10.6 Loss of normal skin markings	1		Other data	No numeric data
7.10.7 Bruising	1		Other data	No numeric data
7.10.8 Pigmentation change	1		Other data	No numeric data
7.11 Number of participants with local site reactions; end of treatment	8		Other data	No numeric data
7.11.1 Burning	2		Other data	No numeric data
7.11.2 Pruritus	2		Other data	No numeric data
7.11.3 Stinging	2		Other data	No numeric data
7.11.4 Burning, itching, or stinging	1		Other data	No numeric data
7.11.5 Irritation	2		Other data	No numeric data
7.11.6 Unspecified	3		Other data	No numeric data
7.12 Number of participants with skin infections; end of treatment	5		Other data	No numeric data
7.12.1 Folliculitis	3		Other data	No numeric data
7.12.2 Impetigo contagiosa	1		Other data	No numeric data
7.12.3 Acne	1		Other data	No numeric data
7.12.4 Papules	1		Other data	No numeric data
7.12.6 Staphylococcus aureus infection (scalp)	1		Other data	No numeric data
7.13 Number of participants with abnormal cortisol	7		Other data	No numeric data

Analysis 7.1. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 1: Cleared or marked improvement (unless stated) on IGA (short term); all ages; all severities



Footnotes

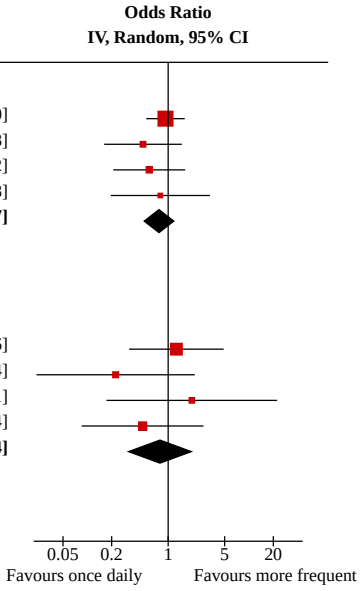
(1) Up to 4 weeks. Cleared/marked/moderate improvement.
(2) Week 2. Very potent TCS.
(3) Week 4.
(4) Week 2. Very potent TCS. Number clear/almost clear/improved.
(5) Day 8.
(6) Week 1. Number with cleared/marked/moderate improvement. Unit of analysis is side; variance is corrected.
(7) Day 8-15.

Analysis 7.1. (Continued)

(6) Week 1. Number with cleared/marked/moderate improvement. Unit of analysis is side; variance is corrected.
(7) Day 8-15.
(8) Week 3.
(9) Week 1.
(10) Day 14 (assumed).
(11) Day 21.
(12) Day 8. Number with 100% clearance.
(13) Day 7.

Analysis 7.2. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 2: Cleared or marked improvement (unless stated) on IGA (short term); split by age; all severities

Study or Subgroup	log[OR]	SE	Twice daily (or more) Total	Once daily Total	Weight	Odds Ratio IV, Random, 95% CI
7.2.1 Adults						
Del Rosso 2009 (1)	-0.076	0.279	102	109	59.5%	0.93 [0.54 , 1.60]
Hoybye 1991 (2)	-0.7167	0.5644	45	49	14.5%	0.49 [0.16 , 1.48]
Marchesi 1994 (3)	-0.539	0.5223	30	30	17.0%	0.58 [0.21 , 1.62]
Nolting 1991 (4)	-0.2231	0.7204	34	33	8.9%	0.80 [0.19 , 3.28]
Subtotal (95% CI)			**211**	**221**	**100.0%**	**0.77 [0.51 , 1.17]**
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
7.2.2 Children						
Lebwohl 1999 (5)	0.2343	0.6873	94	94	44.1%	1.26 [0.33 , 4.86]
Rafanelli 1993 (6)	-1.4955	1.1502	30	30	15.8%	0.22 [0.02 , 2.14]
Rampini 1992a (4)	0.6741	1.2402	53	55	13.6%	1.96 [0.17 , 22.31]
Schlessinger 2006 (7)	-0.7276	0.8857	61	61	26.6%	0.48 [0.09 , 2.74]
Subtotal (95% CI)			**238**	**240**	**100.0%**	**0.79 [0.32 , 1.94]**
Heterogeneity: Tau² = 0.00; Chi² = 2.51, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%						

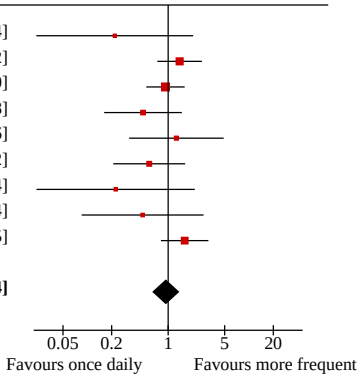


Footnotes
(1) Week 2. Very potent TCS.
(2) Week 3.
(3) Week 1.
(4) Day 21.
(5) Day 8. Number with 100% clearance.
(6) Day 7.
(7) Week 2. Very potent TCS. Number clear/almost clear/improved.

Analysis 7.3. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 3: Cleared or marked improvement (unless stated) on IGA (short term); all ages; moderate to severe eczema

Study or Subgroup	log[OR]	SE	Twice daily (or more) Total	Once daily Total	Weight	Odds Ratio IV, Random, 95% CI
Amerio 1998 (1)	-1.52	1.14	47	50	2.5%	0.22 [0.02 , 2.04]
Bleehen 1995 (2)	0.327	0.324	133	137	21.0%	1.39 [0.73 , 2.62]
Del Rosso 2009 (3)	-0.076	0.279	102	109	25.3%	0.93 [0.54 , 1.60]
Hoybye 1991 (4)	-0.7167	0.5644	45	49	9.0%	0.49 [0.16 , 1.48]
Lebwohl 1999 (5)	0.2343	0.6873	94	94	6.4%	1.26 [0.33 , 4.86]
Marchesi 1994 (6)	-0.539	0.5223	30	30	10.2%	0.58 [0.21 , 1.62]
Rafanelli 1993 (7)	-1.4955	1.1502	30	30	2.4%	0.22 [0.02 , 2.14]
Schlessinger 2006 (8)	-0.7276	0.8857	61	61	4.0%	0.48 [0.09 , 2.74]
Tharp 1996 (9)	0.4705	0.345	76	76	19.3%	1.60 [0.81 , 3.15]
Total (95% CI)			**618**	**636**	**100.0%**	**0.93 [0.65 , 1.34]**

Heterogeneity: Tau² = 0.05; Chi² = 9.87, df = 8 (P = 0.27); I² = 19%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable

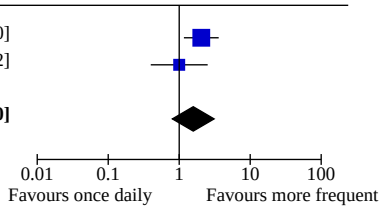


Footnotes
(1) Day 8-15.
(2) Up to 4 weeks.
(3) Week 2. Very potent TCS.
(4) Week 3.
(5) Day 8. Number with 100% clearance.
(6) Week 1.
(7) Day 7.
(8) Week 2. Very potent TCS. Number clear/almost clear/improved.
(9) Day 8.

Analysis 7.4. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 4: Cleared or marked improvement on IGA (end of follow-up); parallel-group; all ages; all severities

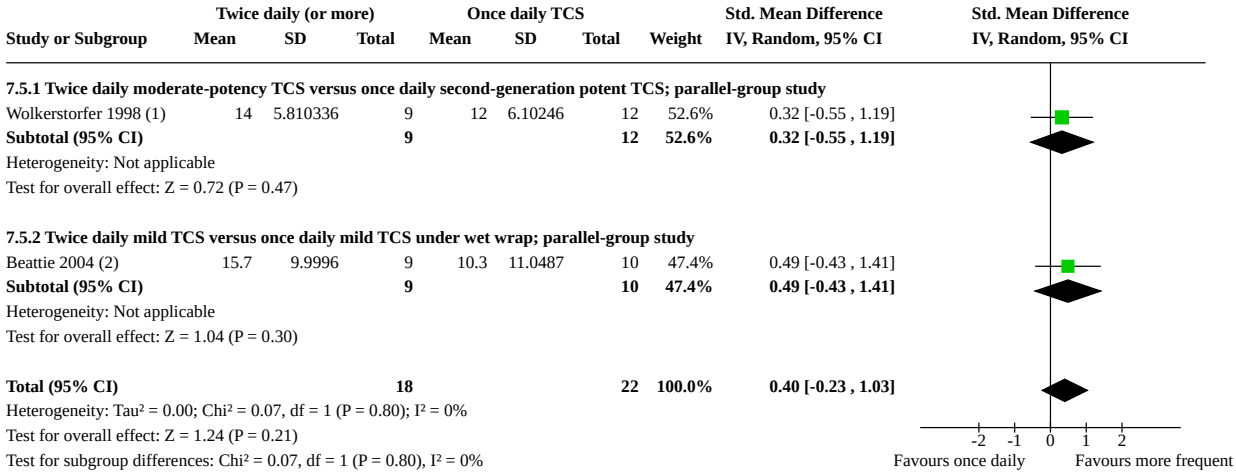
Study or Subgroup	Twice daily (or more) Events	Total	Once daily Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Del Rosso 2009 (1)	48	102	33	109	63.5%	2.05 [1.16 , 3.60]
Schlessinger 2006 (2)	50	61	50	61	36.5%	1.00 [0.40 , 2.52]
Total (95% CI)		**163**		**170**	**100.0%**	**1.58 [0.80 , 3.10]**
Total events:	98		83			

Heterogeneity: Tau² = 0.10; Chi² = 1.68, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



Footnotes
(1) Week 4 (2 weeks post treatment). Very potent TCS. Adults with moderate to severe eczema.
(2) Week 4 (2 weeks post treatment). Very potent TCS. Cleared/marked/moderate improvement. Children with unspecified severity eczema.

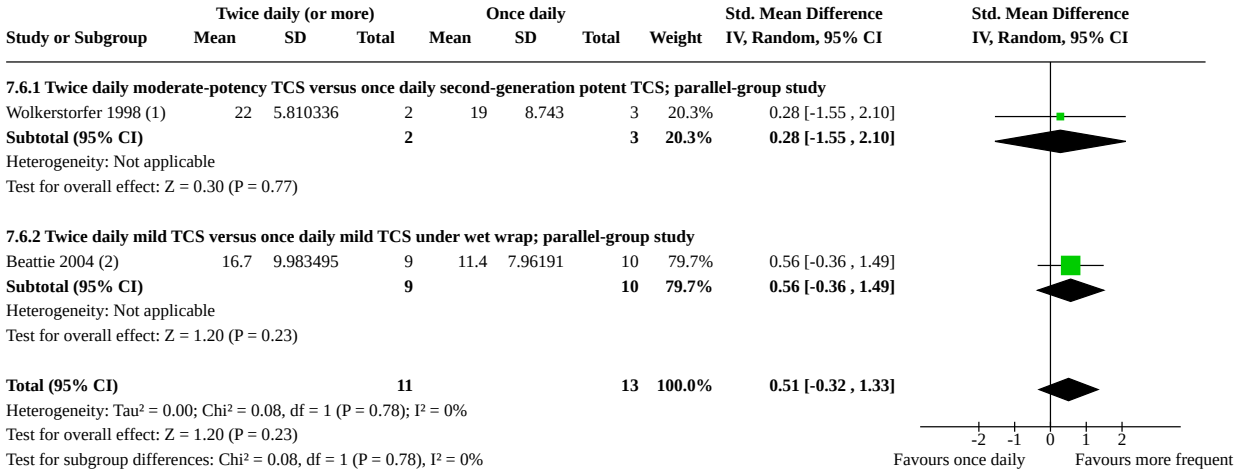
Analysis 7.5. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 5: SMD in investigator assessment of clinical signs (short term); children; moderate-severity eczema



Footnotes

(1) Week 1. Decrease in ObjSCORAD from baseline.
(2) Week 1. Decrease in SASSAD from baseline.

Analysis 7.6. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 6: SMD in investigator assessment of clinical signs (end of treatment); children; moderate-severity eczema



Footnotes

(1) Week 4. Decrease in ObjSCORAD from baseline.
(2) Week 2. Decrease in SASSAD from baseline. Wet wraps twice daily in the first week, then at night in the second week.

Analysis 7.7. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 7: Included studies with no poolable clinician-reported signs data

Included studies with no poolable clinician-reported signs data

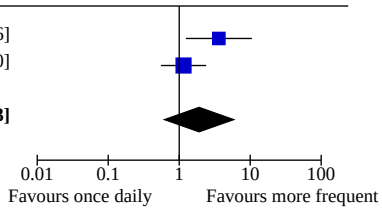
Study	Intervention and comparison	Comments
Beattie 2004	Twice daily mild TCS versus once daily mild TCS under wet wraps	Parallel-group; children; moderate-severity eczema. Short-term and end of treatment values are included in Analysis 7.5 and Analysis 7.6, respectively. At end of follow-up (week 3; 1 week post-treatment follow-up), SASSAD had increased in the twice daily group to 22.8

		(n = 9) and to 21.9 in the once daily group (n = 10). Dispersion data were not given for this time point.
Berth-Jones 2003	Twice daily versus once daily second-generation potent TCS (group D versus group C)	Parallel-group; adults and children; moderate to severe eczema. Number of participants with TIS ≤ 1. Odds ratio after 4-week stabilisation phase was 0.74 [0.38, 1.41]; n = 190
Berth-Jones 2003	Twice daily versus once daily second-generation potent TCS (group B versus group A)	Parallel-group; adults and children; moderate to severe eczema. Number of participants with TIS ≤ 1. Odds ratio after 4-week stabilisation phase was 1.27 [0.60, 2.68]; n = 152
Bryden 2009	Twice daily versus twice daily mild TCS under wet wraps, stepping down to once daily mild TCS after week 1	Parallel-group; children; mild to moderate eczema. Median decrease in SASSAD. No difference at end of treatment (unclear if 2 or 3 weeks; P = 0.74; n = 51)
Goh 1999	Twice daily very potent TCS versus once daily second-generation potent TCS	Within-participant; adults; moderate to severe eczema. At day 8, the number achieving cleared or marked improvement on IGA was 9 on the side treated with twice daily very potent TCS compared to 5 on the side treated with once daily second-generation potent TCS; OR 1.95 (95% CI 0.85 to 4.48; n = 58). At day 22, number achieving cleared or marked improvement was 41 on the side treated with twice daily very potent TCS compared to 16 on the side treated with once daily second-generation potent TCS; OR 6.33 (95% CI 3.58 to 11.20; n = 58)
Haneke 1992	Twice daily versus once daily potent TCS (C versus A)	Within-participant; adults; unspecified severity eczema. Reported no difference in IGA at week 4 (assumed n = 94 randomised)
Haneke 1992	Twice daily versus once daily potent TCS (B versus A)	Within-participant; adults; unspecified severity eczema. Reported no difference in IGA at week 4 (assumed n = 88 randomised)
Meffert 1999	Twice daily versus once daily potent TCS	Parallel-group (assumed); children; mild to moderate eczema. IGA; not clearly reported. Quote: "treatment with MPA milk and HCB lotio in children with atopic dermatitis showed particularly good results"; "in this study the clearest improvement of the target criterion were seen" (assumed n = 102 randomised)
Msika 2008	Twice daily versus once daily mild TCS (group C versus group A)	Parallel-group; children; mild to moderate eczema. Mean difference in SCORAD from baseline; no dispersion. Decrease of 20.01 in the twice daily TCS group (n = 18) and 23.90 in the once daily TCS group (n = 15) at day 7. Decrease of 20.98 in the twice daily TCS group (n = 18) and 20.00 in the once daily TCS group (n = 15) at day 21
Msika 2008	Twice daily versus once daily mild TCS (group D versus group B)	Parallel-group; children; mild to moderate eczema. Mean difference in SCORAD from baseline; no dispersion. Decrease of 20.78 in the twice daily TCS group (n = 17) and 22.36 in the once daily TCS group (n = 17) at day 7. Decrease of 24.94 in the twice daily TCS group (n = 17) and 26.00 in the once daily TCS group (n = 17) at day 21
Richelli 1990	Twice daily (group A+B) versus once daily moderate TCS (group C)	Parallel-group; children; unclear severity of eczema. Mean difference in unnamed scale from baseline; no dispersion. At day 7, mean decrease was 1.02 in the twice daily 8 am/3 pm group (n = 13), 1.10 in the twice daily 3 pm/8 pm group (n = 8), and 0.96 in the once daily group (n = 9). Extracted using WebPlotDigitizer
Vernon 1991	Twice daily mild TCS versus once daily second-generation potent TCS	Parallel-group; children; moderate to severe eczema. Mean decrease in unnamed scale from baseline; no dispersion. At end of treatment (week 6 or sooner if AD clearance was achieved), mean difference was 8.7; n = 24 (assumed) in the twice daily mild group. Mean difference was 10.7 in the once daily potent group; n = 23 (assumed). Extracted using WebPlotDigitizer
Wolkerstorfer 1998	Twice daily moderate-potency TCS with once daily second-generation potent TCS	Parallel-group; children; moderate-severity eczema. Short-term and end of treatment values are included in Analysis 7.5 and Analysis 7.6, respectively. At end of follow-up (week 6; 2 weeks post-treatment follow-up) mean ObjSCORAD was 21 ± 7 in the twice daily group compared to 23 ± 9 in the once daily group; MD = 5.00 [−7.67, 17.67]; n = 5

Analysis 7.8. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 8: Cleared or marked improvement on PGA (short term); parallel-group; all ages; all severities

Study or Subgroup	Twice daily (or more) Events	Total	Once daily Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Koopmans 1995 (1)	70	75	58	73	44.0%	3.62 [1.24 , 10.56]
Tharp 1996 (2)	58	76	56	76	56.0%	1.15 [0.55 , 2.40]
Total (95% CI)		**151**		**149**	**100.0%**	**1.91 [0.62 , 5.83]**
Total events:	128		114			

Heterogeneity: Tau² = 0.44; Chi² = 3.00, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable



Footnotes

(1) Week 4. Unspecified severity eczema.
(2) Day 8. Number 'excellent' or 'good'. Moderate to severe eczema.

Analysis 7.9. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 9: Included studies with no poolable patient-reported symptoms data

Included studies with no poolable patient-reported symptoms data

Study	Intervention and comparison	Comments
Itch		
Amerio 1998	Twice daily older potent TCS versus once daily second-generation potent TCS	Parallel-group; adults and children; moderate-severity eczema. Percentage reduction in patient-assessed itch (assumed; could be a more general symptoms assessment), 55.9% in both the once daily second-generation TCS group and the twice daily older TCS group at day 7. 85.5% in the once daily second-generation group and 77.7% in the twice daily older TCS group at end of treatment (day 8-15). 75.4% in the once daily second-generation group and 65.9% in the twice daily older TCS group at end of follow-up (day 23-30). Throughout, n = 47 (assumed) in the once daily second-generation TCS group and 50 in the twice daily older TCS group. Extracted using WebPlotDigitizer.
Beattie 2004	Twice daily mild potency TCS without occlusion versus once daily mild TCS under wet wraps (twice daily in the first week, then at night in the second week)	Parallel-group; children; moderate eczema. IDQOL score for itch VRS; no dispersion. Mean decrease at end of treatment (week 2) was 1.00 in the twice daily TCS without wet wraps group (n = 9) and 0.99 in the once daily TCS with wet wraps group (n = 10)
Bleehen 1995	Twice daily TCS versus once daily TCS	Parallel-group; adults and children; moderate to severe eczema. Mean itch score. The twice daily group experienced improvement for 5 days (n = 133; assumed) compared to 6 days in the once daily group (n = 137; assumed)
Sleep		
Beattie 2004	Twice daily mild potency TCS without occlusion versus once daily mild TCS under wet wraps (twice daily in the first week, then at night in the second week)	Parallel-group; children; moderate eczema IDQOL score for time taken to get to sleep; no dispersion. Mean decrease at end of treatment (week 2) was 0.89 in the twice daily without wet wraps group (n = 9) and 0.29 in the once daily TCS with wet wraps group (n = 10) IDQOL score for total sleep lost; no dispersion. Mean decrease at end of treatment (week 2) was 1.00 in the twice daily TCS without wet wraps group (n = 9) and 0.69 in the once daily TCS with wet wraps group (n = 10)
Bleehen 1995	Twice daily TCS versus once daily TCS	Parallel-group; adults and children; moderate to severe eczema. Percentage of participants reporting sleep had been "as good as ever has been" or better (week 4). 55% in the twice daily group (n = 133; assumed) and 37% in the once daily group (n = 137; assumed)
Patient global assessment		

Goh 1999	Twice daily very potent TCS versus once daily second-generation potent TCS	Within-participant; adults; moderate to severe eczema. At day 8, the number achieving an excellent response was 9 on the side treated with twice daily very potent TCS compared to 3 on the side treated with once daily second-generation potent TCS; OR 3.37 (95% CI 1.22 to 9.29; n = 58). At day 22, number achieving cleared or marked improvement was 25 on the side treated with twice daily very potent TCS compared to 6 on the side treated with once daily second-generation potent TCS; OR 6.57 (95% CI 3.14 to 13.74; n = 58)
Haneke 1992	Twice daily TCS versus once daily TCS (C versus B)	Within-participant study; adults; unspecified severity eczema. Patient global assessment was stated to be consistent with the investigator global assessment (Analysis 7.7 n = 88; assumed)
Haneke 1992	Twice daily TCS versus once daily TCS (C versus A)	Within-participant study; adults; unspecified severity eczema. Patient global assessment was stated to be consistent with the investigator global assessment (Analysis 7.7; n = 94; assumed)
Hoybye 1991	Twice daily older potent TCS versus once daily second-generation potent TCS	Parallel-group; adults; at least moderate-severity eczema. There was no difference in efficacy between groups at weeks 3 and 6 (VAS; P = 0.30; n = 94; assumed)
Rafanelli 1993	Twice daily moderate potency TCS versus once daily second-generation potent TCS	Parallel-group; children; moderate to severe eczema. Patient global assessment was stated to be consistent with the investigator global assessment (Analysis 7.1; n = 60; assumed)
Unnamed scale		
Richelli 1990	Twice daily TCS (group A+B) versus once daily TCS (group C)	Parallel-group; children; unclear severity of eczema. Mean difference in unnamed scale from baseline; no dispersion. At day 7, mean decrease was 1.14 in the twice daily 8 am/3 pm group (n = 13), 0.60 in the twice daily 3 pm/8 pm group (n = 8), and 0.52 in the once daily group (n = 9). Extracted using WebPlotDigitizer

Analysis 7.10. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 10: Number of participants with skin thinning or related signs; end of treatment

Number of participants with skin thinning or related signs; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Skin thinning								
Amerio 1998	Parallel- group	Twice daily potent	Once daily second-generation potent	Adults and children; ≥ moderate-severity eczema	Up to day 15	0/47	0/50	
Del Rosso 2009	Parallel- group	Twice daily very potent	Once daily very potent	Adults; ≥ moderate-severity eczema	Up to week 2	3/102	3/109	
Goh 1999	Within- participant	Twice daily very potent	Once daily second-generation potent	Adults; moderate to severe eczema	Up to day 22	0/58	0/58	
Haneke 1992	Within- participant	Twice daily potent (C)	Once daily potent (B)	Adults; unspecified severity eczema	Up to week 4	0/88	0/88	
Haneke 1992	Within- participant	Twice daily potent (C)	Once daily potent (A)	Adults; unspecified severity eczema	Up to week 4	0/94	0/94	
Hoybye 1991	Parallel- group	Twice daily potent	Once daily second-generation potent	Adults; ≥ moderate-severity eczema	Up to week 6	0/45	0/49	
Lebwohl 1999	Parallel- group	Twice daily moderate	Once daily second-generation potent	Children; moderate to severe eczema	Up to day 22	0/110	0/109	
Nolting 1991	Parallel- group	Twice daily moderate	Once daily second-generation potent	Adults; unspecified severity eczema	Up to week 3	2/34	2/33	

Rafanelli 1993	Parallel- group	Twice daily moderate	Once daily second-generation potent	Children; moderate to severe eczema	up to week 3	0/30	0/30
Ryu 1997	Parallel- group	Twice daily mild	Once daily second-generation potent	Adults and children; mild- to moderate-severity eczema	Up to day 14	0/12	0/12
Schlessinger 2006	Parallel- group	Twice daily very potent	Once daily very potent	Children; moderate to severe eczema.	Up to week 2	5/62	5/62
Vernon 1991	Parallel- group	Twice daily mild	Once daily second-generation potent	Children; moderate to severe eczema	up to week 6	0/24	0/23
Striae							
Berth-Jones 2003	Parallel- group	Twice daily second-generation potent (group D)	Once daily second-generation potent (group C)	Adults and children; moderate to severe eczema	Up to 4 weeks (acute treatment phase)	0/90	1/100
Berth-Jones 2003	Parallel- group	Twice daily second-generation potent (group B)	Once daily second-generation potent (group A)	Adults and children; moderate to severe eczema	Up to 4 weeks (acute treatment phase)	0/91	0/95
Del Rosso 2009	Parallel- group	Twice daily very potent	Once daily very potent	Adults; ≥ moderate-severity eczema	Up to week 2	1/102	1/109
Haneke 1992	Within- participant	Twice daily potent (C)	Once daily potent (B)	Adults; unspecified severity eczema	Up to week 4	0/88	0/88
Haneke 1992	Within- participant	Twice daily potent (C)	Once daily potent (A)	Adults; unspecified severity eczema	Up to week 4	0/94	0/94
Telangiectasia							
Berth-Jones 2003	Parallel- group	Twice daily second-generation potent (group B)	Once daily second-generation potent (group A)	Adults and children; moderate to severe eczema	Up to 4 weeks (acute treatment phase)	1/91	0/95
Berth-Jones 2003	Parallel- group	Twice daily second-generation potent (group D)	Once daily second-generation potent (group C)	Adults and children; moderate to severe eczema	Up to 4 weeks (acute treatment phase)	0/90	1/100
Del Rosso 2009	Parallel- group	Twice daily very potent	Once daily very potent	Adults; ≥ moderate-severity eczema	Up to week 2	1/102	1/109
Haneke 1992	Within- participant	Twice daily potent (C)	Once daily potent (B)	Adults; unspecified severity eczema	Up to week 4	0/88	0/88
Haneke 1992	Within- participant	Twice daily potent (C)	Once daily potent (A)	Adults; unspecified severity eczema	Up to week 4	0/94	0/94
Transparency							
Del Rosso 2009	Parallel- group	Twice daily very potent	Once daily very potent	Adults; ≥ moderate-severity eczema	Up to week 2	1/102	2/109
Loss of elasticity							
Del Rosso 2009	Parallel- group	Twice daily very potent	Once daily very potent	Adults; ≥ moderate-severity eczema	Up to week 2	5/102	4/109
Loss of normal skin markings							
Del Rosso 2009	Parallel- group	Twice daily very potent	Once daily very potent	Adults; ≥ moderate-severity eczema	Up to week 2	2/102	6/109
Bruising							
Del Rosso 2009	Parallel- group	Twice daily very potent	Once daily very potent	Adults; ≥ moderate-severity eczema	Up to week 2	2/102	0/109
Pigmentation change							

Ryu 1997	Parallel- group	Twice daily mild	Once daily second-generation potent	Adults and children; mild- to moderate-severity eczema	Up to day 14	0/12	0/12	

Analysis 7.11. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 11: Number of participants with local site reactions; end of treatment

Number of participants with local site reactions; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Burning								
Rampini 1992a	Parallel- group	Twice daily moderate	Once daily potent	Children; unspecified severity eczema	Day 21	0/53	0/55	
Tharp 1996	Parallel- group	Twice daily potent	Once daily potent	Adults and children; moderate to severe eczema	Day 29	0/77	2/77	
Pruritus								
Bleehen 1995	Parallel- group	Twice daily second-generation potent	Once daily second-generation potent	Adults and children; moderate to severe eczema	Up to 4 weeks	1/133	4/137	Reported by event rather than participant
Tharp 1996	Parallel- group	Twice daily potent	Once daily potent	Adults and children; moderate to severe eczema	Day 29	1/77	0/77	
Stinging								
Tharp 1996	Parallel- group	Twice daily potent	Once daily potent	Adults and children; moderate to severe eczema	Day 29	1/77	0/77	
Vernon 1991	Parallel- group	Twice daily mild	Once daily second-generation potent	Children; moderate to severe eczema	Week 6	0/24	3/23	N assumed
Burning, itching, or stinging								
Koopmans 1995	Parallel-group	Twice daily potent	Once daily potent	Adults and children; unspecified severity	Week 4	0/75	3/75	
Irritation								
Bleehen 1995	Parallel- group	Twice daily second-generation potent	Once daily second-generation potent	Adults and children; moderate to severe eczema	Up to 4 weeks	2/133	5/137	Reported by event rather than participant
Tharp 1996	Parallel- group	Twice daily potent	Once daily potent	Adults and children; moderate to severe eczema	Day 29	1/77	0/77	
Unspecified								
Lebwohl 1999	Parallel- group	Twice daily moderate	Once daily second-generation potent	Children; moderate to severe eczema	Up to day 22	2/110	4/109	
Marchesi 1994	Parallel- group	Twice daily older TCS	Once daily second-generation potent TCS	Adults; moderate to severe eczema	Up to week 3	0/30	0/30	
Sudilovsky 1981	Within- participant	Three times daily potent TCS	Once daily potent TCS	Unspecified	Up to week 3	?/149	?/149	Quote: "In both parts of the study side effects were generally of a mild nature, the most common being local

								burning, pruritus, and erythema. There were no differences in incidence between halcinonide od and tid regimens and the control vehicle."

Analysis 7.12. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 12: Number of participants with skin infections; end of treatment

Number of participants with skin infections; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Folliculitis								
Beattie 2004	Parallel- group	Twice daily mild without wet wrap	Once daily mild with wet wrap (twice daily in the first week, then at night in the second week)	Children; moderate eczema	Up to week 3	0/10	2/10	No treatment during the third week
Koopmans 1995	Parallel- group	Twice daily potent	Once daily potent	Adults and children; ≥ moderate severity eczema	Up to week 4	1/75	4/75	
Ryu 1997	Parallel- group	Twice daily mild	Once daily second-generation potent	Adults and children; mild to moderate severity eczema	Day 14 (assumed)	0/12	1/12	
Impetigo contagiosa								
Rampini 1992a	Parallel- group	Twice daily moderate	Once daily potent	Children; unspecified severity eczema	Day 21	0/53	1/55	Required a short-term antibiotic, participant continued the trial, complete healing occurred
Acne								
Ryu 1997	Parallel- group	Twice daily mild	Once daily second-generation potent	Adults and children; mild- to moderate-severity eczema	Day 14 (assumed)	0/12	0/12	
Papules								
Ryu 1997	Parallel- group	Twice daily mild	Once daily second-generation potent	Adults and children; mild- to moderate-severity eczema	Day 14 (assumed)	0/12	0/12	Maculopapular rash
Staphylococcus aureus infection (scalp)								
Vernon 1991	Parallel- group	Twice daily mild	Once daily second-generation potent	Children; moderate to severe eczema	Up to week 6	0/24	1/23	N assumed. Occurred at 36 days and resulted in discontinuation

Analysis 7.13. Comparison 7: Twice or more versus once daily topical corticosteroid (TCS), Outcome 13: Number of participants with abnormal cortisol

Number of participants with abnormal cortisol

Study	Intervention and comparison	Cases/N A	Cases/N B	Additional information
Del Rosso 2009	Twice daily very potent TCS versus once daily very potent TCS	1/?	4/?	Adults; moderate to severe eczema. Event defined as serum cortisol (pre-stimulation) ≤ 5 µg/dL, or 30-minute post-stimulation ≤ 18 µg/dL, or post-stimulation increase over the basal level < 7 µg/dL. Cosyntropin stimulation tests were only performed at certain centres (unclear which) at baseline and week 2, and participants with abnormal results were tested again at week 4 (2 weeks' post-treatment). It was stated that there was no significant difference in HPA suppression between groups and that application for 14 days was safe. Levels returned to normal by the follow-up visit in all participants with repeat results (assumed to be all events). No further information was available from the trial authors
Hoybye 1991	Twice daily potent TCS versus once daily second-generation potent TCS	?/9	?/9	Adults; ≥ moderate-severity eczema. Morning plasma cortisol at baseline, week 3 and week 6. It was stated that there was no significant difference in plasma cortisol between the two groups; median (range) was reported with no indication of how many people were outside of the normal range. Twice daily TCS group: 470 (183 to 720; n = 10) at baseline; 420 (183 to 910; n = 9) at week 3; 485 (168 to 1240; n = 6) at week 6 Once daily TCS group: 430 (330 to 920; n = 9) at baseline; 450 (273 to 710; n = 9) at week 3; 460 (167 to 1020; n = 9) at week 6 Normal range was stated to be 190 to 600 nmol/L
Rafanelli 1993	Twice daily moderate TCS versus once daily second-generation potent TCS	0/30	0/30	Children; moderate to severe eczema. Blood cortisol at baseline and week 3
Richelli 1990	Twice daily TCS (group A+B) versus once daily TCS (group C)	?/21	?/9	Children; unclear severity of eczema. Serum cortisol and ACTH concentrations at baseline and day 7, 8 am and 4 pm. Authors report no significant difference in serum cortisol and ACTH after treatment relative to baseline in any of the three groups; insufficient information to judge changes in individual participants' levels. N assumed
Schlessinger 2006	Twice daily very potent TCS versus once daily very potent TCS	3/61	0/60	Children; moderate to severe eczema. Event defined as serum cortisol of ≤ 18 µg/dL (≤ 497 nmol/L) 30 minutes after intravenous cosyntropin stimulation. They were only just below the reference threshold and levels returned to normal within 4 weeks of treatment cessation. Week 2

Vernon 1991	Twice daily mild TCS versus once daily second-generation potent TCS	1/24	0/23	Children; moderate to severe eczema. Morning plasma cortisol at baseline, week 1 and end of treatment (up to week 6). Event detected at week 1 (< 5.0 µg/dL) and was transient. N assumed
Wolkerstorfer 1998	Twice daily moderate TCS versus once daily second-generation potent TCS	1/9	0/12	Children; moderate to severe eczema. Urinary cortisol excretion at baseline and end of treatment (week 4). One participant decreased from 162.8 nmol/24 h at baseline to 67 nmol/24 h at end of treatment, and returned to normal by two weeks' post-treatment follow-up. N assumed

Comparison 8. Daily application versus less frequent application

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Included studies with no poolable clinician-reported signs data	4		Other data	No numeric data

Analysis 8.1. Comparison 8: Daily application versus less frequent application, Outcome 1: Included studies with no poolable clinician-reported signs data

Included studies with no poolable clinician-reported signs data

Study	Intervention and comparison	Comments
Mahrle 1989	Twice daily TCS versus TCS treatment with 1-day interval (A versus B)	Within-participant; adults and children; moderate to severe eczema. Unnamed scale. 51.0% reduction on the continuously-treated side and 47.5% on the interval side at day 7 (n = 15). 97.2% reduction on both sides at end of treatment (day 21). Extracted using WebPlotDigitizer
Mahrle 1989	Twice daily TCS versus TCS treatment with 3-day interval (A versus D)	Within-participant; adults and children; moderate to severe eczema. Unnamed scale. 42.3% reduction on the continuously-treated side and 46.7% on the interval side at day 7 (n = 13). 98.7% reduction on the continuously-treated side and 94.0% on the interval side at end of treatment (day 21). Extracted using WebPlotDigitizer
Mahrle 1989	Twice daily TCS versus TCS treatment with 2-day interval (A versus C)	Within-participant; adults and children; moderate to severe eczema. Unnamed scale. 48.3% reduction on the continuously-treated side and 43.5% on the interval side at day 7 (n = 16). 93.8% reduction on both sides at end of treatment (day 21). Extracted using WebPlotDigitizer
Msika 2008	Daily mild TCS with emollient versus every other day TCS with emollient (group B versus group E)	Parallel-group; children; mild to moderate eczema. Mean difference in SCORAD from baseline; no dispersion. Decrease of 22.36 in the daily TCS group (n = 17) and 19.21 in the every other day TCS group (n = 19) at day 7. Decrease of 26.00 in the daily TCS group (n = 17) and 26.88 in the every other day TCS group (n = 19) at day 21
Sillevis 2000	Daily moderate TCS versus 4-day 'pulse' moderate TCS	Parallel-group; children; moderate to severe eczema. Mean decrease in ObjSCORAD relative to baseline. Mean difference was −8.00 (95% CI −15.41 to -0.59) in favour of less frequent use; week 8; n = 20 in each group
Thomas 2002	3-day 'pulse' of potent TCS versus 7 days of mild TCS	Parallel-group; children; mild to moderate eczema; community patients only. Number of participants with > 20% improvement in SASSAD. Odds ratio at end of

treatment was 0.95 (95% CI 0.52 to 1.74); week 18; n = 87 in both groups

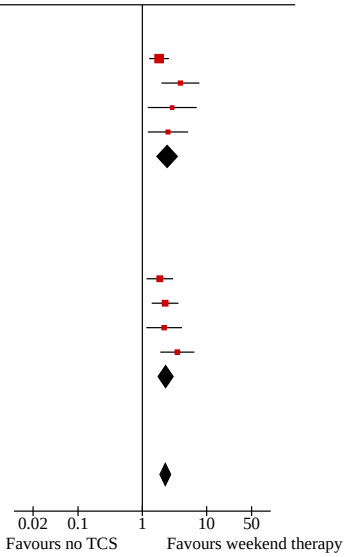
Comparison 9. Weekend therapy versus no topical corticosteroid (TCS)/reactive application

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Time to relapse; parallel-group studies; all ages; all severities	7	1149	Hazard Ratio (IV, Random, 95% CI)	2.28 [1.88, 2.76]
9.1.1 Log rank	4	558	Hazard Ratio (IV, Random, 95% CI)	2.43 [1.68, 3.50]
9.1.2 Cox's proportional hazards	3	591	Hazard Ratio (IV, Random, 95% CI)	2.30 [1.76, 3.01]
9.2 Time to relapse; children; all severities	3	231	Hazard Ratio (IV, Random, 95% CI)	2.87 [1.90, 4.34]
9.3 Time to relapse; all ages; split by severity	7	1149	Hazard Ratio (IV, Random, 95% CI)	2.26 [1.87, 2.73]
9.3.1 Moderate to severe eczema	5	993	Hazard Ratio (IV, Random, 95% CI)	2.12 [1.73, 2.60]
9.3.2 Mild- to moderate-severity eczema	2	156	Hazard Ratio (IV, Random, 95% CI)	3.50 [2.04, 6.00]
9.4 Number of participants with one or more relapses; parallel-group studies; all ages; all severities	7	1149	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.32, 0.57]
9.5 Number of participants with one or more relapses; all severities; split by age	5	633	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.30, 0.56]
9.5.1 Adults	2	171	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.24, 0.75]
9.5.2 Children	4	462	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.24, 0.62]
9.6 Number of participants with one or more relapses; all ages; split by severity	7	1149	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.32, 0.57]
9.6.1 Moderate to severe eczema	5	993	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.35, 0.61]
9.6.2 Mild to moderate eczema	2	156	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.04, 1.24]
9.7 Included studies with no poolable patient-reported symptoms data	4		Other data	No numeric data
9.7.1 Itch	2		Other data	No numeric data
9.7.2 Sleep	2		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.7.3 Patient global assessment	2		Other data	No numeric data
9.8 Number of participants with skin thinning or related signs; end of treatment	7		Other data	No numeric data
9.8.1 Skin thinning	7		Other data	No numeric data
9.8.2 Telangiectasia	3		Other data	No numeric data
9.8.3 Striae	2		Other data	No numeric data
9.9 Number of participants with skin infection; end of treatment	2		Other data	No numeric data
9.9.1 Acne	1		Other data	No numeric data
9.9.2 Eczema herpeticum	1		Other data	No numeric data
9.9.3 Impetigo contagiosa	1		Other data	No numeric data
9.10 Number of participants with abnormal cortisol	5		Other data	No numeric data
9.11 Definition of relapse	7		Other data	No numeric data

Analysis 9.1. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/ reactive application, Outcome 1: Time to relapse; parallel-group studies; all ages; all severities

Study or Subgroup	log[Hazard Ratio]	SE	Weekend therapy Total	No TCS Total	Weight	Hazard Ratio IV, Random, 95% CI
9.1.1 Log rank						
Hanifin 2002 (1)	0.597	0.18	229	119	29.5%	1.82 [1.28 , 2.59]
Liu 2018 (1)	1.363	0.348	54	53	7.9%	3.91 [1.98 , 7.73]
Rubio-Gomis 2018 (2)	1.069	0.448	26	23	4.8%	2.91 [1.21 , 7.01]
Van Der Meer 1999 (3)	0.9171	0.3692	23	31	7.0%	2.50 [1.21 , 5.16]
Subtotal (95% CI)			**332**	**226**	**49.1%**	**2.43 [1.68 , 3.50]**
Heterogeneity: Tau² = 0.04; Chi² = 4.34, df = 3 (P = 0.23); I² = 31%						
Test for overall effect: Z = 4.75 (P < 0.00001)						
9.1.2 Cox's proportional hazards						
Berth-Jones 2003 (4)	0.625	0.243	68	73	16.2%	1.87 [1.16 , 3.01]
Berth-Jones 2003 (5)	0.815	0.245	70	84	15.9%	2.26 [1.40 , 3.65]
Glazenburg 2009 (3)	0.7802	0.3255	39	36	9.0%	2.18 [1.15 , 4.13]
Peserico 2008 (6)	1.2528	0.3117	112	109	9.8%	3.50 [1.90 , 6.45]
Subtotal (95% CI)			**289**	**302**	**50.9%**	**2.30 [1.76 , 3.01]**
Heterogeneity: Tau² = 0.00; Chi² = 2.58, df = 3 (P = 0.46); I² = 0%						
Test for overall effect: Z = 6.08 (P < 0.00001)						
Total (95% CI)			**621**	**528**	**100.0%**	**2.28 [1.88 , 2.76]**
Heterogeneity: Tau² = 0.00; Chi² = 6.93, df = 7 (P = 0.44); I² = 0%						
Test for overall effect: Z = 8.42 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%						

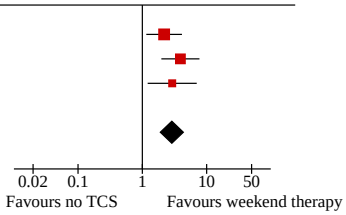


Footnotes

(1) Up to week 20 (+4 weeks acute phase).
(2) Up to week 16 (+2 weeks acute phase).
(3) Up to week 16 (+4 weeks acute phase).
(4) Group H versus group G. Up to week 16 (+4 weeks acute phase).
(5) Group F versus group E. Up to week 16 (+4 weeks acute phase).
(6) Up to week 16 (+4 weeks acute phase). Used methylprednisolone aceponate.

Analysis 9.2. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/reactive application, Outcome 2: Time to relapse; children; all severities

Study or Subgroup	log[Hazard Ratio]	SE	Weekend therapy Total	No TCS Total	Weight	Hazard Ratio IV, Random, 95% CI
Glazenburg 2009 (1)	0.7802	0.3255	39	36	41.6%	2.18 [1.15 , 4.13]
Liu 2018 (2)	1.363	0.348	54	53	36.4%	3.91 [1.98 , 7.73]
Rubio-Gomis 2018 (3)	1.069	0.448	26	23	22.0%	2.91 [1.21 , 7.01]
Total (95% CI)			**119**	**112**	**100.0%**	**2.87 [1.90 , 4.34]**
Heterogeneity: Tau² = 0.00; Chi² = 1.50, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 5.03 (P < 0.00001)						
Test for subgroup differences: Not applicable						

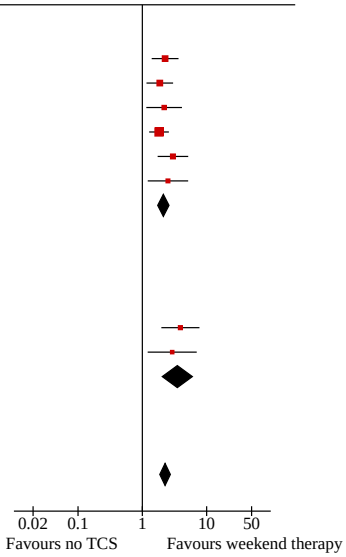


Footnotes

(1) Up to 16 weeks.
(2) Up to week 20 (+4 weeks acute phase).
(3) Up to week 16 (+2 weeks acute phase).

Analysis 9.3. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/reactive application, Outcome 3: Time to relapse; all ages; split by severity

Study or Subgroup	log[Hazard Ratio]	SE	Weekend therapy Total	No TCS Total	Weight	Hazard Ratio IV, Random, 95% CI
9.3.1 Moderate to severe eczema						
Berth-Jones 2003 (1)	0.815	0.245	70	84	15.5%	2.26 [1.40 , 3.65]
Berth-Jones 2003 (2)	0.625	0.243	68	73	15.8%	1.87 [1.16 , 3.01]
Glazenburg 2009 (3)	0.7802	0.3255	39	36	8.8%	2.18 [1.15 , 4.13]
Hanifin 2002 (4)	0.597	0.18	229	119	28.8%	1.82 [1.28 , 2.59]
Peserico 2008 (5)	1.0953	0.2792	112	109	12.0%	2.99 [1.73 , 5.17]
Van Der Meer 1999 (6)	0.9171	0.3692	23	31	6.8%	2.50 [1.21 , 5.16]
Subtotal (95% CI)			**541**	**452**	**87.7%**	**2.12 [1.73 , 2.60]**
Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 5 (P = 0.73); I² = 0%						
Test for overall effect: Z = 7.29 (P < 0.00001)						
9.3.2 Mild- to moderate-severity eczema						
Liu 2018 (4)	1.363	0.348	54	53	7.7%	3.91 [1.98 , 7.73]
Rubio-Gomis 2018 (7)	1.069	0.448	26	23	4.6%	2.91 [1.21 , 7.01]
Subtotal (95% CI)			**80**	**76**	**12.3%**	**3.50 [2.04 , 6.00]**
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 4.56 (P < 0.00001)						
Total (95% CI)			**621**	**528**	**100.0%**	**2.26 [1.87 , 2.73]**
Heterogeneity: Tau² = 0.00; Chi² = 5.97, df = 7 (P = 0.54); I² = 0%						
Test for overall effect: Z = 8.43 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.91, df = 1 (P = 0.09), I² = 65.6%						



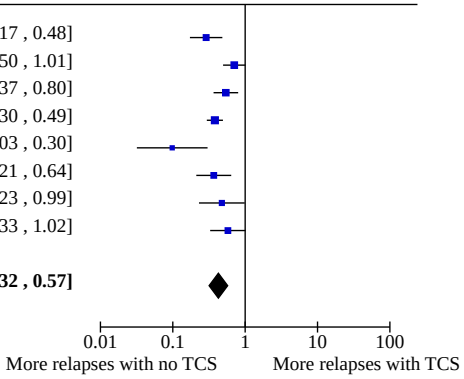
Footnotes

(1) Group F versus group E. Up to week 20 (including 4 weeks acute phase).
(2) Group H versus group G. Up to week 20 (including 4 weeks acute phase).
(3) Up to 16 weeks.
(4) Up to week 20 (+4 weeks acute phase).
(5) Up to 16 weeks. Used methylprednisolone aceponate.
(6) Up to week 16 (+4 weeks acute phase).
(7) Up to week 16 (+2 weeks acute phase).

Analysis 9.4. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/reactive application, Outcome 4: Number of participants with one or more relapses; parallel-group studies; all ages; all severities

Study or Subgroup	Weekend therapy Events	Total	No TCS Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Berth-Jones 2003 (1)	13	70	54	84	12.7%	0.29 [0.17 , 0.48]
Berth-Jones 2003 (2)	27	68	41	73	16.0%	0.71 [0.50 , 1.01]
Glazenburg 2009 (3)	17	39	29	36	15.2%	0.54 [0.37 , 0.80]
Hanifin 2002 (4)	58	229	79	119	18.0%	0.38 [0.30 , 0.49]
Liu 2018 (4)	3	54	30	53	5.2%	0.10 [0.03 , 0.30]
Peserico 2008 (5)	14	112	37	109	12.0%	0.37 [0.21 , 0.64]
Rubio-Gomis 2018 (6)	7	26	13	23	9.2%	0.48 [0.23 , 0.99]
Van Der Meer 1999 (3)	9	23	21	31	11.8%	0.58 [0.33 , 1.02]
Total (95% CI)		**621**		**528**	**100.0%**	**0.43 [0.32 , 0.57]**
Total events:	148		304			

Heterogeneity: Tau² = 0.11; Chi² = 20.99, df = 7 (P = 0.004); I² = 67%
Test for overall effect: Z = 5.67 (P < 0.00001)
Test for subgroup differences: Not applicable

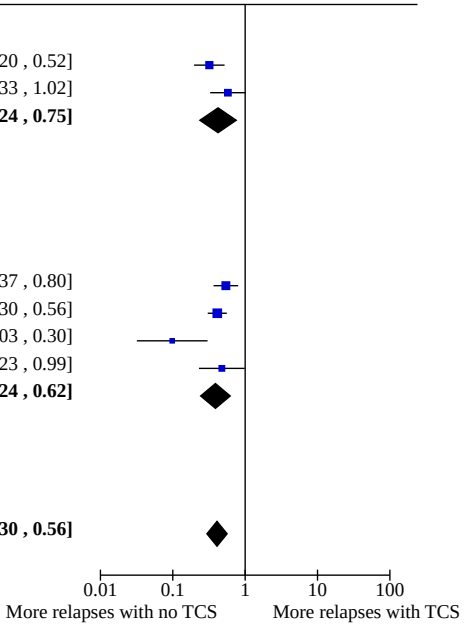


Footnotes

(1) Group F versus group E. Up to week 16 (+4 weeks acute phase).
(2) Group H versus group G. Up to week 16 (+4 weeks acute phase).
(3) Up to week 16 (+4 weeks acute phase).
(4) Up to week 20 (+4 weeks acute phase).
(5) Up to week 16 (+4 weeks acute phase). Used methylprednisolone aceponate.
(6) Up to week 16 (+2 weeks acute phase).

Analysis 9.5. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/reactive application, Outcome 5: Number of participants with one or more relapses; all severities; split by age

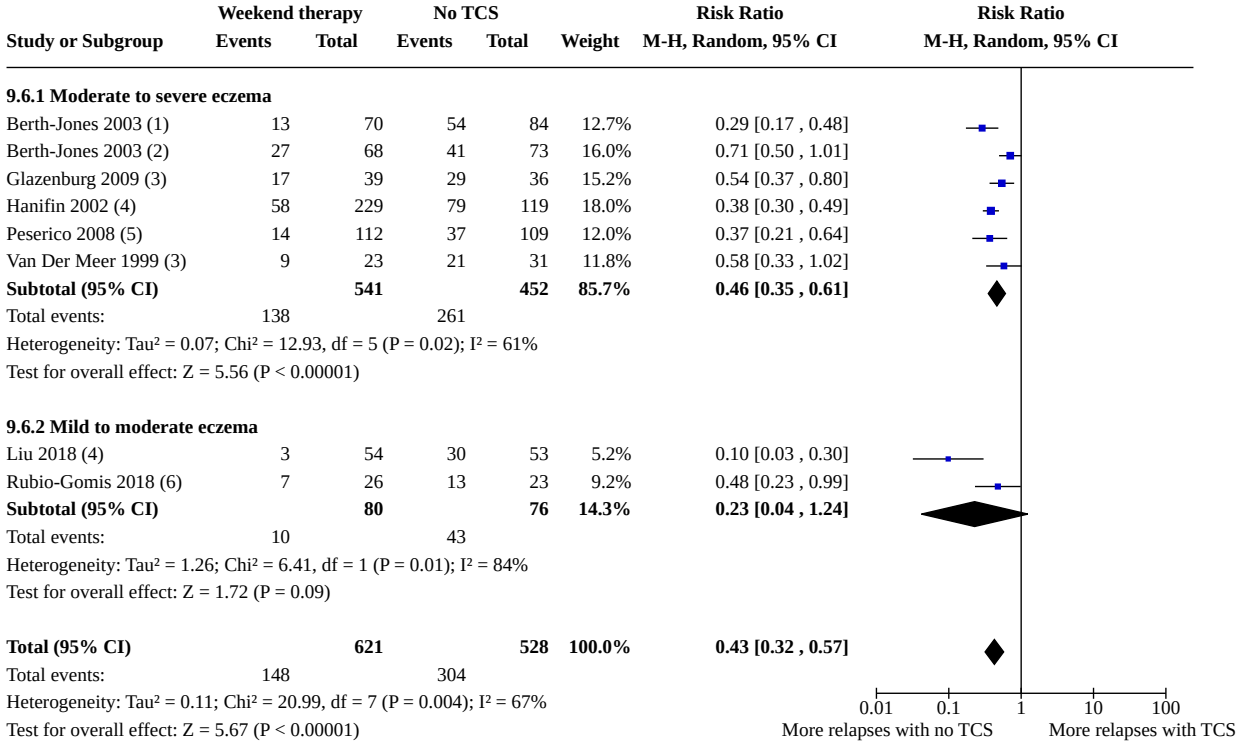
Study or Subgroup	Weekend therapy Events	Total	No TCS Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
9.5.1 Adults						
Hanifin 2002 (1)	16	75	28	42	18.6%	0.32 [0.20 , 0.52]
Van Der Meer 1999 (2)	9	23	21	31	16.1%	0.58 [0.33 , 1.02]
Subtotal (95% CI)		**98**		**73**	**34.7%**	**0.42 [0.24 , 0.75]**
Total events:	25		49			
Heterogeneity: Tau² = 0.10; Chi² = 2.43, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 2.92 (P = 0.003)						
9.5.2 Children						
Glazenburg 2009 (2)	17	39	29	36	21.7%	0.54 [0.37 , 0.80]
Hanifin 2002 (1)	42	154	51	77	25.0%	0.41 [0.30 , 0.56]
Liu 2018 (1)	3	54	30	53	6.5%	0.10 [0.03 , 0.30]
Rubio-Gomis 2018 (3)	7	26	13	23	12.1%	0.48 [0.23 , 0.99]
Subtotal (95% CI)		**273**		**189**	**65.3%**	**0.39 [0.24 , 0.62]**
Total events:	69		123			
Heterogeneity: Tau² = 0.14; Chi² = 9.41, df = 3 (P = 0.02); I² = 68%						
Test for overall effect: Z = 3.94 (P < 0.0001)						
Total (95% CI)		**371**		**262**	**100.0%**	**0.41 [0.30 , 0.56]**
Total events:	94		172			
Heterogeneity: Tau² = 0.08; Chi² = 11.58, df = 5 (P = 0.04); I² = 57%						
Test for overall effect: Z = 5.46 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%						



Footnotes

(1) Up to week 20 (+4 weeks acute phase).
(2) Up to week 16 (+4 weeks acute phase).
(3) Up to week 16 (+2 weeks acute phase).

Analysis 9.6. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/reactive application, Outcome 6: Number of participants with one or more relapses; all ages; split by severity



Footnotes

(1) Group F versus group E. Up to week 16 (+4 weeks acute phase).
(2) Group H versus group G. Up to week 16 (+4 weeks acute phase).
(3) Up to week 16 (+4 weeks acute phase).
(4) Up to week 20 (+4 weeks acute phase).
(5) Up to 16 weeks. Used methylprednisolone aceponate.
(6) Up to week 16 (+2 weeks acute phase).

Analysis 9.7. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/reactive application, Outcome 7: Included studies with no poolable patient-reported symptoms data

Included studies with no poolable patient-reported symptoms data

Study	Intervention and comparison	Comments
Itch		
Peserico 2008	Weekend therapy versus no TCS/reactive application	Parallel-group; adults and children; moderate to severe eczema. Mean change in 100 mm VAS relative to the beginning of the maintenance phase; no dispersion. 3.58 in the weekend therapy group (n = 112) compared to 20.61 in the emollient only group (n = 109) at week 2. 5.6 in the weekend therapy group (n = 112) compared to 23.3 in the emollient only group (n = 109) at week 16. Extracted using WebPlotDigitizer
Rubio-Gomis 2018	Weekend therapy versus no TCS/reactive application	Parallel-group; children; mild to moderate eczema. Itch NRS. Decrease from 5.5 at baseline (week −2; SD 2.2) to 0.8 up to week 16 (+2 weeks acute phase) in the weekend therapy group (95% CI 0.03-1.57; n = 26). Decrease from 5.7 (SD 2.1) to 2.9 in the vehicle group (1.63-4.17; n = 23). Mean difference between groups −1.90 (95% CI −3.26, −0.54) in favour of weekend therapy
Sleep		

Peserico 2008	Weekend therapy versus no TCS/reactive application	Parallel-group; adults and children; moderate to severe eczema. Trial authors state that "mean quality of sleep worsened only slightly under MPA treatment, whereas it clearly deteriorated in patients using emollient alone".
Rubio-Gomis 2018	Weekend therapy versus no TCS/reactive application	Parallel-group; children; mild to moderate eczema. Sleep NRS. Decrease from 1.0 at baseline (week −2; SD: 2.1) to 0.4 up to week 16 (+2 weeks acute phase) in the weekend therapy group (95% CI −0.3 to 1.1; n = 26). Decrease from 1.6 (SD: 2.2) to 0.7 in the vehicle group (0.0 to 1.4; n = 23). Mean difference between groups 0.30 (95% CI −0.80 to 1.40)
Patient global assessment		
Hanifin 2002	Weekend therapy versus no TCS/reactive application	Parallel-group; moderate to severe eczema. Number of participants judging their eczema to be excellent or good. 163 judged their eczema to be excellent or good in the weekend therapy group (n = 225). 38 judged their eczema to be excellent or good in the vehicle group (n = 118). Risk ratio for adults and children at end of treatment (week 20 + 4 weeks acute phase) was 2.25 [1.71, 2.96]; n = 343. Risk ratio for adults only was 2.54 [1.54, 4.18]; n = 115. Risk ratio for children only was 2.12 [1.53, 2.93]; n = 228
Liu 2018	Weekend therapy versus no TCS/reactive application	Parallel-group; children; mild to moderate eczema. Unnamed scale; no dispersion. The weekend therapy arm scored 0.4 at end of treatment (week 20 + 4 weeks acute phase; n = 54) compared to 0.9 in the emollient only arm (n = 53). At week 32 (12 weeks post-treatment), score in the weekend therapy arm was 0.9 (n = 54) compared to 1.8 in the emollient only arm (n = 53)

Analysis 9.8. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/reactive application, Outcome 8: Number of participants with skin thinning or related signs; end of treatment

Number of participants with skin thinning or related signs; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Skin thinning								
Berth-Jones 2003	Parallel group	Twice weekly potent second-generation TCS cream (group F)	Twice weekly placebo cream (group E)	Adults and children; moderate to severe eczema	Up to week 16 (+4 weeks acute phase)	0/70	0/84	
Berth-Jones 2003	Parallel group	Twice weekly potent second-generation TCS ointment (group H)	Twice weekly placebo ointment (group G)	Adults and children; moderate to severe eczema	Up to week 16 (+4 weeks acute phase)	0/68	0/73	
Fukuie 2016	Parallel group	Twice weekly potent TCS unless controlling a flare (twice daily)	No treatment unless controlling a flare (daily emollient for one week, escalating to TCS if no improvement)	Children; moderate to severe eczema	Up to 12 months	0/15	0/15	
Glazenburg 2009	Parallel group	Twice weekly potent second-generation TCS with emollient	Twice weekly placebo with emollient	Children; mild- to moderate-severity eczema	Up to week 16 (+4 weeks acute phase)	0/39	0/36	See Analysis 9.8.2.
Hanifin 2002	Parallel group	Twice weekly potent second-generation TCS with emollient (once daily 4 days/week for 4 weeks followed by once	Twice weekly placebo with emollient (once daily 4 days/ week for 4 weeks followed by once daily 2 days/ week)	Adults and children; moderate to severe eczema	Up to week 20 (+4 weeks acute phase; assumed)	0/229	0/119	

		daily 2 days/ week)						
Peserico 2008	Parallel group	Twice weekly potent TCS with emollient	Emollient alone	Adults and children; moderate to severe eczema	Up to week 16 (+4 weeks acute phase)	0/112	0/109	
Rubio-Gomis 2018	Parallel group	Twice weekly potent second-generation TCS with emollient	Twice weekly placebo with emollient	Children; mild- to moderate-severity eczema	Up to week 16 (+2 weeks acute phase)	0/26	0/23	
Van Der Meer 1999	Parallel group	Twice weekly potent second-generation TCS	Twice weekly placebo	Adults; moderate to severe eczema	Up to week 16 (+4 weeks acute phase)	0/13	0/19	
Telangiectasia								
Fukuie 2016	Parallel- group	Twice weekly TCS unless controlling a flare (twice daily)	No treatment unless controlling a flare (daily emollient for one week, escalating to TCS if no improvement)	Children; moderate to severe eczema	Up to 12 months	0/15	0/15	
Glazenburg 2009	Parallel- group	Twice weekly potent second-generation TCS with emollient	Twice weekly placebo with emollient	Children; mild- to moderate-severity eczema	Up to week 16 (+4 weeks acute phase)	1/39	1/36	Described as "pre-atrophy"; occurred at 8 weeks in the weekend therapy group and at the end of the acute phase in the placebo group
Rubio-Gomis 2018	Parallel- group	Twice weekly potent second-generation TCS with emollient	Twice weekly placebo with emollient	Children; mild- to moderate-severity eczema	Up to week 16 (+2 weeks acute phase)	0/26	0/23	
Striae								
Fukuie 2016	Parallel- group	Twice weekly TCS unless controlling a flare (twice daily)	No treatment unless controlling a flare (daily emollient for one week, escalating to TCS if no improvement)	Children; moderate to severe eczema	Up to 12 months	0/15	0/15	
Rubio-Gomis 2018	Parallel- group	Twice weekly potent second-generation TCS with emollient	Twice weekly placebo with emollient	Children; mild to moderate severity eczema	Up to week 16 (+2 weeks acute phase	0/26	0/23	

Analysis 9.9. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/ reactive application, Outcome 9: Number of participants with skin infection; end of treatment

Number of participants with skin infection; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Acne								
Hanifin 2002	Parallel- group	Twice weekly potent second-generation TCS with emollient (once daily 4 days/week for 4 weeks followed by once	Twice weekly placebo with emollient (once daily 4 days/ week for 4 weeks followed by once daily 2 days/ week)	Adults and children; moderate to severe eczema	Up to week 20 (+4 weeks acute phase)	1/229	0/119	

		daily 2 days/ week)					
Eczema herpeticum							
Fukuie 2016	Parallel- group	Twice weekly TCS unless controlling a flare (twice daily)	No treatment unless controlling a flare (daily emollient for one week, escalating to TCS if no improvement)	Children; moderate to severe eczema	Up to 12 months	1/15	1/15
Impetigo contagiosa							
Fukuie 2016	Parallel- group	Twice weekly TCS unless controlling a flare (twice daily)	No treatment unless controlling a flare (daily emollient for one week, escalating to TCS if no improvement)	Children; moderate to severe eczema	Up to 12 months	4/15	3/15

Analysis 9.10. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/ reactive application, Outcome 10: Number of participants with abnormal cortisol

Number of participants with abnormal cortisol

Study	Intervention and comparison	Cases/N A	Cases/N B	Additional information
Fukuie 2012	Weekend therapy versus no TCS/reactive application	0/?	0/?	Children; moderate to severe eczema. Cortisol and DHEA levels at 0, 3 and 6 months (measured from morning salivary samples collected on three consecutive days); ACTH stimulation test at 3 months. It was stated that morning salivary cortisol levels were comparable between groups, but significantly fluctuated between the three days, regardless of when treatments were applied. Serum cortisol levels after ACTH stimulation were normal in both groups at 3 months. N = unclear; 11 participants were said to be eligible for the study.
Fukuie 2016	Weekend therapy versus no TCS/reactive application	?/?	?/?	Children; moderate to severe eczema. Rapid ACTH stimulation test performed 3 months in to the maintenance phase (serum cortisol measured after 30 and 60 minutes) at 3 months; serum and salivary cortisol measurements taken at 6 and 12 months. ACTH stimulation was only performed on the first 12 participants and it is unclear which treatments they received. It was stated that differences in serum cortisol levels were not statistically significant between groups, however there was insufficient information to judge changes in individual participants' levels.
Glazenburg 2009	Weekend therapy versus no TCS/reactive application	?/39	?/36	Children; moderate to severe eczema. Urinary overnight cortisol/creatinine ratio at enrollment (week −4), at the end of the acute phase (week 0), and at end of treatment (week 16). Trial authors stated no

				evidence of any treatment effect, however it was unclear whether this was concluded from any observed cases.
Hanifin 2002	Weekend therapy versus no TCS/reactive application	1*/?	1*/?	Adults and children; moderate to severe eczema. A single cosyntropin stimulation test at the last study visit for each participant (up to week 48 including 4-week acute treatment phase). N = 44; unclear how many in each group *Event in the weekend therapy group found after 280 days. Event in the vehicle group found after 13 days vehicle followed by 345 days weekend therapy. Neither event was newly observed.
Van Der Meer 1999	Weekend therapy versus no TCS/reactive application	?/13	?/18	Adults; moderate to severe eczema. Fasting serum cortisol at enrollment (week −4), baseline (week 0), and end of treatment (week 16). It was stated that there were no significant changes in cortisol during the maintenance phase in either treatment group, however there was insufficient information to judge changes in individual participants' levels.

Analysis 9.11. Comparison 9: Weekend therapy versus no topical corticosteroid (TCS)/reactive application, Outcome 11: Definition of relapse

Definition of relapse

Study	Definition
Berth-Jones 2003	Relapse (or flare) was defined as TIS ≥ 4
Glazenburg 2009	Relapse defined as TIS ≥ 3. Could occur at the site of the original index lesion or at any new site
Hanifin 2002	Relapse defined as IGA ≥ 3 ("modest clearing") and a score of 2-3 for any two of erythema, pruritus and papulation/induration/oedema
Liu 2018	Relapse defined as ≥ 2-point difference in IGA compared with the score given at patient's treatment success (6-point scale from 0 = clear to 5 = very severe)
Peserico 2008	Relapse defined as a need to intensify treatment (patient's perspective)
Rubio-Gomis 2018	Relapse defined as SCORAD > 5 or ≥ 25% initial SCORAD at week 16 (+2 week acute phase)
Van Der Meer 1999	Relapse not defined. Could occur at the site of the original index lesion or at another site if the initial lesion did not show worsening and another lesion was "symptomatic for the overall severity of the disease"

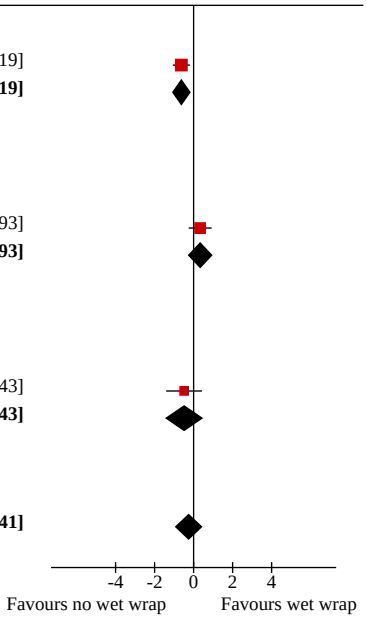
Comparison 10. Wet wrap versus no wet wrap

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 SMD in investigator assessment of clinical signs (short term); all ages; all severities	3	112	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.92, 0.41]
10.1.1 Moderate TCS with wet wrap versus moderate TCS without; within-participant study	1	48	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.07, -0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1.2 Twice daily mild TCS with wet wrap versus twice daily mild TCS without; parallel-group study	1	45	Std. Mean Difference (IV, Random, 95% CI)	0.34 [-0.25, 0.93]
10.1.3 Once daily mild TCS with wet wrap v twice daily mild TCS without; parallel-group study	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-1.41, 0.43]
10.2 SMD in investigator assessment of clinical signs (short term); children; all severities	2	64	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.79, 0.80]
10.3 Included studies with no poolable clinician-reported signs data	3		Other data	No numeric data
10.4 Included studies with no poolable patient-reported symptoms data	2		Other data	No numeric data
10.4.1 Itch	1		Other data	No numeric data
10.4.2 Sleep	1		Other data	No numeric data
10.4.3 Combined itch and sleep VAS (subjective SCORAD)	1		Other data	No numeric data
10.5 Number of participants with skin infection; end of treatment	2		Other data	No numeric data

Analysis 10.1. Comparison 10: Wet wrap versus no wet wrap, Outcome 1: SMD in investigator assessment of clinical signs (short term); all ages; all severities

Study or Subgroup	SMD	SE	Wet wrap Total	No wet wrap Total	Weight	Std. Mean Difference IV, Random, 95% CI
10.1.1 Moderate TCS with wet wrap versus moderate TCS without; within-participant study						
Foelster-Holst 2006 (1)	-0.627935	0.2233412	24	24	39.9%	-0.63 [-1.07 , -0.19]
Subtotal (95% CI)			**24**	**24**	**39.9%**	**-0.63 [-1.07 , -0.19]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.81 (P = 0.005)						
10.1.2 Twice daily mild TCS with wet wrap versus twice daily mild TCS without; parallel-group study						
Hindley 2006 (2)	0.3361	0.3005	23	22	35.0%	0.34 [-0.25 , 0.93]
Subtotal (95% CI)			**23**	**22**	**35.0%**	**0.34 [-0.25 , 0.93]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
10.1.3 Once daily mild TCS with wet wrap v twice daily mild TCS without; parallel-group study						
Beattie 2004 (3)	-0.4881	0.468	10	9	25.1%	-0.49 [-1.41 , 0.43]
Subtotal (95% CI)			**10**	**9**	**25.1%**	**-0.49 [-1.41 , 0.43]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
Total (95% CI)			**57**	**55**	**100.0%**	**-0.26 [-0.92 , 0.41]**
Heterogeneity: Tau² = 0.23; Chi² = 6.79, df = 2 (P = 0.03); I² = 71%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Chi² = 6.79, df = 2 (P = 0.03), I² = 70.6%						

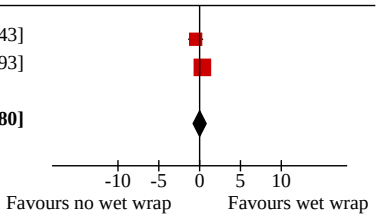


Footnotes

(1) Day 2-3. Objective local SCORAD. Uncorrected for baseline. Unit of analysis is side; variance is corrected.
(2) Week 4. SCORAD adjusted for baseline differences.
(3) Week 1. Decrease in SASSAD from baseline.

Analysis 10.2. Comparison 10: Wet wrap versus no wet wrap, Outcome 2: SMD in investigator assessment of clinical signs (short term); children; all severities

Study or Subgroup	SMD	SE	Wet wrap Total	No wet wrap Total	Weight	Std. Mean Difference IV, Random, 95% CI
Beattie 2004 (1)	-0.4881	0.468	10	9	40.5%	-0.49 [-1.41 , 0.43]
Hindley 2006 (2)	0.3361	0.3005	23	22	59.5%	0.34 [-0.25 , 0.93]
Total (95% CI)			**33**	**31**	**100.0%**	**0.00 [-0.79 , 0.80]**
Heterogeneity: Tau² = 0.18; Chi² = 2.20, df = 1 (P = 0.14); I² = 54%						
Test for overall effect: Z = 0.01 (P = 1.00)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Week 1. Decrease in SASSAD from baseline.
(2) Week 4. SCORAD adjusted for baseline differences.

Analysis 10.3. Comparison 10: Wet wrap versus no wet wrap, Outcome 3: Included studies with no poolable clinician-reported signs data

Included studies with no poolable clinician-reported signs data

Study	Intervention and comparison	Comments
Bryden 2009	Twice daily mild TCS with wet wraps versus twice daily TCS without wet wraps, stepping down to once daily TCS after week 1	Parallel-group; children; mild to moderate eczema. Median decrease in SASSAD. No difference at end of treatment (unclear if 2 or 3 weeks; P = 0.74; n = 51)

Murphy 2003	Mild TCS with wet wraps versus mild TCS without wet wraps	Parallel-group; children; moderate eczema. Quote: "Individuals treated with wet wraps and corticosteroid enjoyed a substantially better and clinically valuable therapeutic response." Week 1; n = 36 (conservative assumption as n = 37 reported in one abstract) across three groups, one of which was excluded from our review
Pei 2001	Once daily second-generation potent TCS with wet wraps versus once daily second-generation potent TCS without wet wraps (group D versus group B)	Parallel-group; children; moderate to severe eczema. Unnamed scale; n = unreported (40 randomised across groups A, B, C and D). Median with wet wraps decreased from 29 (IQR 20.75-59) at baseline to 17 (IQR 10-34.5) at week 1, and to 14 (IQR 7.25-33.75) at week 2. Median without wet wraps decreased from 20 (IQR 8-32) at baseline to 18 (IQR 10-27.5) at week 1, and 22 (IQR 18-53.5) at week 2
Pei 2001	Once daily second-generation potent TCS with wet wraps versus once daily second-generation potent TCS without wet wraps (group C versus group A)	Parallel-group; children; moderate to severe eczema. Unnamed scale; n = unreported (40 randomised across groups A, B, C and D). Median with wet wraps decreased from 22 (IQR 10-45) at baseline to 17 (IQR: 13.5-29) at week 1, and to 16 (IQR 8-26) at week 2. Median without wet wraps decreased from 41 (IQR 21-52) at baseline to 36 (IQR 21-42) at week 1, and 30 (IQR 20-43) at week 2

Analysis 10.4. Comparison 10: Wet wrap versus no wet wrap, Outcome 4: Included studies with no poolable patient-reported symptoms data

Included studies with no poolable patient-reported symptoms data

Study	Intervention and comparison	Comments
Itch		
Beattie 2004	Once daily mild TCS under wet wraps (twice daily in the first week, then at night in the second week) versus twice daily mild TCS without wet wraps	Parallel-group; children; moderate eczema. IDQOL score for itch VRS; no dispersion. Mean decrease at end of treatment (week 2) was 0.99 in the once daily TCS with wet wraps group (n = 10) and 1.00 in the twice daily TCS without wet wraps group (n = 9)
Sleep		
Beattie 2004	Once daily mild TCS under wet wraps (twice daily in the first week, then at night in the second week) versus twice daily mild TCS without wet wraps	Parallel-group; children; moderate eczema IDQOL score for time taken to get to sleep; no dispersion. Mean decrease at end of treatment (week 2) was 0.29 in the once daily TCS with wet wraps group (n = 10) and 0.89 in the twice daily without wet wraps group (n = 9) IDQOL score for total sleep lost; no dispersion. Mean decrease at end of treatment (week 2) was 0.69 in the once daily TCS with wet wraps group (n = 10) and 1.00 in the twice daily TCS without wet wraps group (n = 9)
Combined itch and sleep VAS (subjective SCORAD)		
Hindley 2006	Mild TCS with wet wraps versus mild TCS without wet wraps	Parallel-group; children; moderate eczema. Decrease in combined itch and sleep VAS. Mean difference between groups at week 4 was 2.20 [−1.17, 5.57]; n = 23 with wet wraps; n = 22 without wet wraps

Analysis 10.5. Comparison 10: Wet wrap versus no wet wrap, Outcome 5: Number of participants with skin infection; end of treatment

Number of participants with skin infection; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Beattie 2004	Parallel- group	Once daily mild TCS with wet wrap (twice daily in the first week, then at night in the second week)	Twice daily mild TCS without wet wrap	Children; moderate-severity eczema	Up to week 3	2/10	0/9	Final week was only follow-up

Hindley 2006	Parallel- group	Twice daily mild TCS with wet wrap	Twice daily mild TCS without wet wrap	Children; moderate to severe eczema	Up to week 4	5/23	0/22	Proxy measure: participants required antibiotics

Comparison 11. Topical corticosteroid (TCS) applied before emollient versus TCS applied after emollient

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Number of participants with local site reactions; end of treatment	1		Other data	No numeric data
11.1.1 Burning	1		Other data	No numeric data
11.1.2 Eye irritation	1		Other data	No numeric data
11.1.3 Pruritus	1		Other data	No numeric data
11.1.4 Rash	1		Other data	No numeric data

Analysis 11.1. Comparison 11: Topical corticosteroid (TCS) applied before emollient versus TCS applied after emollient, Outcome 1: Number of participants with local site reactions; end of treatment

Number of participants with local site reactions; end of treatment

Study	Study design	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Additional information
Burning								
Ng 2016	Parallel-group	TCS applied before emollient	TCS applied after emollient	Children; moderate to severe eczema	Week 2	4/20	0/26	
Eye irritation								
Ng 2016	Parallel-group	TCS applied before emollient	TCS applied after emollient	Children; moderate to severe eczema	Week 2	1/20	2/26	
Pruritus								
Ng 2016	Parallel-group	TCS applied before emollient	TCS applied after emollient	Children; moderate to severe eczema	Week 2	6/20	4/26	
Rash								
Ng 2016	Parallel-group	TCS applied before emollient	TCS applied after emollient	Children; moderate to severe eczema	Week 2	1/20	3/26	

Comparison 12. Overall

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Number of participants with cleared or marked improvement on IGA (short term)	40		Other data	No numeric data
12.2 Number of participants with cleared or marked improvement on IGA (end of treatment)	40		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3 Number of participants with skin thinning	33		Other data	No numeric data
12.4 Details of trials with cases of skin thinning	4		Other data	No numeric data

Analysis 12.1. Comparison 12: Overall, Outcome 1: Number of participants with cleared or marked improvement on IGA (short term)

Number of participants with cleared or marked improvement on IGA (short term)

Study	Design	Overall rate	%	Notes
Amerio 1998	Parallel-group	92/97	95	
Bagatell 1983	Parallel-group	79/222	36	
Bleehen 1995	Parallel-group	223/270	83	
Bluefarb 1976	Parallel-group	17/199	9	
Craps 1973	Within-participant	23.5/50	47	Mean of numbers on each side
Cullen 1971	Within-participant	9/12	75	Mean of numbers on each side
Del Rosso 2009	Parallel-group	132/211	63	
Gentry 1973	Parallel-group	1/5	20	
Giannetti 1981	Within-participant	3.5/20	18	
Goh 1999	Within-participant	7/58	12	Outlier study with respect to IGA. Mean of numbers on each side
Handa 1985	Within-participant	5.5/7	79	Mean of numbers on each side
Harder 1983	Parallel-group	62/72	86	
Hoybye 1991	Parallel-group	78/94	83	
Innocenti 1977	Within-participant	3/3	100	Mean of numbers on each side
Jorizzo 1995	Parallel-group	31/111	28	
Kirkup 2003a	Parallel-group	66/127	52	
Kirkup 2003b	Parallel-group	99/108	92	
Koopmans 1995	Parallel-group	129/148	87	
Lassus 1983	Parallel-group	15/40	38	
Lebwohl 1999	Parallel-group	9/188	5	Very low as participants had to be 100% healed
Mali 1976	Parallel-group	5/16	31	
Marchesi 1994	Parallel-group	28/60	47	
Mobacken 1986	Parallel-group	36/58	62	
Nolting 1991	Parallel-group	58/67	87	
Rafanelli 1993	Parallel-group	5/60	8	
Rajka 1986	Within-participant	17.5/30	58	Mean of numbers on each side
Rampini 1992a	Parallel-group	105/108	97	
Rampini 1992b	Parallel-group	77/78	99	
Roth 1978a	Within-participant	22.5/29	78	Mean of numbers on each side
Roth 1978b	Within-participant	14/19	74	Mean of numbers on each side
Ruiz 1976	Within-participant	4/6	67	Mean of numbers on each side. Participants were consulted when judging the IGA
Ryu 1997	Parallel-group	12/23	52	
Savin 1976	Parallel-group	22/27	81	
Schlessinger 2006	Parallel-group	116/122	95	
Sudilovsky 1981	Within-participant	83.5/149	56	Mean of numbers on each side
Tharp 1996	Parallel-group	52/152	34	
Ulrich 1991	Parallel-group	131/165	79	
Van Del Rey 1983	Parallel-group	18/28	64	

Veien 1984	Within-participant	11.5/39	29	Mean of numbers on each side
Wortzel 1975	Parallel-group	98/128	77	

Analysis 12.2. Comparison 12: Overall, Outcome 2: Number of participants with cleared or marked improvement on IGA (end of treatment)

Number of participants with cleared or marked improvement on IGA (end of treatment)

Study	Design	Overall rate	%	Notes
Amerio 1998	Parallel-group	92/97	95	
Bagatell 1983	Parallel-group	140/229	61	
Bleehen 1995	Parallel-group	223/270	83	
Bluefarb 1976	Parallel-group	73/170	43	
Busch-Heidger 1993	Parallel-group	67/75	89	
Craps 1973	Within-participant	23.5/50	47	Mean of numbers on each side
Cullen 1971	Within-participant	9/12	75	Mean of numbers on each side
Del Rosso 2009	Parallel-group	132/211	63	
Gentry 1973	Parallel-group	1/5	20	
Giannetti 1981	Within-participant	13/20	65	
Goh 1999	Within-participant	28.5/58	49	Outlier study with respect to IGA. Mean of numbers on each side
Handa 1985	Within-participant	5.5/7	79	Mean of numbers on each side
Harder 1983	Parallel-group	68/72	94	
Hoybye 1991	Parallel-group	68/86	79	
Innocenti 1977	Within-participant	3/3	100	Mean of numbers on each side
Jorizzo 1995	Parallel-group	61/111	55	
Koopmans 1995	Parallel-group	129/148	87	
Lassus 1983	Parallel-group	15/40	38	
Lebwohl 1999	Parallel-group	34/163	21	Very low as these were those 100% healed
Mali 1976	Parallel-group	5/16	31	
Marchesi 1994	Parallel-group	30/30	100	
Mobacken 1986	Parallel-group	45/58	78	
Nolting 1991	Parallel-group	58/67	87	
Prado de Oliveira 2002	Parallel-group	18/24	75	
Rafanelli 1993	Parallel-group	37/60	62	
Rajka 1986	Within-participant	17.5/30	58	Mean of numbers on each side
Rampini 1992a	Parallel-group	105/108	97	
Rampini 1992b	Parallel-group	77/78	99	
Roth 1978a	Within-participant	22.5/29	78	Mean of numbers on each side
Roth 1978b	Within-participant	14/19	74	Mean of numbers on each side
Ruiz 1976	Within-participant	4/6	67	Mean of numbers on each side. Patients were consulted when judging the IGA
Ryu 1997	Parallel-group	12/23	52	
Savin 1976	Parallel-group	16/22	73	N assumed as one participant was repored as "no visit or fail"; unclear which
Schlessinger 2006	Parallel-group	116/122	95	
Sudilovsky 1981	Within-participant	99.5/116	86	Mean of numbers on each side
Tharp 1996	Parallel-group	92/125	74	
Ulrich 1991	Parallel-group	131/165	79	
Van Del Rey 1983	Parallel-group	23/29	79	
Veien 1984	Within-participant	18/40	45	Mean of numbers on each side
Wortzel 1975	Parallel-group	98/128	77	

Analysis 12.3. Comparison 12: Overall, Outcome 3: Number of participants with skin thinning

Number of participants with skin thinning

Study	Study design	Design; age; severity	Time point	Cases/N	Additional information
Amerio 1998	Twice daily potent versus once daily second-generation potent	Parallel-group; adults and children; ≥ moderate-severity eczema	Up to day 15	0/97	
Bagatell 1983	Moderate TCS versus mild TCS	Parallel-group; adults and children; moderate to severe eczema	Up to week 3	0/249	
Berth-Jones 2003	Twice weekly potent second-generation TCS cream versus twice weekly placebo cream (group F versus group E)	Parallel-group; adults and children; moderate to severe eczema	Up to 20 weeks (includes 4 week acute treatment phase)	0/154	
Berth-Jones 2003	Twice weekly potent second-generation TCS ointment versus twice weekly placebo ointment (group H versus group G)	Parallel-group; adults and children; moderate to severe eczema	Up to 20 weeks (includes 4 week acute treatment phase)	0/141	
Cullen 1971	Potent TCS versus moderate TCS	Within-participant; unspecified ages; moderate to severe eczema	Up to week 2	0/12	
Del Rosso 2009	Twice daily very potent versus once daily very potent	Parallel-group; adults; ≥ moderate-severity eczema	Up to week 2	6/211	
Dolle 2015	2% GW870086 VERSUS 0.2% GW870086	Within-participant; adults; moderate to severe eczema	Up to week 5 including (7-14 days post-treatment follow-up)	0/35	
EUCTR2009-012028-98-DE	TCS cream versus TCS ointment	Parallel-group; adults; mild to severe eczema	Up to day 21	0/50	N assumed
Fukuie 2016	Twice weekly potent TCS unless controlling a flare (twice daily) versus no treatment unless controlling a flare (daily emollient for one week, escalating to TCS if no improvement)	Parallel-group; children; moderate to severe eczema	Up to 12 months	0/30	
Glazenburg 2009	Twice weekly potent second-generation TCS with emollient versus twice weekly placebo with emollient	Parallel-group; children; mild to moderate-severity eczema	Up to 20 weeks (including 4-week acute treatment phase)	0/75	See Analysis 6.8.2
Goh 1999	Three times daily very potent versus once daily second-generation potent	Within-participant; adults; moderate to severe eczema	Up to day 22	0/58	
Haneke 1992	Twice daily potent versus once daily potent (C versus A)	Within-participant; adults; unspecified severity eczema	Up to week 4	0/94	
Haneke 1992	Twice daily potent versus once daily potent (C versus B)	Within-participant; adults; unspecified severity eczema	Up to week 4	0/88	
Hanifin 2002	Twice weekly potent second-generation TCS with emollient (once daily 4 days/week for 4 weeks followed by once daily 2 days/week) versus twice weekly placebo with emollient (once daily 4 days/ week for 4 weeks followed by once daily 2 days/week)	Parallel-group; adults and children; moderate to severe eczema.	At least 24 weeks (including 4-week acute treatment phase)	0/348	
Haribhakti 1982	Moderate TCS versus mild TCS	Within-participant; children; unspecified eczema severity	Up to week 3	0/21	Assumed number randomised
Hoybye 1991	Twice daily potent versus once daily second-generation potent	Parallel-group; adults; ≥ moderate-severity eczema	Up to week 6	0/96	

Innocenti 1977	Potent TCS versus moderate TCS	Within-participant; unspecified ages; moderate to severe eczema	Up to week 1	0/3		
Jorizzo 1995	Moderate TCS versus mild TCS	Parallel-group; children; mild to moderate eczema	Up to week 5	0/113		0/36 treated for up to 25 weeks
Kirkup 2003a	Second-generation potent TCS versus mild TCS	Parallel-group; children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/137		Assumed number randomised
Kirkup 2003b	Second-generation potent TCS versus older potent TCS	Parallel-group; children; moderate to severe eczema	Up to week 16 (includes 4 weeks acute treatment phase)	0/128		Assumed number randomised
Kohn 2016	Application to wet skin versus application to dry skin	Parallel-group; children; mild to severe eczema	Up to week 2	0/45		Cross-over study; data from first phase
Kuokkanen 1987	Moderate TCS versus mild TCS	Within-participant; children; moderate to severe eczema.	Up to week 3	0/34		
Lebwohl 1999	Twice daily moderate versus once daily second-generation potent	Parallel-group; children; moderate to severe eczema	Up to day 22	0/219		
Nolting 1991	Twice daily moderate versus once daily second-generation potent	Parallel-group; adults; unspecified severity eczema	Up to week 3	4/67		
Peserico 2008	Twice weekly potent TCS with emollient versus emollient alone	Parallel-group; adults and children; moderate to severe eczema	Up to 20 weeks (including 4 week acute treatment phase).	0/221		
Prado de Oliveira 2002	Second-generation potent TCS versus mild TCS	Parallel-group; children; moderate to severe eczema	Up to day 42.	6/25		
Rafanelli 1993	Twice daily moderate versus once daily second-generation potent	Parallel-group; children; moderate to severe eczema	Up to week 3	0/60		
Rubio-Gomis 2018	Twice weekly potent second-generation TCS with emollient versus twice weekly placebo with emollient	Parallel-group; children; mild- to moderate-severity eczema.	Up to 18 weeks (including 2-week acute treatment phase)	0/49		
Ryu 1997	Twice daily mild versus once daily second-generation potent	Parallel-group; adults and children; mild- to moderate-severity eczema	Up to day 14	0/24		
Schlessinger 2006	Twice daily very potent versus once daily very potent	Parallel-group; children; moderate to severe eczema	Up to week 2	10/124		
Thomas 2002	3 consecutive days potent TCS per week versus daily mild TCS	Parallel-group; children; mild to moderate eczema	Up to week 18	0/207		Assumed number randomised. Not used continuously
Ulrich 1991	Potent TCS versus moderate TCS	Parallel-group; adults and children; moderate to severe eczema	Up to week 2 (assumed)	0/165		
Van Der Meer 1999	Twice weekly potent second-generation TCS versus twice weekly placebo	Parallel-group; adults; moderate to severe eczema	Up to week 16 (including 4-week acute treatment phase)	0/32		
Vernon 1991	Twice daily mild versus once daily second-generation potent	Parallel-group; children; moderate to severe eczema	Up to week 6	0/47		
Yawalkar 1991	Very potent TCS versus potent TCS	Parallel-group; adults; moderate to severe eczema	Up to week 2	0/117		

Analysis 12.4. Comparison 12: Overall, Outcome 4: Details of trials with cases of skin thinning

Details of trials with cases of skin thinning

Study	Strategy A	Strategy B	Age; severity	Time point	Cases/N A	Cases/N B	Excluded if skin thinning at baseline?

Del Rosso 2009	Twice daily very potent	Once daily very potent	Adults; ≥ moderate-severity eczema	Up to week 2	3/102	3/109	No
Nolting 1991	Once daily second-generation potent	Twice daily moderate	Adults; unspecified severity eczema	Up to week 3	2/33	2/34	Yes
Prado de Oliveira 2002	Second-generation potent TCS	Mild TCS	Children; moderate to severe eczema.	Up to day 42	4/13	2/12	Yes
Schlessinger 2006	Twice daily very potent	Once daily very potent	Children; moderate to severe eczema	Up to week 2	5/62	5/62	No

ADDITIONAL TABLES

Table 1. Abbreviations

Abbreviation	Full form
AD	Atopic dermatitis
ACTH	Adrenocorticotropic hormone
ADCT	Atopic Dermatitis Control Test
BNF	British National Formulary
CI	Confidence interval
EASI	Eczema Area and Severity Index
ECO	Eczema Care Online
FLG	Filaggrin gene
GIV	Generic inverse variance
GREAT	Global Resource for EczemA Trials
HOME	Harmonizing Outcome Measures for Eczema
HPA	Hypothalamic pituitary axis
HR	Hazard ratio
ICC	Intra-class correlation coefficient
ICTRP	The World Health Organization International Clinical Trials Registry Platform
IGA	Investigator Global Assessment
IgE	Immunoglobulin E
IQR	Interquartile range
MCID	Minimal clinically important difference

Table 1. Abbreviations *(Continued)*

MD	Mean difference
NHS	National Health Service (United Kingdom)
NICE	The National Institute for Health and Care Excellence (United Kingdom)
NIHR	National Institute for Health Research
NRS	Numerical Rating Scale
ObjSCORAD	Objective SCORing Atopic Dermatitis
OR	Odds ratio
PGA	Patient Global Assessment
POEM	Patient-Oriented Eczema Measure
PO-SCORAD	Patient-Oriented SCORAD
RCT	randomised controlled trial
RECAP	Recap of Atopic Eczema
RR	Risk ratio
SA-EASI	Self-Administered EASI
SASSAD	Six Area, Six Sign Atopic Dermatitis
SCORAD	SCORing Atopic Dermatitis
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standardised mean difference
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
TIS	Three Item Severity score
VAS	Visual Analogue Scale
WHO	World Health Organization

Table 2. Classification of topical corticosteroid potency

Drug Name	Strength	Preparation	Second-generation?	Potency	Source	Notes

Table 2. Classification of topical corticosteroid potency *(Continued)*

Alclometasone dipropionate	0.05%	Ointment	No	Moderate	British National Formulary 2010	
Alclometasone dipropionate	0.05%	Cream	No	Moderate	British National Formulary 2010	
Alclometasone dipropionate			No	Moderate	Inferred from British National Formulary 2010	0.05% is moderate in UK - No other strengths in the classification
Betamethasone 17-valerate	0.1%	Ointment	No	Potent	British National Formulary 2018	
Betamethasone dipropionate	0.05%	Cream	No	Potent	British National Formulary 2018	
Betamethasone dipropionate	0.05%	Ointment	No	Potent	British National Formulary 2018	
Betamethasone dipropionate		Cream	No	Potent	Inferred from British National Formulary 2018	0.05% is potent in UK
Betamethasone valerate			No	Potent	Inferred from British National Formulary 2018	Assume a standard preparation unless specified, therefore potent
Betamethasone valerate	0.1%	Cream	No	Potent	British National Formulary 2018	
Betamethasone valerate	0.12%	Ointment	No	Potent	British National Formulary 2018	
Betamethasone valerate	0.1%	Fatty ointment	No	Potent	British National Formulary 2018	Other preparations are potent in UK at this strength
Betamethasone valerate		Cream	No	Potent	Inferred from British National Formulary 2018	Although 0.025% is moderate in UK, assume no dilution from the standard unless specified, therefore potent
Betamethasone valerate		Ointment	No	Potent	Inferred from British National Formulary 2018	Although 0.025% is moderate in UK, assume no dilution from the standard unless specified, therefore potent
Clobetasol propionate	0.05%	Cream	No	Very potent	British National Formulary 2018	
Clobetasol propionate	0.05%	Ointment	No	Very potent	British National Formulary 2018	

Table 2. Classification of topical corticosteroid potency *(Continued)*

Clobetasone	0.05%	Cream	No	Moderate	European Directorate for the Quality of Medicines	Not listed in any other charts without the salt; assume moderate
Clobetasone 17-butyrate	0.05%	Lotion	No	Moderate	Inferred from British National Formulary 2018	Lotion not listed, therefore assume moderate as for other preparations
Clobetasone butyrate	0.05%	Cream	No	Moderate	British National Formulary 2018	
Clobetasone butyrate	0.05%	Ointment	No	Moderate	British National Formulary 2018	
Clobetasone butyrate		Cream	No	Moderate	Inferred from British National Formulary 2018	No strength given so assume moderate unless specified
Clocortolone pivalate	0.1%	Cream	No	Moderate	European Directorate for the Quality of Medicines	In USA moderate is 0.1% cream. Clocortolone is moderate in EDQM without strength or salt
Desonide	0.05%		No	Mild	WHO 1997	Assume cream formulation
Desonide	0.05%	Cream	No	Mild	WHO 1997	
Desonide	0.1%	Micronised cream	No	Mild	WHO 1997	Assume as cream formulation, therefore mild
Desonide	0.1%	Ointment	No	Moderate	Inferred from Resource Clinical (USA)	Information for 0.05%, therefore moderate as it's a higher-strength ointment
Desonide	0.05%	Lotion	No	Mild	Inferred from WHO 1997	Assuming mild as for the cream
Desonide	0.05%	Ointment	No	Moderate	Resource Clinical (USA)	Ointment appears in one of the USA charts only as moderate
Desonide	0.1%	Cream	No	Moderate	Inferred from WHO 1997	Assuming moderate to be consistent with ointment
Diflorasone diacetate	0.05%	Cream	No	Moderate	WHO 1997	
Diflorasone diacetate	0.05%	Ointment	No	Very potent	WHO 1997	
Diflucortolone valerate	0.1%	Ointment	No	Potent	British National Formulary 2015	

Table 2. Classification of topical corticosteroid potency *(Continued)*

Diflucortolone valerate	0.1%	Water/oil emulsion	No	Potent	Inferred from British National Formulary 2015	Assume potent as for the ointment
Difluorocortolone valerianate	0.1%	Cream	No	Potent	Inferred from British National Formulary 2015	Assume as for diflucortolone valerate 0.1% cream, which is potent in UK chart
Fluclorolone acetonide		Cream	No	Potent	European Directorate for the Quality of Medicines	Fluclorolone unspecified as potent, but no salt, preparation or % given
Fluclorolone acetonide		Ointment	No	Potent	European Directorate for the Quality of Medicines	Fluclorolone unspecified as potent, but no salt, preparation or % given
Flumethasone pivalate	0.02%	Cream	No	Mild	Kim 2015	Only appears in the Korean classification
Flumethasone pivalate	0.2%	Ointment	No	Moderate	European Directorate for the Quality of Medicines	10 times strength; EDQM states moderate where no strength is specified
Fluocinolone acetonide	0.025%	Cream	No	Potent	British National Formulary 2018	
Fluocinolone acetonide	0.01%	Cream	No	Moderate	British Association of Dermatologists 2015	
Fluocinolone acetonide	0.025%	Ointment	No	Potent	British National Formulary 2018	
Fluocinonide	0.1%	Cream	No	Very potent	National Psoriasis Foundation (USA)	Schlessinger 2006 refers to it as superpotent
Fluocinonide	0.05%	Cream	No	Potent	British National Formulary 2018	
Fluocinonide		FAPG	No	Potent	Inferred from British National Formulary 2018	No strengths given, but 0.05% potent in UK 2018 for cream and ointment preparations
Fluocortin butylester	0.75%	Cream	No	Mild	Kim 2015	Not listed in any of the other charts
Fluocortolone	0.2%		No	Moderate	Inferred from British National Formulary 2015	Assume moderate as for 0.25%
Fluocortolone	0.5%	Ointment	No	Moderate	Inferred from British National Formulary 2015	Assume moderate as for 0.25%
Fluocortolone/fluocortolone caproate	0.25%	water/oil emulsion	No	Moderate	Inferred from British National Formulary 2015	

Table 2. Classification of topical corticosteroid potency *(Continued)*

Fluocortolone/fluocortolone caproate	0.25%	Ointment	No	Moderate	British National Formulary 2015	
Fluprednidene-21-acetate	0.1%	Cream	No	Moderate	Inferred from European Directorate for the Quality of Medicines	Fluprednidene in European Directorate for the Quality of Medicines as moderate (no % given)
Flurandrenolone acetonide	0.05%	Ointment	No	Moderate	WHO 1997	Assumed to be the same as Flurandrenolide and Fludroxycortide
Fluticasone propionate	0.005%	Ointment	Yes	Potent	British National Formulary 2018	
Fluticasone propionate	0.05%	Cream	Yes	Potent	British National Formulary 2018	
GW870086X	2%	Cream	NA	NA	NA	Novel corticosteroid
GW870086X	0.2%	Cream	NA	NA	NA	Novel corticosteroid
Halcinonide	0.1%	Cream	No	Potent	WHO 1997	
Halobetasol propionate	0.05%	Cream	No	Very potent	Resource Clinical (USA)	Not listed in any of the other charts
Halometasone	0.05%	Cream	No	Potent	European Directorate for the Quality of Medicines	In European Directorate for the Quality of Medicines as potent but no % given or preparation and not in any other charts listed
Hydrocortisone	1%	Cream	No	Mild	British National Formulary 2018	
Hydrocortisone	1%	Fatty cream	No	Mild	Inferred from British National Formulary 2018	Assume as for a standard preparation, therefore mild
Hydrocortisone	1%		No	Mild	British National Formulary 2018	
Hydrocortisone		Cream	No	Mild	Inferred from British National Formulary 2018	Assume a standard strength, therefore mild
Hydrocortisone	1%	Ointment	No	Mild	British National Formulary 2018	
Hydrocortisone	2.5%	Ointment	No	Mild	British National Formulary 2018	
Hydrocortisone	0.5%	Cream	No	Mild	British National Formulary 2018	

Table 2. Classification of topical corticosteroid potency *(Continued)*

Hydrocortisone	0.5%	Hydrophilic ointment	No	Mild	Inferred from British National Formulary 2018	Assume as for a standard 0.5% ointment, therefore mild
Hydrocortisone 17-butyrate	0.1%	Cream	No	Potent	British National Formulary 2015	
Hydrocortisone 17-butyrate	0.1%	Fatty cream	No	Potent	Inferred from British National Formulary 2015	Assuming potent as for ointment and cream
Hydrocortisone 17-butyrate	0.1%	Lotion	No	Potent	Inferred from British National Formulary 2015	Assuming potent as for ointment and cream
Hydrocortisone 17-butyrate	0.1%	Ointment	No	Potent	British National Formulary 2015	
Hydrocortisone acetate	1%	Ointment	No	Mild	WHO 1997	Assume mild as for the cream
Hydrocortisone buteprate	0.1%	Fatty cream	No	Moderate	European Directorate for the Quality of Medicines	Hydrocortisone 17-butyrate, 21-propionate
Hydrocortisone butyrate			No	Potent	Inferred from British National Formulary 2015	No strength or preparation given, so assuming potent as for standard 0.1% cream or ointment
Hydrocortisone valerate	0.2%	Cream	No	Moderate	WHO 1997	
Hydrocortisone valerate	0.2%	Ointment	No	Moderate	WHO 1997	
Methylprednisolone aceponate	0.1%	Cream	No	Potent	European Directorate for the Quality of Medicines	
Methylprednisolone aceponate	0.1%	Ointment	No	Potent	European Directorate for the Quality of Medicines	
Methylprednisolone aceponate	0.1%	Fatty ointment	No	Potent	Australian Pharmaceutical Benefits Scheme	
Methylprednisolone aceponate	0.1%	Lotion	No	Potent	Australian Pharmaceutical Benefits Scheme	Only chart where it is listed as a lotion
Methylprednisolone aceponate		Cream	No	Potent	European Directorate for the Quality of Medicines	Assume 0.1% and therefore potent
Mometasone furoate	0.1%	Ointment	Yes	Potent	British National Formulary 2018	

Table 2. Classification of topical corticosteroid potency *(Continued)*

Mometasone furoate	0.1%	Cream	Yes	Potent	British National Formulary 2018	
Mometasone furoate	0.1%	Fatty cream	Yes	Potent	British National Formulary 2018	
Mometasone furoate		Cream	Yes	Potent	Inferred from British National Formulary 2018	Assume 0.1%, therefore potent
Prednicarbate	0.25%	Cream	No	Moderate	Kim 2015	
Prednicarbate	0.25%	Ointment	No	Moderate	Kim 2015	
Prednicarbate		Ointment	No	Moderate	National Psoriasis Foundation (USA)	No % given - in USA charts as prednicarbate 0.1% cream (Dermatop) as moderate potency
Prednisolone 17-valerate 21-acetate	0.3%		No	Moderate	Kim 2015	
Tralonide	0.025%	Ointment	No	Potent	Scherrer 1974	Discussed with other old potent preparation and it is fluorinated, therefore we assume potent
Triamcinolone	0.1%	Cream	No	Potent	Inferred from British National Formulary 2015	Assume triamcinolone acetonide and as for the ointment
Triamcinolone	0.1%	Ointment	No	Potent	Inferred from British National Formulary 2015	Assume this is triamcinolone acetonide, therefore ointment is potent
Triamcinolone acetonide	0.1%	Ointment	No	Potent	British National Formulary 2015	

EDQM: European Directorate for the Quality of Medicines; **FAPG:** fatty alcohol propylene glycol

Table 3. Correspondence with investigators

Study ID	Correspondence	Response
Thomas 2002	Personal communication regarding additional SASSAD data	Additional information received; no further usable data were available.
Del Rosso 2009	Emails sent: 29 January 2021 and 4 February 2021 to jqdelrosso@yahoo.com	Replies received: 29 January 2021 and 4 February 2021.

Table 3. Correspondence with investigators *(Continued)*

	Regarding exact numbers of participants with skin thinning at baseline and after 4 weeks of treatment	Additional information no longer available
EUC-TR2016-004542-28-NL	Emails sent: 15 October 2020 and 10 March 2021 to Marijke.Kamsteeg@radboudumc.nl Regarding eligibility for inclusion into this review	No reply received
EUC-TR2016-004687-19-NL	Email sent: 10 March 2021 to Marijke.Kamsteeg@radboudumc.nl Regarding eligibility for inclusion into this review	No reply received
EUC-TR2018-001743-31-DE	Email sent: 10 March 2021 to Clinicaltrials.Dermapharm@dermapharm.com Regarding eligibility for inclusion into this review	Reply received 16 March 2021 confirming trial was prematurely ended and no data were available
JPRN-UMIN000028043	Email sent: 10 March 2021 to ohya-y@ncchd.go.jp Regarding eligibility and availability of data for inclusion into this review	No reply received
JPRN-UMIN000006955	Email sent: 15 October 2020 to h-murota@derma.med.osaka-u.ac.jp Regarding eligibility for inclusion into this review	No reply received
Sillevis 2000	Emails sent: 7 June 2019 to ph.i.splus@amsterdamumc.nl and 5 July 2019 to a.h.musters@amc.uva.nl Regarding effectiveness, safety, and risk of bias	Reply received: 28 June 2019 Received additional information
Hanifin 2002	Email sent: 28 January 2021 to hanifinj@ohsu.edu and syd11400@gsk.com Regarding exact numbers of participants receiving cosyntropin stimulation tests in each group	No reply/undeliverable
EUC-TR2009-012028-98-DE	Emails sent: 7 July 2020, 8 July 2020 to neujahr@galenpharma.de and kruse@galenpharma.de Regarding eligibility for inclusion into this review	Replies received: 8 July 2020 and 9 July 2020 Received additional information
Kim 2013	Email sent: 19 November 2020 to drchosh@hotmail.com Regarding exact data for investigator assessment of clinical signs	No reply received

Table 3. Correspondence with investigators *(Continued)*

Berth-Jones 2003	Email sent: 1, 3 and 5 February 2021 to johnberthjones@aol.com Regarding log rank HR to pool with time to relapse data	Replies received: 3 and 6 February 2021 Additional information no longer available
Glazenburg 2009	Email sent: 25 November 2020 to a.wolkerstorfer@amsterdamumc.nl Regarding log rank HR to pool with time to relapse data	No reply received
Sikder 2005	Email sent: 29 August 2019 to sikder_derma@yahoo.com and bmuderma@bol-online.com To confirm contact details with the intention of following up with specific data queries	No reply/undeliverable
Cadmus 2019	Email sent: 03 February 2021 to lzdiaz@ascension.org Regarding number of participants that reported stinging	Replies received: 3 and 4 February 2021 Received additional information
Cadmus 2019	Email sent: 6 May 2021 to lzdiaz@ascension.org Regarding POEM data	Reply received: 11 May 2021 Additional information not available
Beattie 2004	Email sent: 23 March 2021 to paula_e_beattie@hotmail.com To request dispersion of SASSAD data at end of follow-up	Email was undeliverable
Noren 1989	Correspondence via www.atopicskindisease.com 21 April 2021, and subsequent personal communication 26 April 2021	Additional information no longer available
Vernon 1991	Attempted to contact via Commonwealth Dermatology (tel: 1-804-282-0831) and subsequent personal communication 21 April 2021	No reply received
Bleehen 1995	Email sent: 5 May 2021 to colin.holden1@nhs.net To obtain adverse event data by participant rather than by event	No reply received
GSK 1995	Email sent: 25 May 2021 to C.Green@exeter.ac.uk To obtain a copy of the GSK report they included in their systematic review of twice daily vs once daily TCS (Green 2004)	No reply received

Table 3. Correspondence with investigators *(Continued)*

GSK: GlaxoSmithKline; **SASSAD:** Six Area, Six Sign Atopic Dermatitis severity score;

Table 4. Correspondence with pharmaceutical companies

We sent the following email to the companies documented below

We are conducting a Cochrane Systematic Review of randomised controlled trials looking at different ways of using topical corticosteroids. Please see the link to our protocol https://www.cochrane.org/CD013356/SKIN_different-strategies-using-topical-corticosteroids-people-eczema

In this review we have a range of comparisons in which topical corticosteroids (TCS) are used in different ways. For example, our main comparisons are (but this does not include all, please see the protocol):

- frequency of use of TCS e.g. once daily v twice daily
- use of different potencies of TCS e.g. mild vs moderate
- weekend use vs placebo

I am writing to request a list of any relevant topical corticosteroid trials so that we can check they have been included in our review. Trials must have TCS in 2 or more arms (except for those that include weekend therapy).

Company name	Products	Email address	Outcome
GlaxoSmithKline	Betnovate (betamethasone valerate) plus Betnovate RD, Cutivate (fluticasone propionate), Efcortelan (hydrocortisone), Eumovate (clobetasone butyrate), Propaderm (beclometasone dipropionate), Dermovate (clobetasol propionate)	medical.information@gsk.com	Email reply 21 October 2020 "Regarding your enquiry about Topical Corticosteroids manufactured by GSK, please refer to the Clinical Trials.gov link provided in the previous email, where you will be able to find the information requested for any topical corticosteroids".
Leo Pharma	Locoid (hydrocortisone butyrate)	medical-info.uk@leo-pharma.com	Email reply 5 November 2020 "Unfortunately, we are not aware of any trials that fit the criteria outlined in your inquiry".
Meadow Laboratories	Nerisone cream (diflucortolone valerate), Ultralanum (fluocortolone)	enquiries@meadowlabs.co.uk	Email reply 16 October 2020 "Thank you for your message. Unfortunately the Nerisone range of products have now been discontinued".
MSD	Diprosone (betamethasone dipropionate) Elocon (mometasone)	medicalinformationuk@merck.com	Email reply 22 October 2020. The Company sent a list of trials, all of which are accounted for in the review.
Reig Jofre UK Ltd	Synalar (fluocinolone), Metosyn FAPG (fluocinonide)	medinfouk@reigjofre.com	No reply, request sent 16 October 2020

Table 4. Correspondence with pharmaceutical companies *(Continued)*

Typharm	Haelen (fludroxycortide)	medinfo@typharm.com	No reply, request sent 16 October 2020

Table 5. Sensitivity analyses: effect of Becker-Balagtas correction of within-participant studies using a range of ICC* (0.25, 0.5, 0.75)

Analysis	ICC = 0.25	ICC = 0.5	ICC = 0.75
Moderate vs mild-potency TCS; IGA; short-term (Analysis 1.1)	OR 2.00 (95% CI 1.35 to 2.98)	OR 2.07 (95% CI 1.41 to 3.04)	OR 2.22 (95% CI 1.56 to 3.17)
Moderate vs mild-potency TCS; IGA; end of treatment (Analysis 1.3)	OR 2.72 (95% CI 1.43 to 5.17)	OR 2.74 (95% CI 1.47 to 5.11)	OR 2.77 (95% CI 1.53 to 5.01)
Moderate vs mild-potency TCS; SMD; short-term (Analysis 1.5)	SMD 0.13 (95% CI -0.37 to 0.63)	SMD 0.15 (95% CI -0.27 to 0.56)	SMD 0.19 (95% CI -0.10 to 0.49)
Moderate vs mild-potency TCS; SMD; end of treatment (Analysis 1.6)	SMD 0.36 (95% CI -0.15 to 0.87)	SMD 0.43 (95% CI 0.00 to 0.86)	SMD 0.59 (95% CI 0.27 to 0.91)
Moderate vs mild-potency TCS; clinician and patient assessment (by preference); short term and end of treatment (Analysis 1.7)	OR 2.96 (95% CI 1.27 to 6.87)	OR 3.14 (95% CI 1.39 to 7.13)	OR 3.39 (95% CI 1.57 to 7.31)
Potent vs mild-potency TCS; IGA; short term (Analysis 2.1)	OR 3.80 (95% CI 2.12 to 6.83)	OR 3.71 (95% CI 2.04 to 6.72)	OR 3.61 (95% CI 1.99 to 6.56)
Potent vs mild-potency TCS; clinician assessment (by preference); short term (Analysis 2.5)	OR 11.99 (95% CI 5.08 to 28.29)	OR 11.70 (95% CI 5.67 to 24.15)	OR 11.27 (95% CI 6.41 to 19.79)
Potent vs mild-potency TCS; patient assessment; short term, narrative (Analysis 2.7; Giannetti 1981 with ICC 0.5 assumed for imputation of SD. See Table 7)	MD 0.60 (95% CI 0.21 to 0.99)	MD 0.60 (95% CI 0.28 to 0.92)	MD 0.60 (95% CI 0.37 to 0.83)
Potent vs mild-potency TCS; patient assessment; end of treatment, narrative (Analysis 2.7; Giannetti 1981 with ICC 0.5 assumed for imputation of SD. See Table 7)	MD 0.50 (95% CI 0.14 to 0.86)	MD 0.50 (95% CI 0.20 to 0.80)	MD 0.50 (95% CI 0.27 to 0.73)
Potent vs moderate-potency TCS; IGA; short term (Analysis 3.1)	OR 1.26 (95% CI 0.90 to 1.77)	OR 1.33 (95% CI 0.93 to 1.89)	OR 1.46 (95% CI 0.99 to 2.17)
Potent vs moderate-potency TCS; SMD; short term (Analysis 3.4)	SMD 0.03 (95% CI -0.73 to 0.79)	SMD 0.01 (95% CI -0.70 to 0.72)	SMD -0.03 (95% CI -0.66 to 0.60)
Potent vs moderate-potency TCS; SMD; end of treatment (Analysis 3.5)	SMD 0.34 (95% CI -0.65 to 1.32)	SMD 0.29 (95% CI -0.62 to 1.20)	SMD 0.20 (95% CI -0.56 to 0.96)
Potent vs moderate-potency TCS; clinician assessment (by preference); short term (Analysis 3.6)	OR 3.85 (95% CI 2.19 to 6.78)	OR 3.86 (95% CI 2.42 to 6.14)	OR 3.75 (95% CI 2.44 to 5.76)
Very potent vs potent TCS; cleared or marked improvement on IGA; short term (Analysis 4.1)	OR 0.50 (95% CI 0.11 to 2.17)	OR 0.53 (95% CI 0.13 to 2.09)	OR 0.58 (95% CI 0.17 to 1.99)
Very potent vs potent TCS; clinician assessment (by preference); short term and end of treatment (Analysis 4.2)	OR 1.70 (95% CI 1.01 to 2.85)	OR 1.68 (95% CI 1.00 to 2.83)	OR 1.67 (95% CI 1.00 to 2.80)

Table 5. Sensitivity analyses: effect of Becker-Balagtas correction of within-participant studies using a range of ICC* (0.25, 0.5, 0.75) *(Continued)*

Very potent vs potent TCS; narrative IGA data; short term (Goh 1999)	OR 1.95 (95% CI 0.71 to 5.35)	OR 1.95 (95% CI 0.85 to 4.48)	OR 1.95 (95% CI 1.06 to 3.57)
Very potent vs potent TCS; narrative IGA data; end of treatment (Goh 1999)	OR 6.33 (95% CI 3.15 to 12.73)	OR 6.33 (95% CI 3.58 to 11.20)	OR 6.33 (95% CI 4.23 to 9.48)
Very potent vs potent TCS; narrative IGA data; short term (Guttman-Yassky 2017)	MD -0.04 (95% CI -0.40 to 0.33)	MD -0.04 (95% CI -0.33 to 0.26)	MD -0.04 (95% CI -0.24 to 0.17)
Very potent vs potent TCS; narrative IGA data; end of treatment (Guttman-Yassky 2017)	MD -0.07 (95% CI -0.43 to 0.29)	MD -0.07 (95% CI -0.36 to 0.23)	MD -0.07 (95% CI -0.28 to 0.14)
Twice daily very potent TCS vs once daily second-generation potent TCS; narrative PGA data; short term (Goh 1999)	OR 3.37 (95% CI 1.01 to 11.19)	OR 3.37 (95% CI 1.22 to 9.29)	OR 3.37 (95% CI 1.54 to 7.38)
Twice daily very potent TCS vs once daily second-generation potent TCS; narrative PGA data; end of treatment (Goh 1999)	OR 6.57 (95% CI 2.74 to 15.74)	OR 6.57 (95% CI 3.14 to 13.74)	OR 6.57 (95% CI 3.71 to 11.62)
TCS cream vs TCS ointment; IGA; short term and end of treatment (Analysis 5.1)	OR 1.52 (95% CI 0.41 to 5.67)	OR 1.65 (95% CI 0.41 to 6.60)	OR 1.80 (95% CI 0.43 to 7.52)
TCS cream vs TCS ointment; narrative (Analysis 5.2; Cadmus 2019)	MD 0.13 (95% CI -0.12 to 0.38)	MD 0.13 (95% CI -0.07 to 0.33)	MD 0.13 (95% CI -0.02 to 0.27)
Second-generation vs older TCS; SMD; short term (Analysis 6.8)	SMD 0.14 (95% CI -0.38 to 0.66)	SMD 0.16 (95% CI -0.45 to 0.77)	SMD 0.21 (95% CI -0.57 to 0.99)
Second-generation vs older TCS; IGA (narrative; Analysis 6.9; Goh 1999); short term	OR 0.51 (95% CI 0.19 to 1.41)	OR 0.51 (95% CI 0.22 to 1.18)	OR 0.51 (95% CI 0.28 to 0.94)
Second-generation vs older TCS; IGA (narrative; Analysis 6.9; Goh 1999); end of treatment	OR 0.16 (95% CI 0.08 to 0.32)	OR 0.16 (95% CI 0.09 to 0.28)	OR 0.16 (95% CI 0.11 to 0.24)
Second-generation TCS vs older TCS; itch, narrative; short term and end of treatment (Analysis 6.14; Kim 2013 with ICC 0.5 assumed for imputation of SD. See Table 7)	MD 0.34 (95% CI -0.05 to 0.73)	MD 0.34 (95% CI 0.02 to 0.66)	MD 0.34 (95% CI 0.11 to 0.57)
Second-generation vs older TCS; patient assessment (narrative; Analysis 6.14; Goh 1999); short-term	OR 0.30 (95% CI 0.09 to 0.99)	OR 0.30 (95% CI 0.11 to 0.82)	OR 0.30 (95% CI 0.14 to 0.65)
Second-generation vs older TCS; patient assessment (narrative; Analysis 6.14; Goh 1999); end of treatment	OR 0.15 (95% CI 0.06 to 0.37)	OR 0.15 (95% CI 0.07 to 0.32)	OR 0.15 (95% CI 0.09 to 0.27)
Twice or more vs once daily TCS; IGA; short term (Analysis 7.1)	OR 0.96 (95% CI 0.67 to 1.39)	OR 0.97 (95% CI 0.68 to 1.38)	OR 0.98 (95% CI 0.69 to 1.38)
Wet wrap vs no wet wrap; SMD; short term (Analysis 10.1)	SMD -0.20 (95% CI -0.79 to 0.40)	SMD -0.26 (95% CI -0.92 to 0.41)	SMD -0.36 (95% CI -1.19 to 0.48)

CI: confidence interval; **ICC:** intraclass correlation coefficient; **IGA:** Investigator Global Assessment; **MD:** mean difference; **OR:** odds ratio; **PGA:** Patient Global Assessment; **TCS:** topical corticosteroid; **SD:** standard deviation; **SMD:** standardised mean difference

*ICC refers to the intraclass correlation coefficient assumed in order to use the Becker-Balagtas method to correct the standard errors derived from the pooled within-participant trials.

Table 6. Sensitivity analyses: effect of studies with high risk of bias

Analysis	All trials	Excluding trials with high risk of bias in one or more domains
Analysis 1.1	OR 2.07 (95% CI 1.41 to 3.04)	OR 1.81 (95% CI 0.62 to 5.29; 1 trial; Mobacken 1986)
Analysis 1.3	OR 2.74 (95% CI 1.47 to 5.11)	OR 8.25 (95% CI 1.63 to 41.70; 1 trial; Mobacken 1986)
Analysis 1.5	SMD 0.15 (95% CI −0.27 to 0.56)	SMD 0.13 (95% CI −0.29 to 0.56; 1 trial; Haribhakti 1982)
Analysis 1.6	SMD 0.43 (95% CI 0.00 to 0.86)	SMD 0.44 (95% CI −0.01 to 0.89; 1 trial; Haribhakti 1982)
Analysis 1.7	OR 3.14 (95% CI 1.39 to 7.13)	OR 37.51 (95% CI 0.34 to 4133.15)
Analysis 2.1	OR 3.71 (95% CI 2.04 to 6.72)	OR 2.56 (95% CI 1.59 to 4.14)
Analysis 2.4	SMD 0.63 (95% CI −0.95 to 2.21)	SMD −0.12 (95% CI −0.85 to 0.61; 1 trial; Lebrun-Vignes 2000)
Analysis 2.5	OR 11.70 (95% CI 5.67 to 24.15)	OR 13.43 (95% CI 3.10 to 58.23)
Analysis 3.1	OR 1.33 (95% CI 0.93 to 1.89)	OR 1.90 (95% CI 0.83 to 4.35)
Analysis 3.4	SMD 0.01 (95% CI −0.70 to 0.72)	SMD −0.23 (95% CI −0.93 to 0.46)
Analysis 3.5	SMD 0.29 (95% CI −0.62 to 1.20)	SMD −0.10 (95% CI −1.21 to 1.00)
Analysis 3.6	OR 3.86 (95% CI 2.42 to 6.14)	All trials were judged high risk of bias
Analysis 4.1	OR 0.53 (95% CI 0.13 to 2.09)	OR 1.00 (95% CI 0.24 to 4.22; 1 trial; Bleeker 1975)
Analysis 4.2	OR 1.68 (95% CI 1.00 to 2.83)	All trials were judged high risk of bias
Analysis 5.1	OR 1.65 (95% CI 0.41 to 6.60)	No trials were judged high risk of bias
Analysis 6.1	OR 2.52 (95% CI 1.47 to 4.30)	OR 3.61 (95% CI 1.87 to 6.96)
Analysis 6.4	OR 2.79 (95% CI 1.71 to 4.56)	OR 2.12 (95% CI 0.51 to 8.81)
Analysis 6.7	MD −1.63 (95% CI −2.57 to −0.69)	No trials were judged high risk of bias
Analysis 6.8	SMD 0.16 (95% CI −0.45 to 0.77)	SMD −0.32 (95% CI −1.19 to 0.55; 1 trial; Wolkerstorfer 1998)
Analysis 6.10	OR 2.26 (95% CI 1.24 to 4.14)	No trials were judged high risk of bias
Analysis 6.11	OR 1.16 (95% CI 0.60 to 2.25)	No trials were judged high risk of bias
Analysis 6.12	OR 2.09 (95% CI 1.15 to 3.81)	No trials were judged high risk of bias
Analysis 6.13	OR 2.41 (95% CI 1.03 to 5.65)	No trials were judged high risk of bias
Analysis 7.1	OR 0.97 (95% CI 0.68 to 1.38)	OR 1.26 (95% CI 0.96 to 1.65)
Analysis 7.4	OR 1.58 (95% CI 0.80 to 3.10)	All trials were judged high risk of bias
Analysis 7.5	SMD 0.40 (95% CI −0.23 to 1.03)	SMD 0.32 (95% CI −0.55 to 1.19; 1 trial; Wolkerstorfer 1998)
Analysis 7.6	SMD 0.51 (95% CI −0.32 to 1.33)	SMD 0.28 (95% CI −1.55 to 2.10; 1 trial; Wolkerstorfer 1998)

Table 6. Sensitivity analyses: effect of studies with high risk of bias *(Continued)*

Analysis 7.8	OR 1.91 (95% CI 0.62 to 5.83)	OR 3.62 (95% CI 1.24 to 10.56; 1 trial; Koopmans 1995)
Analysis 9.1	HR 2.28 (95% CI 1.88 to 2.76)	HR 2.36 (95% CI 1.86 to 3.01)
Analysis 9.4	RR 0.43 (95% CI 0.32 to 0.57)	RR 0.49 (95% CI 0.37 to 0.65)
Analysis 10.1	SMD −0.26 (95% CI −0.92 to 0.41)	All trials were judged high risk of bias

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **SMD:** standardised mean difference

Table 7. Sensitivity analyses: effect of imputing missing SD using a range of ICC* (0.25, 0.5, 0.75)

Analysis	ICC = 0.25	ICC = 0.5	ICC = 0.75
Potent TCS vs mild TCS; itch narrative; short term (Analysis 2.7; Giannetti 1981 with ICC 0.5 assumed for BB correction. See Table 5)	MD 0.60 (95% CI 0.22 to 0.98)	MD 0.60 (95% CI 0.28 to 0.92)	MD 0.60 (95% CI 0.36 to 0.84)
Potent TCS vs mild TCS; itch narrative; end of treatment (Analysis 2.7; Giannetti 1981 with ICC 0.5 assumed for BB correction. See Table 5)	MD 0.50 (95% CI 0.13 to 0.87)	MD 0.50 (95% CI 0.20 to 0.80)	MD 0.50 (95% CI 0.27 to 0.73)
Potent TCS vs moderate TCS; SMD; short term (Analysis 3.4)	SMD 0.03 (95% CI −0.65 to 0.70)	SMD 0.01 (95% CI −0.70 to 0.72)	SMD −0.02 (95% CI −0.81 to 0.76)
Potent TCS vs moderate TCS; SMD; end of treatment (Analysis 3.5)	SMD 0.30 (95% CI −0.61 to 1.21)	SMD 0.29 (95% CI −0.62 to 1.20)	SMD 0.27 (95% CI −0.64 to 1.19)
Potent TCS vs moderate TCS; narrative; end of follow-up (Analysis 3.7; Wolkerstorfer 1998)	MD −5.00 (95% CI −20.29 to 10.29)	MD −5.00 (95% CI −17.67 to 7.67)	MD −5.00 (95% CI −14.34 to 4.34)
TCS cream vs TCS ointment; narrative (Analysis 5.2; EUCTR2009-012028-98-DE)	MD 0.40 (95% CI −5.89 to 6.69)	MD 0.40 (95% CI −4.79 to 5.59)	MD 0.40 (95% CI −3.39 to 4.19)
Second-generation TCS vs older TCS; SMD; short term (Analysis 6.8)	SMD 0.20 (95% CI −0.33 to 0.73)	SMD 0.16 (95% CI −0.45 to 0.77)	SMD 0.07 (95% CI −0.69 to 0.84)
Second-generation TCS vs older TCS; narrative; end of follow-up (Analysis 6.9; Wolkerstorfer 1998)	MD −5.00 (95% CI −20.29 to 10.29)	MD −5.00 (95% CI −17.67 to 7.67)	MD −5.00 (95% CI −14.34 to 4.34)
Second-generation TCS vs older TCS; itch, narrative; short term and end of treatment (Analysis 6.14; Kim 2013)	MD 0.34 (95% CI −0.05 to 0.73)	MD 0.34 (95% CI 0.02 to 0.66)	MD 0.34 (95% CI 0.10 to 0.58)
Twice or more vs once daily TCS; SMD; short term (Analysis 7.5)	SMD 0.34 (95% CI −0.29 to 0.97)	SMD 0.40 (95% CI −0.23 to 1.03)	SMD 0.53 (95% CI −0.11 to 1.17)
Twice or more vs once daily TCS; SMD; end of treatment (Analysis 7.6)	SMD 0.42 (95% CI −0.39 to 1.24)	SMD 0.51 (95% CI −0.32 to 1.33)	SMD 0.67 (95% CI −0.17 to 1.51)
Twice or more vs once daily TCS; narrative MD; end of follow-up (Analysis 7.7; Wolkerstorfer 1998)	MD 5.00 (95% CI −10.29 to 20.29)	MD 5.00 (95% CI −7.67 to 17.67)	MD 5.00 (95% CI −4.34 to 14.34)
Daily application vs less frequent application; narrative; end of treatment (Analysis 8.1; Sillevis 2000)	MD −8.00 (95% CI −16.99 to 0.99)	MD −8.00 (95% CI −15.41 to −0.59)	MD −8.00 (95% CI −13.37 to −2.63)

Table 7. Sensitivity analyses: effect of imputing missing SD using a range of ICC* (0.25, 0.5, 0.75) *(Continued)*

Weekend therapy; narrative to MD (Analysis 9.7 itch; Rubio-Gomis 2018)	MD −1.90 (95% CI −3.54 to −0.26)	MD −1.90 (95% CI −3.26 to −0.54)	MD −1.90 (95% CI −2.90 to −0.90)
Weekend therapy; narrative, MD (Analysis 9.7 sleep; Rubio-Gomis 2018)	MD 0.30 (95% CI −1.03 to 1.63)	MD 0.30 (95% CI −0.80 to 1.40)	MD 0.30 (95% CI −0.50 to 1.10)
Application to wet vs dry skin; mean EASI narrative; end of treatment (Kohn 2016)	MD 0.80 (95% CI −3.93 to 5.53)	MD 0.80 (95% CI −3.34 to 4.94)	MD 0.80 (95% CI −2.64 to 4.24)
Application to wet vs dry skin; itch, narrative; short term (Kohn 2016)	MD 0.70 (95% CI −1.26 to 2.66)	MD 0.70 (95% CI −0.91 to 2.31)	MD 0.70 (95% CI −0.46 to 1.86)
Application to wet vs dry skin; itch, narrative; end of treatment (Kohn 2016)	MD 1.20 (95% CI −0.73 to 3.13)	MD 1.20 (95% CI −0.40 to 2.80)	MD 1.20 (95% CI 0.03 to 2.37)
Application to wet vs dry skin; sleep, narrative; short term (Kohn 2016)	MD 0.10 (95% CI −0.58 to 0.78)	MD 0.10 (95% CI −0.47 to 0.67)	MD 0.10 (95% CI −0.33 to 0.53)
Application to wet vs dry skin; sleep, narrative; end of treatment (Kohn 2016)	MD 0.20 (95% CI −0.48 to 0.88)	MD 0.20 (95% CI −0.37 to 0.77)	MD 0.20 (95% CI −0.23 to 0.63)
Wet wrap vs no wet wrap; SMD; short term (Analysis 10.1)	SMD −0.26 (95% CI −0.87 to 0.35)	SMD −0.26 (95% CI −0.92 to 0.41)	SMD −0.24 (95% CI −1.01 to 0.53)
Wet wrap vs no wet wrap; itch and sleep, narrative; short term and end of treatment (Analysis 10.4; Hindley 2006; MD (95% CI))	MD 2.20 (95% CI −1.89 to 6.29)	MD 2.20 (95% CI −1.17 to 5.57)	MD 2.20 (95% CI −0.24 to 4.64)

BB: Becker-Balagtas; **CI:** confidence interval; **EASI:** Eczema Area and Severity Index; **ICC:** intraclass correlation coefficient; **IGA:** Investigator Global Assessment; **MD:** mean difference; **PGA:** Patient Global Assessment; **TCS:** topical corticosteroid; **SD:** standard deviation; **SMD:** standardised mean difference

*ICC refers to the intraclass correlation coefficient assumed in order to impute missing standard deviations.

Table 8. Post-hoc sensitivity analyses: effect of industry sponsorship in trials of second-generation versus older topical corticosteroids

Analysis	All trials	Without trials with clear links to industry
Cleared or marked improvement on IGA (short term; Analysis 6.1)	2.52 (1.47 to 4.30)	OR 4.11 (95% CI 1.15 to 14.63)
Cleared or marked improvement on IGA (end of treatment; Analysis 6.4)	2.79 (1.71 to 4.56)	OR 3.46 (95% CI 1.32, 9.06)

CI: confidence interval; **IGA:** Investigator Global Assessment; **OR:** odds ratio

Table 9. Comparison of recommendations for topical corticosteroid use from international guidelines

Location	UK	USA	Europe	Japan	Evidence from this systematic review

Table 9. Comparison of recommendations for topical corticosteroid use from international guidelines *(Continued)*

Team	NICE	American Academy of Dermatology		Committee for Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018	
Title	Clinical guideline [CG57]. Atopic eczema in under 12s: diagnosis and management	Atopic dermatitis clinical guideline	Consensus-based European Guidelines for treatment of atopic eczema in adults and children	Clinical practice guidelines for management of atopic dermatitis 2018	
Authors	NICE 2007	Eichenfield 2014b	Wollenberg 2018	Katoh 2019	
Potency recommendation in relation to AD severity	Start[a] with mild potency for mild AD, moderate potency for moderate AD etc	Acknowledges lack of good data means variation in dosing exists (e.g. some clinicians use short-burst, high-potency TCS, some stepped approach), states least potent TCS should be used to minimise AE	Class II for mild AD. Class II/III for moderate AD. No TCS are listed for severe AD[b]	Medium or weak rank first-line TCS for mild AD. Strong or medium rank first-line for moderate. Very strong or strong rank first- line for severe. Strongest rank can be used for some indications[c]	Evidence identified in review is lacking[d] and there are variations in severity and potency classifications between countries
Once daily administration	Once or twice daily	Recommends twice daily but says once can be used	Recommends twice daily but says once can be used	Twice daily in acute exacerbation reduced to once daily after inflammation reduced	Moderate-certainty evidence to support the use of potent TCS once daily. For mild and moderate TCS there is a lack of evidence regarding once or twice daily application
Advocates weekend (proactive) use	Yes - but suggests there is only limited evidence to support use	Yes – states good-quality evidence	Yes – strong recommendation. States longest duration of trials 20 weeks	Yes – evidence level is high, monitoring required by experienced physician	Moderate-certainty evidence to support weekend (proactive) use. Trials up to 12 months long
Advocates monitoring of cutaneous AE	Does not refer directly to monitoring for AE in recommendations. Includes restrictions on use e.g. potent TCS not to be used < 12 months[e]	Yes	Yes	States patients should be referred to a dermatologist if cutaneous AE observed	Low- or very low-certainty evidence to suggest cutaneous AE are rare

Table 9. Comparison of recommendations for topical corticosteroid use from international guidelines *(Continued)*

Advocates monitoring of systemic AE	Does not refer directly to monitoring for AE in recommendations. Includes restrictions on use e.g. potent TCS not to be used < 12 months[e]	Consider potential for systemic AE but no specific monitoring required. If HPA suppression is a concern perform cortisol stimulation test	Does not refer directly to monitoring, links risk with potency, specifies threshold (in grams TCS) below which AE do not usually occur	Does not refer directly to monitoring for AE but does mention there have been cases of adrenal suppression with strong but not weak TCS	Very low-certainty evidence reporting cases of abnormal cortisol levels. Unclear how these biochemical changes relate to health

AD: atopic dermatitis; **AE:** adverse events; **HPA:** hypothalamic pituitary axis; **TCS:** topical corticosteroids

[a]Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments. Guideline includes a description of the different severities of AD.
[b]SCORAD (SCORing Atopic Dermatitis) assessments provided to aid assessment of severity, e.g. severe SCORAD > 50/ persistent eczema. Topical steroid classification by Niedner 2001 (mild (group I) to superpotent (group IV). Superpotent TCS are not recommended.
[c]TCS are classified into five ranks, strongest, very strong, strong, medium and weak. The guideline includes descriptions of the different severities of AD.
[d]Within the potent vs mild TCS comparison, there was no difference between mild and potent TCS in participants with mild to moderate eczema suggesting that mild steroids may work well enough for this group, however this only considered 43 participants from two trials and the confidence interval was wide compared to the data in moderate to severe eczema, which favoured potent TCS. Furthermore, as there were more reports of skin thinning in more potent steroids, the trade-off of more effectiveness from higher-potency TCS does not seem necessary for this group unless it fails to control the flare.
[e]Without specialist dermatologist supervision.

APPENDICES

Appendix 1. Cochrane Skin Specialised Register (CRSW)

1. eczema or dermatitis or neurodermatitis AND INREGISTER
2. besnier* prurigo AND INREGISTER
3. prurigo diathesique AND INREGISTER
4. #1 OR #2 OR #3 AND INREGISTER
5. alclometasone or amcinonide or beclometasone or beclomethasone or betamethasone or budesonide or clobetasol or clobetasone or clocortolone or Deprodone or desonide or desoximetasone or dexamethasone or dichlorisone or diflorasone or diflucortolone or difluprednate or fluclorolone or flucloronide or fludrocortisone or fludroxycortide or flumetasone or flumethasone or fluocinolone or fluocinonide or fluocortin or fluocortolone or fluorometholone or fluprednidene or flurandrenolide or flurandrenolone or fluticasone or halcinonide or halobetasol or halometasone or hydrocortisone or masipredone or mazipredone or methylprednisolone or mometasone or prednicarbat* or prednisolone or prednisone or triamcinolone or ulobetasol AND INREGISTER
6. (topical and (steroid* or corticosteroid* or glucocorticoid* or corticoid* or cortisone or cortisol)) AND INREGISTER
7. #5 OR #6
8. #4 AND #7

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL; Cochrane Library) search strategy

#1 MeSH descriptor: [Eczema] explode all trees
#2 MeSH descriptor: [Dermatitis, Atopic] explode all trees
#3 MeSH descriptor: [Neurodermatitis] explode all trees
#4 MeSH descriptor: [Dermatitis] explode all trees
#5 (eczema or dermatitis or neurodermatitis):ti,ab,kw
#6 besnier* prurigo:ti,ab,kw
#7 prurigo diathesique:ti,ab,kw
#8 {or #1-#7}
#9 (topical* next corticosteroid*):ti,ab,kw
#10 (topical* next steroid*):ti,ab,kw
#11 (topical* next glucocorticoid*):ti,ab,kw
#12 (topical* next corticoid*):ti,ab,kw

#13 [mh desonide]
#14 desonide:ti,ab,kw
#15 alclometasone:ti,ab,kw
#16 amcinonide:ti,ab,kw
#17 [mh Beclomethasone]
#18 (beclometasone or beclomethasone):ti,ab,kw
#19 [mh Betamethasone]
#20 betamethasone:ti,ab,kw
#21 budesonide:ti,ab,kw
#22 [mh budesonide]
#23 clobetasol:ti,ab,kw
#24 [mh Clobetasol]
#25 clobetasone:ti,ab,kw
#26 clocortolone:ti,ab,kw
#27 ([mh cortisone] or cortisone:ti,ab,kw) and topical*:ti,ab,kw
#28 Deprodone:ti,ab,kw
#29 [mh desoximetasone]
#30 desoximetasone:ti,ab,kw
#31 [mh Dexamethasone]
#32 Dexamethasone:ti,ab,kw
#33 dichlorisone:ti,ab,kw
#34 diflorasone:ti,ab,kw
#35 [mh Diflucortolone]
#36 diflucortolone:ti,ab,kw
#37 Difluprednate:ti,ab,kw
#38 fluclorolone:ti,ab,kw
#39 Flucloronide:ti,ab,kw
#40 Fludrocortisone:ti,ab,kw
#41 fludroxycortide:ti,ab,kw
#42 (flumetasone or flumethasone):ti,ab,kw
#43 [mh Flumethasone]
#44 fluocinolone:ti,ab,kw
#45 [mh "Fluocinolone Acetonide"]
#46 fluocinonide:ti,ab,kw
#47 [mh Fluocinonide]
#48 fluocortin:ti,ab,kw
#49 [mh Fluocortolone]
#50 fluocortolone:ti,ab,kw
#51 Fluorometholone:ti,ab,kw
#52 fluprednidene:ti,ab,kw
#53 flurandrenolide:ti,ab,kw
#54 flurandrenolone:ti,ab,kw
#55 [mh Flurandrenolone]
#56 fluticasone:ti,ab,kw
#57 halcinonide:ti,ab,kw
#58 [mh Halcinonide]
#59 halobetasol:ti,ab,kw
#60 halometasone:ti,ab,kw
#61 [mh Hydrocortisone]
#62 (cortisol):ti,ab,kw and topical*:ti,ab,kw
#63 hydrocortisone:ti,ab,kw
#64 (masipredone or Mazipredone):ti,ab,kw
#65 [mh Methylprednisolone]
#66 methylprednisolone:ti,ab,kw
#67 mometasone:ti,ab,kw
#68 prednicarbat*:ti,ab,kw
#69 [mh Prednisolone]
#70 (Prednisolone or prednisone):ti,ab,kw
#71 triamcinolone:ti,ab,kw
#72 [mh Triamcinolone]
#73 ulobetasol:ti,ab,kw
#74 [mh "Adrenal Cortex Hormones"] and topical*:ti,ab,kw

#75 [mh Glucocorticoids] and topical*:ti,ab,kw
#76 {or #9-#75}
#77 #8 and #76

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Eczema/ or eczema$.ti,ab.
2. exp Dermatitis, Atopic/
3. neurodermatitis.ti,ab. or exp Neurodermatitis/
4. exp Dermatitis/ or dermatitis.ti,ab.
5. besnier$ prurigo.ti,ab.
6. prurigo diathesique.ti,ab.
7. or/1-6
8. (topical$ adj3 corticosteroid$).ti,ab.
9. (topical$ adj3 steroid$).ti,ab.
10. (topical$ adj3 corticoid$).ti,ab.
11. (topical$ adj3 glucocorticoid$).ti,ab.
12. exp Desonide/
13. desonide.mp.
14. alclometasone.mp.
15. amcinonide.mp.
16. exp Beclomethasone/
17. (beclometasone or beclomethasone).mp.
18. exp Betamethasone/
19. Betamethasone.mp.
20. budesonide.mp. or exp Budesonide/
21. clobetasol$.mp. or exp Clobetasol/
22. clobetasone$.mp.
23. clocortolone.mp.
24. (exp Cortisone/ or cortisone.ti,ab.) and (exp Administration, Topical/ or exp Ointments/ or Dermatologic Agents/)
25. Deprodone.mp.
26. desoximetasone.mp. or exp Desoximetasone/
27. exp Dexamethasone/ or dexamethasone.mp.
28. dichlorisone.mp.
29. diflorasone.mp.
30. exp Diflucortolone/ or diflucortolone.mp.
31. Difluprednate.mp.
32. fluclorolone.mp.
33. Flucloronide.mp.
34. Fludrocortisone.mp.
35. fludroxycortide.mp.
36. (flumetasone or flumethasone).mp.
37. exp Flumethasone/
38. fluocinolone.mp.
39. fluocinonide.mp. or exp Fluocinonide/
40. fluocortin.mp.
41. exp Fluocortolone/
42. fluocortolone.mp.
43. Fluorometholone.mp.
44. fluprednidene.mp.
45. flurandrenolide.mp.
46. flurandrenolone.mp. or exp Flurandrenolone/
47. fluticasone.mp.
48. halcinonide.mp. or exp Halcinonide/
49. halobetasol.mp.
50. halometasone.mp.
51. exp Hydrocortisone/
52. cortisol.ti,ab. and (exp Administration, Topical/ or exp Ointments/ or Dermatologic Agents/)
53. hydrocortisone$.mp.
54. (masipredone or Mazipredone).mp.
55. exp Methylprednisolone/
56. methylprednisolone.mp.

57. mometasone.mp.
58. prednicarbat$.mp.
59. exp Prednisolone/
60. (Prednisolone or prednisone).mp.
61. ulobetasol.mp.
62. triamcinolone.mp. or exp Triamcinolone/
63. exp Adrenal Cortex Hormones/ and (exp Administration, Topical/ or exp Ointments/ or Dermatologic Agents/)
64. exp Glucocorticoids/ and (exp Administration, Topical/ or exp Ointments/ or Dermatologic Agents/)
65. or/8-64
66. randomized controlled trial.pt.
67. controlled clinical trial.pt.
68. randomized.ab.
69. placebo.ab.
70. clinical trials as topic.sh.
71. randomly.ab.
72. trial.ti.
73. 66 or 67 or 68 or 69 or 70 or 71 or 72
74. exp animals/ not humans.sh.
75. 73 not 74
76. 7 and 65 and 75

Lines 66-75: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format (Lefebvre 2021, section 3.6.1).

Appendix 4. Embase (Ovid) search strategy

1. exp eczema/
2. eczema$.ti,ab.
3. exp atopic dermatitis/
4. exp neurodermatitis/
5. neurodermatitis.ti,ab.
6. exp dermatitis/
7. dermatitis.ti,ab.
8. besnier$ prurigo.ti,ab.
9. prurigo diathesique.ti,ab.
10. or/1-9
11. (topical$ adj3 corticosteroid$).ti,ab.
12. (topical$ adj3 steroid$).ti,ab.
13. (topical$ adj3 corticoid$).ti,ab.
14. (topical$ adj3 glucocorticoid$).ti,ab.
15. exp desonide/
16. desonide.mp.
17. exp alclometasone/
18. alclometasone.mp.
19. exp amcinonide/
20. amcinonide.mp.
21. exp beclometasone/
22. (beclometasone or beclomethasone).mp.
23. exp betamethasone/
24. Betamethasone.mp.
25. exp budesonide/
26. budesonide.mp.
27. exp clobetasol/
28. clobetasol$.mp.
29. clobetasone$.mp.
30. clocortolone.mp.
31. exp clocortolone/
32. exp clobetasone/
33. Deprodone.mp.
34. exp desoximetasone/
35. desoximetasone.mp.
36. exp dexamethasone/

37. dexamethasone.mp.
38. Dichlorisone.mp.
39. exp diflorasone/
40. diflorasone.mp.
41. exp diflucortolone/
42. diflucortolone.mp.
43. exp difluprednate/
44. Difluprednate.mp.
45. exp fluclorolone/
46. fluclorolone.mp.
47. Flucloronide.mp.
48. exp fludrocortisone/
49. Fludrocortisone.mp.
50. exp fludroxycortide/
51. fludroxycortide.mp.
52. (flumetasone or flumethasone).mp.
53. exp flumetasone/
54. exp fluocinolone/
55. fluocinolone.mp.
56. exp fluocinonide/
57. fluocinonide.mp.
58. exp fluocortin/
59. fluocortin.mp.
60. exp fluocortolone/
61. fluocortolone.mp.
62. exp fluorometholone/
63. Fluorometholone.mp.
64. exp fluprednidene/
65. fluprednidene.mp.
66. flurandrenolide.mp.
67. flurandrenolone.mp.
68. exp fluticasone/
69. fluticasone.mp.
70. exp halcinonide/
71. halcinonide.mp.
72. halobetasol.mp.
73. exp halometasone/
74. halometasone.mp.
75. exp hydrocortisone/
76. hydrocortisone$.mp.
77. exp mazipredone/
78. (masipredone or Mazipredone).mp.
79. exp methylprednisolone/
80. methylprednisolone.mp.
81. mometasone.mp.
82. prednicarbat$.mp.
83. exp prednicarbate/
84. exp prednisolone/
85. (Prednisolone or prednisone).mp.
86. exp prednisone/
87. ulobetasol.mp.
88. exp triamcinolone/
89. Triamcinolone.mp.
90. (exp glucocorticoid/ or exp corticosteroid/) and (exp topical treatment/ or exp topical agent/ or exp topical drug administration/)
91. (cortisone.mp. or exp cortisone/) and (exp topical treatment/ or exp topical agent/ or exp topical drug administration/)
92. cortisol.mp. and (exp topical treatment/ or exp topical agent/ or exp topical drug administration/)
93. or/11-92
94. crossover procedure.sh.
95. double-blind procedure.sh.
96. single-blind procedure.sh.
97. (crossover$ or cross over$).tw.
98. placebo$.tw.

99. (doubl$ adj blind$).tw.
100. allocat$.tw.
101. trial.ti.
102. randomized controlled trial.sh.
103. random$.tw.
104. or/94-103
105. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
106. human/ or normal human/
107. 105 and 106
108. 105 not 107
109. 104 not 108
110. 10 and 93 and 109

Lines 94-104: based on terms suggested for identifying RCTs in Embase (Lefebvre 2021, section 3.6.2).

HISTORY

Protocol first published: Issue 6, 2019

CONTRIBUTIONS OF AUTHORS

SJL, JH and EA were the contact people with the editorial base.
SJL, JH and JRC co-ordinated contributions from the co-authors and wrote the final draft of the review.
SJL, JH and EA screened papers against eligibility criteria.
SJL and JH obtained data on ongoing and unpublished trials.
SJL, JH, EA, LH and JRC appraised the quality of papers.
SJL, JH, EA and LH extracted data for the review and sought additional information about papers.
SJL and JH entered data into Review Manager 5 (Review Manager 2020).
SJL, JH, EA, LH, MS, MJR, SLaw, SLan, AR, AA, IM, LCM, SP, PC, BC, HCW, KST and JRC analysed and interpreted data.
SJL, JH, JRC and KST wrote the first draft of the review. SJL, JH, EA and KST responded to the comments of the referees. EA, LH, BC, MS, MJR, SLaw, SLan, AR, AA, IM, LCM, SP, PC, and HCW commented on and approved the review and responses to comments.

JRC, EA, JH, and BC drafted the protocol. MS, MJR, SLaw, SLan, AR, AA, IM, LCM,SP, PC, HCW, KST provided comments on the protocol draft. AR and AA were the consumer co-authors and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.
SJL and JH are guarantors of the update.

DECLARATIONS OF INTEREST

*This report presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research programme (grant ref No. RP-PG-0216-20007) and via Cochrane Infrastructure funding to the Cochrane Skin Group. The views and opinions expressed herein are those of the author(s) and not necessarily those of the Systematic Reviews Programme, NHS, the NIHR or the department of Health and Social Care*SJL: has declared that they have no conflict of interest.

JH: has declared that they have no conflict of interest.

EA: has declared that they have no conflict of interest.

LH: received consultation fees from the University of Oxford on an educational grant funded by Pfizer and expenses to assist a speaker at the 9th International Immunology Summit in March 2018 (UCB Biopharma SPRL), both unrelated to the submitted work. Member of the HOME executive.

MS: ECO joint-lead-applicant.

MJR: funded by National Institute for Health Research (NIHR) Post-doctoral Fellowship (PDF-2014-07-013). ECO co-applicant.

SLaw: ECO co-applicant.

SLan: ECO co-applicant. Funded by Wellcome Senior Clinical fellowship.

AR: ECO co-applicant.

AA: ECO co-applicant.

IM: ECO co-applicant.

LCM: has declared that they have no conflict of interest.

SP: Merck, FDC & GSK-Stiefel (who produce products that may be used in atopic eczema) have been advertisers in the Indian Journal of Dermatology, Venereology & Leprology of which I am the Editor-in-Chief. I am a Consultant Dermatologist at a private practice.

PC: has declared that they have no conflict of interest.

BC: has declared that they have no conflict of interest.

HCW: Chair of the HOME executive, co-developed the POEM scale, ECO co-applicant. I was an investigator on the following trial published in the BMJ 19 years ago: *Thomas KS, Armstrong S, Avery A, Po AL, O'Neill C, Young S, Williams HC. Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. BMJ. 2002 Mar 30;324(7340):768. doi: 10.1136/bmj.324.7340.768. PMID: 11923161; PMCID: PMC100318* (Thomas 2002). This is an included trial in this review.

KST: member of the HOME executive, ECO joint-lead-applicant. I conducted an independent trial of short bursts of a potent topical corticosteroid compared to longer bursts of mild topical corticosteroid (University of Nottingham) (Thomas 2002). This is an included trial in this review.

JRC: member of the HOME executive, ECO co-applicant.

Disclaimer

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- No sources of support provided

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  The NIHR, UK, is the largest single funder of Cochrane Skin
- NIHR, UK

  This review forms part of a body of work funded by the National Institute for Health Research (NIHR) Programme Grants for Applied Research (grant no: RP-PG-0216-20007) to develop an online behavioural intervention to support self-care of atopic eczema in children, adolescents and young adults and the findings will contribute to development of the intervention by providing data on the best and safest ways to use topical corticosteroids.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of participants: we added clarification on what to do when it was unclear if participants had atopic eczema. We sought expert clinical advice as to whether the trial was to be included, primarily based upon the pattern of symptoms described.

Types of interventions: whilst the protocol included some example strategies, the review now lists all strategies considered. We added detail to clarify the difference between a comparison of daily versus less frequent application per week and a comparison of longer- versus shorter-term duration of use for induction of remission. We added a hierarchy of sources used to classify topical corticosteroid potency.

Types of outcome measures: we removed the following: “Where appropriate, the total number of relevant adverse events (of a particular type) per treatment group was reported to allow pooling of the data.” This reads as a contradiction with the previous sentence that states we focused on individual adverse events previously identified as relevant. We could not pool these data due to the low number of events.

Electronic searches: trials registers: ISRCTN, Australian/NZ and EU registers were only searched to 21 November 2018 as no unique records were identified. WHO platform was unavailable during the January 2021 search.

Searching other resources: we added sections, including cross-references to relevant tables, to detail correspondence with pharmaceutical companies and regulatory agencies.

Data collection and analysis: we added the following to clarify the system used for data extraction: “a Microsoft Access database (designed by SJL; piloted by SJL, JH and EA)”.

Data extraction and management: we removed topical corticosteroid potency from the list of fields to extract under 'Interventions and comparators' as we determined this objectively using the hierarchy of sources detailed in Types of interventions, the results of which are given in Table 2.

We provided clarification on the process of translation of non-English texts.

Measures of treatment effect: we removed the following statement: "We will report dichotomous data as risk ratios (RR) with associated 95% confidence intervals (CI)." We replaced it with a description of our use of the generic inverse variance approach to enable pooling of data from both parallel-group and within-participant trials within the same meta-analyses.

Regarding adverse event data, we removed the following: ", and hence we will report RR." We simplified the remainder of this paragraph to reflect the fact that, as low numbers of adverse events were detected in relatively small numbers of participants, it was not meaningful to calculate risk ratios or odds ratios.

Unit of analysis issues: we revised this section to clarify the process for including data from within-participant trials in the same meta-analyses as parallel-group trials. We have also now included detail on how summaries were generated from reports of skin thinning and related signs.

Dealing with missing data: we added clarification as to assumptions made about number of participants included in a given analysis where it was not clearly reported in the paper.

We detailed calculations done to enable pooling of both dichotomous and continuous data, along with the reference we used to calculate hazard ratios when not reported in papers measuring time to relapse.

Data synthesis: "rate ratios" changed to 'odds ratios' owing to the use of the generic inverse variance approach to enable pooling of within-participant trials alongside parallel-group trials. We removed the following statement: "and may use it to compare trials that have presented a group difference, or have adjusted analysis only."

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; *Dermatologic Agents [adverse effects]; *Eczema [drug therapy]; Emollients [therapeutic use]; Glucocorticoids [therapeutic use]; Immunoglobulin A; Recurrence

MeSH check words

Adult; Child; Humans