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Clinical and cost-effectiveness of once daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation

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The final report and any errors remain the responsibility of the Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, University of Southampton. Colin Green is guarantor.

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SUMMARY

Background

Atopic eczema (atopic dermatitis) is a chronic relapsing condition, characterised by frequent flare-ups on the skin (patches of red, dry, scaly and itchy skin), and treatments are aimed at symptom relief and the prevention of complications (e.g. infections), until remission occurs. It is a major public-health problem, thought to affect around 15-20% of school-age children at some stage, and 2-10% of adults, giving a likely patient group in excess of two million people (in England and Wales).

Atopic eczema is generally classified according to mild, moderate or severe disease, using a range of clinical characteristics, with the majority (over 80%) of patients experiencing mild disease, and only a small proportion (around 2-4%) having severe atopic eczema. The condition is associated with considerable morbidity, which varies with disease severity. The physical impact of the condition affects everyday activities (e.g. school, work, sleep), and sufferers may experience distress and anxiety that diminishes their psychological wellbeing and functional capacity.

The mainstay of treatment for atopic eczema is the use of topical corticosteroids, in combination with emollients and soap substitutes. There are a large number of topical corticosteroids available, classified according to potency (mild, moderate, potent or very potent). The frequency of the application of topical corticosteroids in atopic eczema seems to have developed empirically over time, with twice-daily use as the most dominant prescribing strategy.

Aim of the review

To assess the clinical and cost-effectiveness of once-daily use of topical corticosteroids versus more frequent use of same potency topical corticosteroids in the treatment of people with atopic eczema.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Data sources

Electronic databases were searched from inception to October 2003. Bibliographies of included studies and related papers were checked for relevant studies and experts were contacted for advice and peer review and to identify additional published and unpublished studies. Manufacturer submissions to the National Institute for Clinical Excellence were reviewed.

Study selection

Studies were included if they met the following criteria.

- Intervention: once daily versus more frequent application of topical corticosteroids of the same potency. Studies comparing different potency corticosteroids or compound preparations were excluded.
- Participants: children and adults with atopic eczema (atopic dermatitis). Patients with other types of eczema (e.g. contact dermatitis, seborrhoeic eczema, varicose eczema and discoid eczema) were excluded.

- Design: systematic reviews of randomised controlled trials (RCTs) and RCTs. Controlled clinical trials (CCTs) were considered where no RCT evidence was identified for a given potency group.
- Outcomes: overall response to treatment, impact on clinical features of the condition, relapse/flare-up rate, side-effects, compliance, tolerability, patient preference measures, and quality of life.

Studies in non-English language and studies only published as abstracts were excluded. Titles and abstracts were screened for eligibility by one reviewer and checked by a second reviewer. Inclusion criteria were applied to the full text of selected papers by two reviewers. Any differences in opinion were resolved though discussion or consultation with a third reviewer.

Data extraction and quality assessment
Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any differences in opinion resolved through discussion. The quality of included systematic reviews was assessed using criteria developed by the NHS Centre for Reviews and Dissemination (CRD), and the quality of RCTs was assessed in accordance with NHS CRD Report 4.

Data synthesis
The clinical effectiveness data were synthesised through a narrative review with full tabulation of the results of included studies. Meta-analysis was considered inappropriate as the studies were too dissimilar, however forest plots with risk ratios were presented for illustration of the most commonly reported outcomes.

Results

Number and quality of studies
One systematic review and ten RCTs were included in the systematic review. One RCT compared moderately potent corticosteroids, eight RCTs compared potent corticosteroids, and one RCT compared very potent corticosteroids. No RCTs or CCTs of mild corticosteroids were eligible for inclusion. The systematic review was of good quality. Most of the RCTs were of poor methodological quality, although two RCTs were judged to be of good quality.

Summary of benefits

Moderately potent corticosteroids
The one study that compared moderately potent corticosteroids found no significant difference in severity of symptoms between once and twice daily application, but the study was small and of poor quality.

Potent corticosteroids
Numbers responding to treatment
Overall, studies found little difference in the number of patients responding to treatment between once and twice daily application of potent corticosteroids. Some statistically significant differences favouring twice daily treatment were identified; however these were inconsistent between outcome assessors (physicians versus patients) and outcomes selected for analysis.

Severity of symptoms
Once-daily mometasone furorate (Elocon®) compared with twice daily application of a different active compound was found to result in a greater percent improvement in total atopic dermatitis scores in one study, and an improvement in pruritus only in another study, while a third study found no statistically significant differences. Again, these studies were poor quality. One good quality study favoured twice daily application of fluticasone propionate ointment (Cutivate®), while other studies found no significant difference or an improvement in one symptom but not others with twice daily application. The validity and reliability of the severity scales used was not reported by any of the studies, and the clinical meaning of these scores is not clear.

Very potent corticosteroids
Only one study considered very potent corticosteroids, comparing once versus three times daily application. This study found a statistically significant difference in comparative clinical response in favour of three times daily treatment, but no significant difference in the number of patients with at least a good response.

Adverse effects
The extent of reporting of adverse effects was variable between studies. There appears to be little difference in the frequency or severity of short term adverse events between once daily and more frequent application of potent or very potent topical corticosteroids, however data are limited. No data on late onset adverse events such as skin atrophy were available.

Cost-effectiveness
A search of the literature revealed no published cost-effectiveness studies comparing frequency of application of same potency topical corticosteroids. Given that our review of clinical effectiveness has shown outcomes from the comparators are similar, the relative cost-effectiveness of once- versus more frequent application of topical corticosteroids becomes a case of cost-minimisation, where the least cost alternative should be favoured, all else being equal. A review of the topical corticosteroid products available has revealed a wide range of products and a wide variation in the price of these products; the cost per 30g/30ml for topical corticosteroids included in this review varies between £0.60 (for generic hydrocortisone) and £4.88 (for mometasone furoate, Elocon®). Specific decisions on the least cost alternative, between once-daily and more frequent application of products, will be determined by the relative price of the products being compared. In the case of the ten RCTs included in this review, on the basis of response to treatment, six of these comparisons would favour the once-daily option as 'least cost', and three of the comparisons would favour the 'twice-daily' option as the 'least cost' treatment option. In the remaining RCT the clinical effectiveness findings favoured the twice-daily treatment regimen, with a greater number of patients classed as successful treatment responders, at an additional cost. Given the relatively small costs associated with treatment per patient, it is difficult to imagine that such additional costs are not a cost-effective use of NHS funds, where a successfully treated flare-up is regarded as a good thing.

Where patients can be appropriately prescribed once-daily treatment of a similarly priced product, a reduction in the quantity of topical corticosteroid used will be expected. Therefore, it is feasible that a move to once-daily application of topical

corticosteroids will result in some cost-savings to the NHS. However, in the absence of information on the quantity of product used by treatment regimen, and on the present prescribing patterns, it is not possible to make reliable estimates of potential cost savings. Furthermore, issues related to pack size for prescribed products and subsequent waste (unused product) could easily erode any potential saving. The potential cost-savings on prescribed products are very small at a patient level; although given the large numbers of patients with atopic eczema cost savings in theory could be substantial. The presence of specifically marketed 'once-daily' topical corticosteroids, which are relatively expensive (per unit price), may result in additional costs to the NHS should there be a general recommendation in favour of once-daily use of topical corticosteroids, compared to more frequent use.

Conclusions

The literature to inform on the clinical effectiveness of once-daily versus more frequent application of topical corticosteroids is very limited. The available literature indicates that the clinical effectiveness of once-daily and more frequent application of potent topical corticosteroids is very similar, but it does not offer a basis for favouring either option. The cost-effectiveness of once-daily versus more frequent use of topical corticosteroids will depend on the generalisability of the findings to the specific treatment decision and the relativities in product prices.

The trials included in this review generally refer to moderate to severe atopic eczema, whilst the vast majority of patients have mild disease, furthermore most of the included trials report on potent topical corticosteroids (eight of ten RCTs); therefore the generalisability of the findings presented in the review is severely limited.

Recommendations for further research

Further research is required on the clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids, across a broader range of patient groups, and across a broader range of topical corticosteroids. Specifically, further information is needed on the effectiveness of mild potency products (e.g. hydrocortisone products) for the treatment of mild to moderate atopic eczema, by frequency of application (i.e. once-daily versus more frequent use).

Research is particularly required to inform on areas of expected benefit related to a reduction in the use of topical corticosteroids (e.g. improved compliance, impact on quality of life).

GLOSSARY AND LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
b.d.	Twice-daily
BNF	British National Formulary
CCT	Controlled clinical trial
CI	Confidence interval
Erythema	Redness
GSK	GlaxoSmithKline
HRQL	Health-related quality of life
I-gE	Immunoglobulin E
ITT	Intention-to-treat
Lichenification	Thickening of the skin as a result of chronic scratching
NHS CRD	NHS Centre for Reviews and Dissemination
NIC	Net ingredient cost
o.d.	Once-daily
OR	Odds ration
p=ns	Not statistically significant
PCA	Department of Health Prescription Cost Analysis
Pruritus	Itching
RCT	Randomised controlled trial
RR	Risk ratio / relative risk
SCORAD	Severity Scoring of Atopic Dermatitis
SD	Standard deviation
SF-36	Medical Outcomes Study Short-Form 36, generic health status measure
SPCs	Manufacturers' data sheets or Summaries of Product Characteristics
Telangiectasia	A permanent dilation of preexisting blood vessels, creating small focal red lesions

1 AIM OF THE REVIEW

To assess the clinical and cost-effectiveness of once-daily use of topical corticosteroids versus more frequent use of same potency topical corticosteroids in the treatment of people with atopic eczema.

2 BACKGROUND

2.1 Description of underlying health problem

Atopic eczema (synonymous with atopic dermatitis) is a chronic inflammatory skin condition characterised by an itchy red rash, most commonly found in skin creases such as folds of elbows or behind the knees. The eczema lesions vary in appearance from collections of fluid in the skin (vesicles) to a thickening of the skin (lichenification) on a background of poorly demarcated redness.[1] Other features such as crusting, scaling, cracking and swelling of the skin can occur, and the severity of atopic eczema may range from mild (usually of limited extent) to severe disease with widespread angry inflammation on most areas of the body.[2]

Atopic eczema is a difficult disease to define as the clinical features are highly variable.[1] There is no specific diagnostic test, and immunological tests, such as total serum IgE level, immediate (type I) skin test reactivity (prick tests) and radioallergosorbent tests (RASTs), have limited usefulness.[3] Therefore, diagnosis is based on clinical assessment, involving patient history and physical examination, in conjunction with personal and family history of atopy.[3]

Historically there have been uncertainties raised over the clinical definition and diagnosis of atopic eczema. One recent advance is the work of a UK Working Party on the diagnosis of the condition. Williams and colleagues,[4] building on earlier work on the clinical features of atopic dermatitis,[5] developed criteria (Table 2.1) for use in epidemiological studies. These criteria are now commonly used, and although the members of the Working Party accept that further work is required on the validity of the criteria, they have been shown to have good repeatability, and have been validated in many different populations.[6]

Table 2.1 The UK refinement of the Hanifin and Rajka diagnostic criteria[5] for atopic dermatitis for use in epidemiological studies.

To qualify as a case of atopic dermatitis with the UK Diagnostic Criteria, the child must have: An itchy skin condition in the last 12 months Plus three more of:	
(i)	onset below the age of two years*
(ii)	history of flexural involvement
(iii)	history of a generally dry skin
(iv)	personal history of other atopic disease**
(v)	visible flexural dermatitis as per photographic protocol
* Not used in children under 4 years of age ** In children under 4 years, history of atopic disease in a first-degree relative may be included.	

The severity of atopic eczema can vary enormously, from an occasional dry, scaly patch of eczema, easy to treat with emollients, to a debilitating disease, with much of the body being covered by excoriated, bleeding, infected lesions, and the patient severely distressed.[3] Furthermore, the course of the disease may be continuous for

prolonged periods or of a relapsing, remitting nature, characterised by acute flare-ups.[7] Unfortunately, little is known about short to medium term fluctuations in disease activity.[8]

Disease severity influences prognosis and treatment, and is generally categorised as mild, moderate, or severe in severity. The strongest and most consistent factors which appear to predict more persistent atopic eczema are early disease onset, severe widespread disease in early life, concomitant asthma or hay fever and a family history of atopic eczema.[8]

Although atopic eczema is a very common condition there is still much uncertainty and a lack of standardisation when it comes to a clinical scoring or assessment of disease severity, both in practice and in a trial setting.[9] There are a number of scoring systems which have been used to categorise disease into mild, moderate or severe disease (e.g. SCORAD,[10] SASSAD[11]). Such scoring systems generally aggregate scores from a range of symptoms/disease characteristics. For example the SASSAD Index[11] involves the assessment of six clinical features on a scale of 0 to 3, at six defined body sites, giving a maximum score of 108, or the ADSI[11] which assesses five clinical features on a scale of 0 to3, to give a maximum score of 15. However, none of these scoring systems is classed as a 'gold standard' and there is general debate over their use.[9,12] Charman and Williams[9] present findings from a literature search on severity scales for use in atopic eczema, identifying 13 scales, reporting that nearly all of the scales have not been adequately tested, and the authors warn that in general the properties of severity scales require some consideration as the clinical relevance of a change in score is not easily understood. A recent review by Charman and colleagues[12] finds that the literature on atopic eczema is characterised by a confusing array of severity indices.

Epidemiology

Atopic eczema is a major public-health problem. There are difficulties associated with estimating prevalence and incidence of atopic eczema from the present literature, due to the small number of community studies, the dominance of cross-sectional rather that longitudinal study designs, and differences in definition of disease and differences in study-specific methodology.[13] Specifically, there are a number of studies reporting estimates based on different age groupings and there are variations across studies in the reporting of either point prevalence or period prevalence; only a small number of studies report both (see Appendix 1). Rates for period prevalence tend to reflect a rate of half that shown in estimates related to lifetime prevalence of disease.[4,14] Generally, in the UK, the condition is thought to affect around 15-20% of school-age children at some stage (circa. 1.4-1.9 million children, for England and Wales),[15] and 2-10% of adults (circa. 800,000 adults, for England and Wales).[4] The prevalence of atopic diseases, including eczema, has risen steadily over the past 30 years, although the reasons for this are unclear.[2]

Appendix 1 illustrates some of the differences in the methods and the reported prevalence estimates across a number of studies.

Given the varied literature, Williams[4] estimates the cumulative prevalence of atopic eczema to be between 5% and 20% by the age of 11 years. Herd and colleagues[16]

provide estimates of prevalence in adults, in a semi-rural Scottish community, reporting 1-year period prevalence rates at 2.1%, 2.0% and 0.2% for age groups 16-24 years, 25-40 years and over 40 years respectively. However, they also report that adults over 16 years of age made up 38% of all atopic eczema cases in that community.

There is little convincing evidence of differences in the prevalence of atopic eczema by gender,[13] but there is evidence of variation by age. Atopic eczema most commonly begins in infancy. However, there are some variations in the prevalence estimates related to age of onset. Friedman[2] reports that 65% of cases present before the age of six months and 80% in the first year of life, whilst a review by Hoare and colleagues[1] reports that approximately 80% of cases start before the age of five years. Kay and colleagues[14] report that atopic eczema developed in the first twelve months of life in 60% of children who had the condition in their study, and that it had developed in the first six months of life in three quarters of these children. Williams[6] suggests that epidemiological studies undertaken in a secondary care setting may over-estimate the proportion of cases occurring in the earlier years of childhood, as more severe cases of eczema predominate in secondary care. Furthermore, Williams reports that 60% of childhood cases of atopic eczema are clear and free from symptoms in early adolescence, but that many such apparently clear cases are likely to recur in adulthood.[8]

There is little evidence on difference in the prevalence of atopic eczema amongst different ethnic groups.[13] One community study of 322 children in Leicester, England, found that there were no apparent ethnic differences in prevalence, but that Asian children were three times more likely to be referred to secondary care than their white counterparts.[17]

There is some evidence of a difference in the prevalence of atopic eczema across different socioeconomic groups. Williams and colleagues report an inverse socio economic relation, whereby reported and examined eczema was almost twice as common in children of higher socioeconomic groups, among the 8,279 children followed up in the UK 1958 National Child Development Study.[18,19]

Table 2.2 below provides estimates of prevalence of atopic eczema across England and Wales, and across a typical former health authority population, using examples of reported prevalence from the published literature.

Incidence of atopic eczema varies by age, but it is not possible to present a reliable estimate of the incidence; the systematic review from Hoare and colleagues[1] concluded that no reliable incidence estimates are available' (p2). However, findings from the National Child Development Study developed from the birth cohort of 1958 suggest around 50 cases per 1000 in the first year of life, falling to 5 new cases per 1000 per year for the rest of childhood.[4]

The distribution of disease by severity is reported by Emerson and colleagues[20] from a cross-sectional survey of 1,760 children aged 1-5 years (selected from general practice lists in Nottingham), as 84% mild, 14% moderate, and 2% severe. There is not an extensive literature reporting the severity distribution of the condition from

epidemiological studies, yet a number of commentators have supported the fact that only a small number of cases are regarded as severe.

Table 2.2 Estimates of prevalence of atopic eczema in England and Wales

	England	Wales	England & Wales	Former Health Region of (North & Mid Hampshire)
Population	49,138,831	2,903,085	52,049,916	554,529
Prevalence Estimate:				
Williams[4] 5%-20% 0-11 yrs	367,802 – 1,471,208	21,570 – 86,282	389,373 – 1,557,491	3,987 – 15,949
Friedman[2] 12%-26% under 12 yrs	882,725 – 1,912,571	57,769 – 112,167	934,494 - 2,024,738	11,135 – 20,414
Williams[4] 2%-10% adults	772,000 – 3,860,010	45,530 – 227,650	817,532 – 4,087,660	8,675 – 43,376
Herd[16] 2.3% in UK population	1,130,193	66,771	1,196,964	12,754

Aetiology

Aetiology of atopic eczema is complex. There is some evidence of genetic influences [13,21] and a number of environmental factors have been implicated in the onset or exacerbation, or both, of atopic eczema, including house dust mites, pollen, tobacco, air pollution and low humidity. Factors such as excessive use of soaps and other household irritants are also thought to exacerbate the condition.[13] Prenatal factors have also been considered as potentially important in the onset of the condition (e.g. higher maternal age and maternal diet).[18]

Significance in terms of ill-health

Atopic eczema has implications for health-related quality of life (HRQL) because it can have an impact on work, sleep, and social relations. Patients with atopic eczema may experience distress and anxiety that diminishes their psychological wellbeing and functional capacity, and the long-term nature of the condition can result in recurring physical, social, and psychological impairments.[22]

Atopic eczema is associated with considerable morbidity, which varies with disease severity. Much of the literature on the impact of the condition relates to childhood atopic eczema, where studies have shown that the physical impact of the condition affects everyday activities and may also influence the child's emotional and social development.[21] School-aged children with moderate and severe eczema are thought to be at a high risk of developing psychological difficulties.[23] Severe atopic eczema in children can have a significant impact on family life and the role of the parents, who must cope with the severe physical demands associated with caring for a child with a chronic illness.[24] However, atopic eczema in adults is also associated with a significant burden related to physical, functional, psychosocial and financial impact.[25]

Itch is a major symptom of atopic eczema and patients find themselves in a vicious itch-scratch circle, where itch and scratch damage the skin and increase inflammation, which in turn increases the itch.[26] Sleep disturbance is a common problem, especially during flare-ups,[13] and this in turn leads to problems with irritability and lack of concentration. Controlled studies have shown that sleep disturbances are much more common in children with atopic eczema than in controls,[26] resulting in tiredness and irritability during the day.

Skin diseases such as atopic eczema can produce anxiety, depression and other psychological problems that affect patients' and carers' lives (in ways comparable to other disabling illnesses such as arthritis).[25] Average daily treatment time for eczema can be considerable,[27] and usual activities and lifestyle can be limited by constraints of care of the skin. Care of the skin may separate patients from their peers (e.g. restrictions in sporting activities, dietary restrictions), and may cause patients to feel unattractive and different, leading to problems with self image and self confidence.[21]

Clinical observations have suggested that stressful life events may often precede exacerbations in the symptoms of atopic eczema in children. Gil and colleagues[28] suggested that measures of stress and family environment were important predictors of symptom severity in children with atopic eczema. Chronic problems related to atopic eczema (e.g. administration of medications, exclusionary diets or behavioural restrictions) were strongly related to atopic eczema symptom severity, whereas life events and more common everyday problems typically experienced by children were not related to symptom severity.

2.2 Current service provision

Treatment of atopic eczema involves a combination of preventative measures aimed at suppressing the symptoms of disease and individualised treatment for controlling and preventing complications. The successful management of atopic eczema requires a multi-pronged approach and treatment largely comprises general recommendations to use soap substitutes, emollients, topical corticosteroids to suppress inflammation, antibiotics to treat bacterial infection, antihistamines (usually the older sedative varieties), and bandages (wet dressings, or impregnated bandages). Systemic corticosteroids are effective for acute flares in severe eczema, but their repeated use may lead to severe adverse effects, therefore their use should be limited to one or two courses per year.[29] Recently introduced advanced immunosuppressive therapy (calcineurin inhibitors) is also thought to offer an effective treatment option.[30]

Topical corticosteroids are the mainstay of treatment for atopic eczema.[1,29,31] they are predominantly used for symptomatic relief when disease flare-ups occur. Topical corticosteroids have anti-inflammatory, immunosuppressive, and vasoconstrictor effects, and they act by suppressing various components of the inflammatory reaction (although the mechanism of the anti-inflammatory activity of topical steroids in general is unclear).

There is a large range of topical corticosteroid preparations available (over 60 products are listed in the British National Formulary (BNF)).[32] In this review we consider over 30 eligible products, with many other compound preparations, products

with antimicrobials included, and over the counter products also available. Products have different formulations and different strengths (e.g. 0.025%, 0.1%, 0.5%) and are available in various preparations (e.g. ointment, cream, lotion, foam). Topical corticosteroids are classified according to their potency, which is determined by the amount of vaso constriction they produce and also relates to the degree to which they inhibit inflammation and to their potential for causing side-effects.[33] In the UK, four potencies are recognised: mild (e.g. hydrocortisone acetate); moderately potent (e.g. clobetasone butyrate); potent (e.g. mometasone furoate, fluticasone propionate); and very potent (e.g. halcinonide). Topical corticosteroids are classified in the BNF according to their potency. The BNF lists most topical corticosteroids for use one to two times daily, however, specific market authorisation information on products indicates that some products are licensed for more frequent use[34] (we assume all products can be prescribed for once daily use).

Data from the Department of Health Prescription Cost Analysis (PCA)[35] report that over 12.3 million prescriptions for topical corticosteroids (BNF chapter 13.4, skin conditions) were dispensed in the community (England) in 2002, with a total net prescription cost of over £45 million. These data refer to aggregate prescription data, and are not limited to treatment for atopic eczema (i.e. prescribing activity relates to other treatment areas, such as treatment for psoriasis). Figures 2.1 and 2.2 below show the distribution of total prescriptions and total cost by product potency. However, over 43% of the topical corticosteroids dispensed (circa. 5.3 million prescriptions, totalling £23.7 million) were either compound preparations or products containing antimicrobials, and these products are not included in the scope of the present review.[36] Prescription cost analysis, by the Department of Health reports prescribing activity by product and by BNF section.

Information from the National Eczema Society indicates that 25.8% of prescriptions for topical corticosteroids are for atopic eczema,[37] giving an estimate of prescribing cost of over £11.6 million for atopic eczema (community dispensed prescriptions, 2002).

Figure 2.1 Proportion of total prescriptions (community dispensed) of topical corticosteroids, by potency groupings

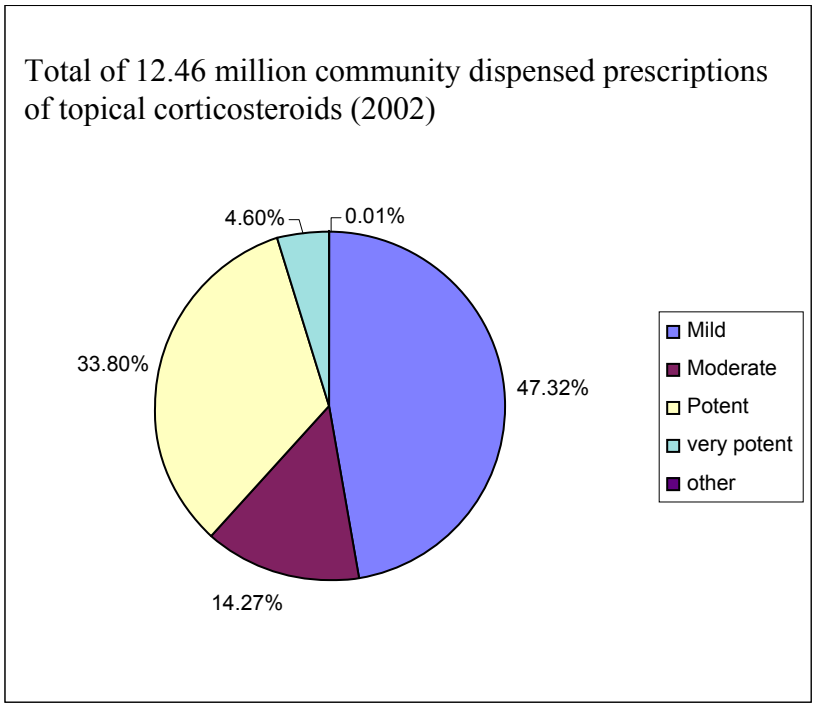
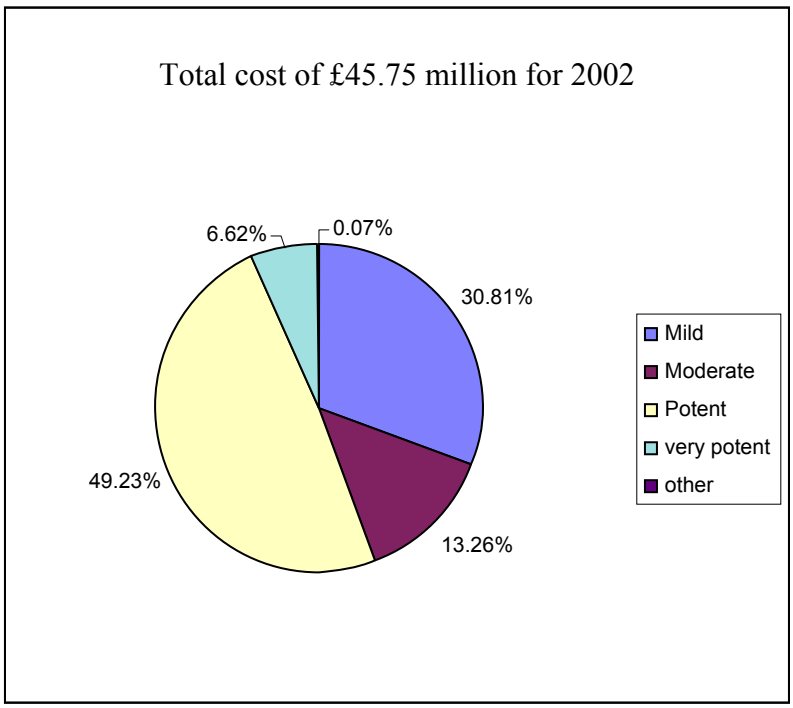


Figure 2.2 Total cost* for all community dispensed prescriptions (2002) of topical corticosteroids by potency groupings



* These data cover net ingredient costs (NIC) only, excluding those products prescribed generically but only available as a proprietary product (PCA refer to these costs as 'owc2 costs'). NIC refers to the cost before discounts and does not include dispensing costs or fees. It does not include any adjustment for income obtained where a prescription charge is paid at the time the prescription is dispensed or where a patient has purchased a pre-payment certificate.

Atopic eczema is predominantly treated in the community, with patient care being delivered through a primary health care team (e.g. GP, practice nurse, health visitor), with few patients referred on to secondary care.[38] From a survey of children aged 1-5 years Emerson and colleagues[38] report that over a 12-month period 6% of children were seen in a secondary care setting. The authors report that over the same time period 96% of children were seen by their GP (over 70% seeing the GP on multiple occasions), 11% visited the health visitor and approximately 4% visited the practice nurse for advice. Referral to secondary care was associated with disease severity.

Treatment regimens for topical steroids vary with disease severity, with clinicians recommended to use the mildest products possible to treat the condition, in order to minimise side-effects; the risk of side-effects increases with the potency of the topical corticosteroid.[33,39] One of the potential long term side-effects of topical corticosteroid treatment, and a matter of great concern to patients, is skin atrophy. This is a condition whereby the skin becomes thin and loses some of its function. The negative consequences of this are easy bruising and impaired wound healing. Over longer periods of time skin can become so badly damaged that it loses its elasticity with the development of 'stretch marks'. The likelihood of skin atrophy is thought to be determined by the potency of the preparation, the site at which it is being used, and the age of the patient in question.

Guidelines from the British Association of Dermatologists[40] suggest that the use of topical corticosteroids should be limited to a few days to a week for acute eczema, and for periods of up to four to six weeks to gain initial remission for chronic eczema. The National Prescribing Centre recommends that in general practice they should be used in short bursts (for 3-7 days) to treat exacerbations of disease.

Treatment regimens will differ greatly by disease severity and those patients treated in a hospital setting are likely to be treated more intensively than those managed in primary care. Regardless of severity, the bulk, or burden, of care for patients with eczema is carried out at home, with infrequent health service contact (either in a GP or hospital setting) to establish the treatment regimens.[13]

Topical corticosteroids are available as water-miscible creams, ointments, lotions, and other preparations (e.g. mousse). Ointments are thought to be clinically preferable to creams, as they have a deeper more prolonged emollient effect and increase the penetration of the steroid,[33] but the decision on which product to prescribe should be informed by the patient preference, as acceptability of the product and preparation to the patient will greatly affect adherence. In this respect, explanation and counselling are a vital part of the successful management of atopic eczema.[21]

2.3 Topical corticosteroids: frequency of use

There is no standard management plan for the long term treatment of atopic eczema. For each patient there are a number of considerations when deciding on the optimal overall management of the condition. The frequency of application is a key clinical issue when prescribing topical corticosteroids. Topical corticosteroids are available for application one to four times per day. Most products are recommended for use 1-2 times daily in the BNF.[32] Although there are few empirical data to assess the patterns

of prescribing with respect to frequency of application, it is generally accepted that a twice-daily regimen is the most widespread approach to the use of topical corticosteroids in atopic eczema. This twice-daily approach to the frequency of application seems to have developed empirically.[41]

Recently concerns have been raised over the merits of differing approaches to the frequency of application of topical corticosteroids. Clinical trials have, for some time now, suggested less frequent applications are equally effective,[42-44] but with 'newer' products being marketed specifically for once-daily use questions have been raised more generally over the relative merits of different approaches to the frequency of the application of topical corticosteroids. In this report we consider the clinical and cost-effectiveness of once-daily application versus more frequent application of same potency topical corticosteroids, in atopic eczema.

We consider the frequency of the application of topical corticosteroids in all patients with atopic eczema. Children are not regarded as a specific subgroup, as they form a significant proportion of the overall patient group. However, where trial results are presented by age we report them separately. Other important sub-groups are (a) those patients treated in the community versus those treated in a hospital setting, and (b) those patients classified according to severity of disease (mild, moderate or severe). The sparse literature has not allowed us to consider these subgroups separately. Products have been assessed according to the classification of potency reported in the BNF (mild, moderate, potent, and very potent).[32] Products that are compound preparations or those containing antimicrobials are outside of the scope of this report. Products of particular interest are listed in Table 2.3, together with available information on licensed frequency of use. Two potent topical corticosteroids are licensed specifically for once-daily use only, mometasone furoate (Elocon®), and fluticasone propionate cream (Cutivate®), with betamethasone dipropionate (Diprosone®) licensed for use once to twice daily. Other products licensed for once daily use are clobetasone 17-butyrate (Eumovate®), a moderate potency product, licensed for use up to four times daily, and clobetasol propionate (Dermovate®), a very potent product, licensed for use one to two times daily. In this report we assume all topical corticosteroid products listed in the BNF can be prescribed for once-daily use.[32]

Figure 2.3 shows the general pattern/distribution of community dispensed prescriptions for these products in 2002 (the specific product cost per 30mg/30ml is reported later in the report, see Table 4.1). Although there are a wide range of products available, Figure 2.3 shows that prescribing (2002) was most frequent in a small number of product groupings; generic hydrocortisone dominates the mild potency products, clobetasone butyrate (Eumovate®) and betamethasone valerate (Betnovate®) are the dominant products in the moderate potency products, mometasone furorate (Elocon®), betamethasone valerate (Betnovate®), and generic betamethasone valerate are the three most common products in the potent grouping, with clobetasol propionate (Dermovate®) dominating amongst the very potent products.

When prescribing topical corticosteroids, as part of the management of the condition, the clinician is faced with a wide range of products, classified by potency, available in

various formulations (e.g. 0.025%, 0.1%) and preparations (e.g. creams, ointments, lotions). The literature to inform on the relative merits of these products is not extensive, and there is a lack of comparative data to help clinicians decide on what may be the best treatment option for their patient.[45]

Anticipated Costs

The acquisition cost for topical corticosteroids, per patient per year, varies according to the prescribed topical corticosteroid, and the number of flare-ups that the patient needs to treat, both of these being associated with the severity of disease. We discuss in a later section of this report (Section 4.4) the variations in product costs; the cost per 30g/30ml for topical corticosteroids included in this review varies between £0.60 (for generic hydrocortisone) and £4.88 (for mometasone furoate; Elocon®).

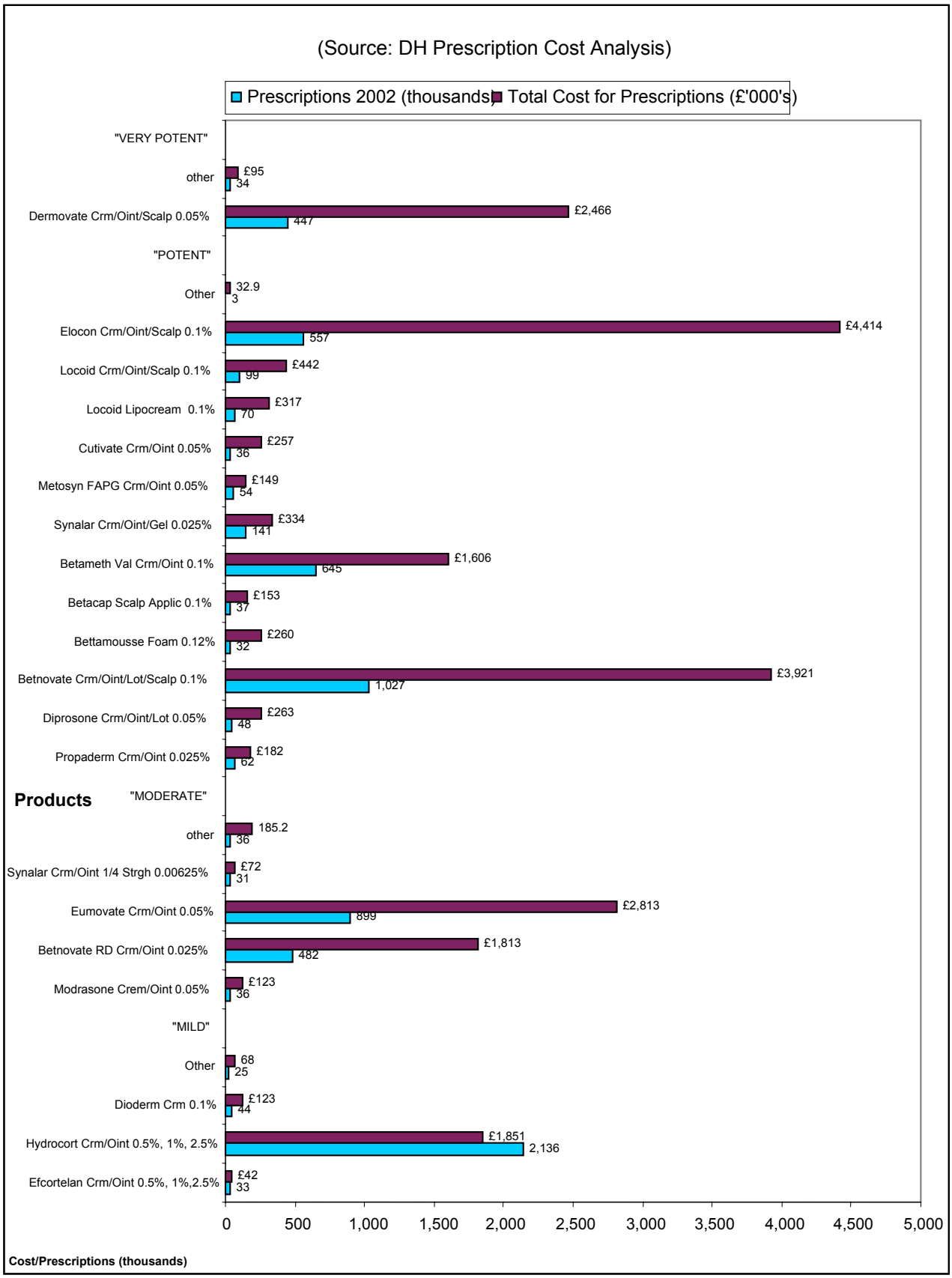
Given the variety of products available, it is not possible to offer a general point estimate of the anticipated cost for treatment, but we would not expect the annual cost for topical corticosteroids to exceed £50 for most patients, and in many cases the cost associated with prescribed products will be between £5 and £15. However, given the large number of patients treated for atopic eczema the overall costs to the NHS are very large. Although atopic eczema is a prevalent condition in childhood, where prescriptions costs fall on the NHS budget, a large number of adult patients will be liable to pay a prescription fee (presently £6.30 per item), and this will impact on the overall NHS costs associated with prescription of topical corticosteroids for atopic eczema.

Table 2.3 Topical corticosteroids eligible for inclusion in the review, by BNF potency, with BNF licence frequency information, and licence frequency from the SPC where available.

Potency / BNF Chemical Name	Product Name (®)	BNF License Frequency	Licence frequency from SPC,[34] where available
MILD POTENCY:			
Hydrocortisone	Generic* hydrocortisone cream/ointment 0.5%, 1%, 2.5%	1-2 times daily	N/A
Hydrocortisone	Efcortelan cream/ointment 0.5%, 1%, 2.5%	1-2 times daily	2-3 times daily
Hydrocortisone	Mildison Lipocream 1%	1-2 times daily	2-3 times daily
Hydrocortisone	Dioderm cream 0.1%	1-2 times daily	Twice daily
Fluocinolone Acetonide	Synalar cream 1/10, 0.0025%	1-2 times daily	N/A
MODERATE:			
Alclometasone Dipropionate	Modrasone cream/ointment 0.05%	1-2 times daily	N/A
Betamethasone Valerate	Betnovate RD cream/oint 0.025%	1-2 times daily	2-3times daily
Clobetasone Butyrate	Eumovate cream/oint 0.05%	1-2 times daily	Up to 4 times daily
Desoxymethasone	Stiedex LP oily cream 0.05%	1-2 times daily	2-3 times daily
Fluocinolone Acetonide	Synalar cream/oint 1/4, 0.00625%	1-2 times daily	N/A
Fluocortolone	Ultralanum cream/oint Plain	1-2 times daily	N/A
Flurandrenolone	Haelan cream/oint 0.0125%	1-2 times daily	2-3 times daily
POTENT:			
Beclomethasone Dipropionate	Propaderm cream/oint 0.025%	1-2 times daily	N/A
Betamethasone Dipropionate	Diprosone cream/oint/lotion 0.05%	1-2 times daily	1-2 times daily
Betamethasone Valerate	Betnovate cream/oint/lotion/scalp applic 0.1%	1-2 times daily	2-3 times daily
Betamethasone Valerate	Bettamousse foam 0.12%	1-2 times daily	Twice daily
Betamethasone Valerate	Betacap scalp applic 0.1%	1-2 times daily	-
Betamethasone Valerate	Generic betamethasone valerate cream/oint 0.1%	1-2 times daily	N/A
Fluocinolone Acetonide	Synalar cream/ointment/gel 0.025%	1-2 times daily	N/A
Fluocinonide	Metosyn FAPG cream/oint 0.05%	1-2 times daily	N/A
Fluticasone Propionate	Cutivate cream 0.05%	1-2 times daily	Once daily
Fluticasone Propionate	Cutivate oint 0.05%	1-2 times daily	Twice daily
Hydrocortisone Butyrate	Locoid Lipocream 0.1%	1-2 times daily	2-3 times daily
Hydrocortisone Butyrate	Locoid cream/oint/scalp lotion 0.1%	1-2 times daily	2-4 times daily
Hydrocortisone Butyrate	Locoid Crelo 0.1%	1-2 times daily	2-3 times daily
Mometasone Furoate	Elocon cream/oint/scalp lotion 0.1%	Once daily	Once daily
VERY POTENT:			
Clobetasol Propionate	Dermovate cream/oint/scalp applic 0.05%	1-2 times daily up to 4 weeks	1-2 times daily
Diflucortolone Valerate	Nerisone Forte oint/oily cream 0.3%	1-2 times daily up to 4 weeks	N/A
Diflucortolone Valerate	Nerisone cream/oint/oily cream 0.1%	1-2 times daily up to 4 weeks	N/A
Halcinonide	Halciderm_cream 0.1%	1-2 times daily	2-3 times daily

* Include generic hydrocortisone products from scope
N/A = not available/identified

Figure 2.3 Prescribing patterns for eligible topical corticosteroids (community dispensed prescriptions (2002)



3 CLINICAL EFFECTIVENESS

3.1 Methods

The *a priori* methods for systematically reviewing the evidence of clinical effectiveness are described in the research protocol (Appendix 2), which was sent to members of the advisory panel for comment (see *Acknowledgements*, p2). Although helpful comments were received relating to the general content of the research protocol, there were none that identified specific problems with the methods of the review. As a point of clarification, rather than stating that controlled clinical trials (CCTs) would be included if insufficient RCTs were identified, the protocol was reworded to state that where no evidence from RCTs was available for a particular potency of corticosteroid, CCTs would be included.

Sources of information, search terms and a flow chart outlining the identification of studies are described in Appendix 3. The most recent search was performed in October 2003.

Manufactures' submissions to NICE were reviewed for additional studies. The full unpublished reports of a study[46] and its subgroup analysis,[47] published as abstracts only,[48,49] were obtained from GlaxoSmithKline (GSK). The full report of subgroup analysis[50] from the eligible study by Bleehen and colleagues[43] was also obtained from GSK, also previously published as an abstract.[51]

The data from the manufacturers' submissions were not classed as commercial in confidence.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by one reviewer and checked by a second reviewer. The full text of relevant papers was then obtained and inclusion criteria applied by two reviewers. Data were extracted by one reviewer using a standard data extraction form and checked by a second reviewer.

The quality of included systematic reviews was assessed using criteria recommended by NHS Centre for Reviews and Dissemination (CRD) (Appendix 4), and RCTs were judged in accordance with chapters II.5 of NHS CRD Report 4[52] (Appendix 5). Quality criteria were applied by one reviewer and checked by a second reviewer.

At each stage, any differences in opinion were resolved through discussion or consultation with a third reviewer.

Inclusion criteria

Studies comparing once daily versus more frequent application of topical corticosteroids of the same potency were included in the review. Studies comparing corticosteroids with different potencies were excluded. The review included topical corticosteroids reported in section 13.4 of the BNF,[32] excluding compound preparations (i.e. antimicrobials, preparations containing added ingredients).

The review includes children and adults with atopic eczema (atopic dermatitis). Patients with other types of eczema such as contact dermatitis, seborrhoeic eczema,

varicose eczema and discoid eczema were excluded. Where uncertainty existed over the classification of disease in published studies, a clinical advisor determined the appropriateness of inclusion of the study in the review.

Systematic reviews and meta-analyses of RCTs as well as individual RCTs were included. The review considers products by potency grouping and where no RCT evidence was identified for a potency group the inclusion of CCTs (with concurrent controls) was considered. Reports published only as abstracts and non-English language studies were excluded.

Studies were included if they reported one or more of the following as primary outcomes; overall response to treatment (e.g. using severity scores), impact on clinical features of the condition (e.g. erythema, induration, pruritus, excoriation, thickening), relapse/flare-up rate, side-effects, compliance, tolerability, patient preference measures, and quality of life.

Data synthesis
Data were synthesised through a narrative review with tabulation of results of all included studies. Full data extraction forms can be seen in Appendix 6 to Appendix 9. It was considered inappropriate to combine the studies in a meta-analysis due to clinical heterogeneity (e.g. differences in product and comparators used, differences in patient group, outcomes and method of assessing outcomes, and differences in duration of follow-up), however forest plots using risk ratios (RR) are presented for illustration of the most commonly reported outcomes. Results are based on data from available participants rather than numbers randomised, as it was assumed that study withdrawals and missing data could reasonably be due to either an improvement or worsening of symptoms.

3.2 Results

3.2.1 Quantity and quality of research available

Four thousand four hundred and twenty nine references were identified, and of these one systematic review[1] (Appendix 6) and ten randomised controlled trials met the inclusion criteria for the review. One RCT compared moderately potent corticosteroids[53] (Appendix 7), eight RCTs compared potent corticosteroids, [43,44,46,54-58] (Appendix 8) and one RCT compared very potent corticosteroids[42] (Appendix 9). Most studies compared once versus twice daily application, but the study comparing very potent corticosteroids compared once versus three times daily application.[42] Of the ten RCTs, seven compared frequency of application of the same active compound, while three RCTs compared once daily application of mometasone furoate with twice daily application of a different active compound (hydrocortisone butyrate,[55] betamethasone valerate[57] or betamethasone dipropionate[56]). A summary of products compared in the studies can be seen in Table 3.1. No RCTs or CCTs of mild corticosteroids were eligible for inclusion in this review.

A list of selected excluded studies can be seen in Appendix 10. No studies available as abstracts only were identified.

Table 3.1 Summary of comparisons

Study	Once daily application	More frequent application	UK brand name and manufacturer *
MODERATE			
Richelli et al. 1990 [53]	Clobetasone 17-butyrate 0.05% lotion at 9pm.	Clobetasone 17-butyrate 0.05% lotion 1.at 8am and 3pm 2. at 3pm and 8pm	Eumovate® GSK
POTENT (comparisons of the same active compound)			
Bleehen et al. 1995 [43]	Fluticasone propionate cream 0.05% once daily Vehicle once daily	Fluticasone propionate cream 0.05% twice daily	Cutivate® GSK
Tharp 1996 [58]	Fluticasone propionate cream 0.05% once daily Vehicle once daily	Fluticasone propionate cream 0.05% twice daily	Cutivate® GSK
Berth-Jones et al. 2003 [54]	1. Fluticasone propionate cream 0.05% once daily 2. Fluticasone propionate ointment 0.005% once daily	1. Fluticasone propionate cream 0.05% twice daily 2. Fluticasone propionate ointment 0.005% twice daily	Cutivate® GSK
GSK Report 1995[46]	Fluticasone propionate ointment 0.005% once daily Placebo once daily	Fluticasone propionate ointment 0.005% twice daily	Cutivate® GSK
Koopmans et al. 1995 [44]	Locoid Lipocream fatty cream (0.1% hydrocortisone 17-butyrate) once daily Locobase once daily	Locoid Lipocream fatty cream twice daily	Locoid® Yamanouchi
POTENT (comparisons of different active compounds)			
Hoybye et al. 1991 [55]	Mometasone furoate in fatty cream base once daily	Hydrocortisone 17-butyrate in fatty cream base twice daily	Elocon® Schering-Plough vs. Locoid® Yamanouchi
Rajka et al. 1993 [57]	Mometasone furoate fatty cream 0.1% once daily	Betamethasone valerate cream 0.1% twice daily	Elocon® Schering-Plough vs. Betnovate® GSK
Marchesi et al. 1994 [56]	Mometasone furoate ointment 0.1% once daily	Betamethasone dipropionate ointment 0.05% twice daily	Elocon® Schering-Plough vs. Diprosone® Schering Plough
VERY POTENT			
Sudilovsky et al. [42]	Halcinonide cream 0.1% once daily Placebo twice daily	Halcinonide cream 0.1% three times daily	Halciderm Topical® Squibb

*This may not be the brand used in the trials, especially for non-UK studies.

The systematic review[1] was judged to be of good methodological quality (Table 3.2), although the eligibility criteria for trials comparing once daily versus more frequent use of the same topical corticosteroid were not clearly stated.

Apart from the GSK Report[46] and the study by Berth-Jones and colleagues,[54] the quality of reporting and methodology of the included RCTs was generally poor (Table 3.3). The method of randomisation was adequate in just three studies,[42,46,54] however concealment of allocation was not reported in one of these.[42] Therefore most of the studies included in this review may be subject to selection bias, with the allocation sequence open to possible manipulation. Three of the RCTs[42,55,57] failed to report

whether the comparison groups were similar at baseline, while two RCTs compared just age[43] or age and sex[53] of participants without commenting on other relevant baseline characteristics. All RCTs reported eligibility criteria. The study by Tharp and colleagues[58] included patients with an 'established diagnosis of eczema', but did not define it as atopic eczema. However, after considering the exclusion criteria reported by the study (such as contact dermatitis), it was agreed that this study should be included in the review.

Six trials were described as double-blind.[42-44,46,54,58] Four of these trials that used the base cream or ointment as a placebo and described the tubes as identical were judged to be adequately blinded for both the outcome assessor and patient. However, two studies simply described the trial as double-blind without further description of procedures,[44,54] and Berth-Jones and colleagues did not report the use of a placebo treatment in the once-daily group.[54] Three trials were described as single-blind (investigators blinded), but without details of methods or procedures, or use of a placebo treatment in the once-daily group. [55-57] The study by Richelli and colleagues does not mention blinding of either outcome assessors or patients, and does not use a placebo treatment in the once-daily group.[53]

Only three studies[43,46,54] adequately reported the point estimates and measures of variability and included an intention to treat analysis.

The study setting was hospital or secondary care for four of the studies,[43,46,54,57] but not reported in the remaining studies. Duration of treatment was up to seven days in the study by Richelli and colleagues, and up to either three weeks [42,55-57] or four weeks [43,44,46,54,58] in the other studies.

Outcome measures reported by the studies were subjective, and often relied on recall of the baseline state, either by investigators or patients.

Where reported, patients included in the studies had moderate to severe atopic eczema, apart from the study by Rajka and colleagues, who included adults with mild to moderate severity eczema. Three studies did not report the minimum severity of eczema for included patients.[42,44,53]

Richelli and colleagues included only children in their study,[53] while the other studies included both children and adults,[43] patients aged over 12 years[44,54,58] or 16 years,[57] or adults only.[55,56] The age range of patients included in the study by Sudilovsky and colleagues was not reported.[42]

Subgroup analyses of patients aged 12 years or less were reported for the GSK Report[47] and the study by Bleehen and colleagues.[50] Power to detect any differences within the subgroups would be less than in the main analyses.

Table 3.2 Summary of quality assessment of published systematic review

	Hoare 2000[1]
Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Partial
Is there evidence of a substantial effort to search for all relevant research?	Yes
Is the validity of included studies adequately assessed?	Yes
Is sufficient detail of the individual studies presented?	Yes
Are the primary studies summarised appropriately?	Yes

Table 3.3 Summary of quality assessment of RCTs

	Moderate	Potent								Very potent
	Richelli 1990[53]	**Berth-Jones 2003[54]**	**Bleehen 1995[43]**	**GSK Report 1995[46]**	**Hoybye 1991[55]**	**Koopmans 1995[44]**	**Marchesi 1994[56]**	**Rajka 1993[57]**	**Tharp 1996[58]**	**Sudilovsky 1981[42]**
Was the assignment to the treatment groups really random?	Unknown	Adequate	Unknown	Adequate	Unknown	Unknown	Unknown	Unknown	Unknown	Adequate
Was the treatment allocation concealed?	Unknown	Adequate	Unknown	Adequate	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Were the groups similar at baseline in terms of prognostic factors?	Partial	Reported	Partial	Adequate	Unknown	Reported	Reported	Unknown	Reported	Unknown
Were the eligibility criteria specified?	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Were outcome assessors blinded to the treatment allocation?	Inadequate	Partial	Adequate	Adequate	Partial	Partial	Partial	Partial	Adequate	Adequate
Was the care provider blinded?	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Was the patient blinded?	Inadequate	Partial	Adequate	Adequate	Inadequate	Partial	Inadequate	Inadequate	Adequate	Adequate
Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate	Adequate	Adequate	Adequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Did the analyses include an intention to treat analysis?	Inadequate	Adequate	Adequate	Adequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate

n/a = not applicable

3.2.2 Assessment of effectiveness: published systematic review

The systematic review[1] (Appendix 6) of treatments for atopic eczema included three RCTs comparing once-daily and more frequent application of the same active compound,[42-44] all of which are included in the present systematic review. Using estimated differences in response rates (proportion of patients who obtained at least a good response), the authors found that in none of the studies was more frequent application superior to once-daily application (see Appendix 6 for estimated risk differences for the individual studies). They concluded that while point estimates suggest that a small difference in favour of more frequent application cannot be excluded, it is doubtful whether this is practically meaningful.

3.2.3 Assessment of effectiveness: results of included RCTs

The studies expressed effectiveness of the treatments using a variety of different outcome measures, most of which were subjective measures assessed by the investigator and / or patient. This is likely to introduce bias as six of the ten trials did not have adequate blinding of either the outcome assessors or the patients (Table 3.3).

3.2.3.1 Response rates

All studies apart from Richelli and colleagues[53] and Rajka and colleagues[57] reported the number of patients responding to treatment, and these results are displayed in Table 3.4. However, response to treatment was defined in different ways by the studies. For example, Berth-Jones and colleagues reported the number of patients with controlled (absent or mild) dermatitis,[54] while Bleehen and colleagues reported the number of patients with at least a good response (at least 50% improvement),[43] and others reported numbers with defined categories such as ‘cleared’, ‘marked improvement’, ‘moderate improvement’, ‘slight improvement’, ‘no change’ or ‘exacerbation’. Therefore, two outcomes are considered here: number of patients with at least a good response or 50% improvement, and number of patients rated cleared or controlled.

Patients with at least a good response
Seven studies reported the number of patients with at least a good response, or at least 50% improvement by the end of the study,[43,44,46,54-56,58] and are summarised in Figure 3.1, which displays the risk ratios. Due to the clinical and statistical heterogeneity between the studies, it was considered inappropriate to combine them in a meta-analysis. There was generally little difference between once and more frequent application. Only one study[46] found a statistically significant difference, where once-daily application of fluticasone propionate ointment reduced the chance of success (assessed by the physician) by 14% of that in the twice daily group, although the 95% confidence interval was close to no effect (RR 0.86, 95% CI 0.75 to 0.99). The reduction in the chance of success with once-daily treatment when assessed by patients in this study was not, however, statistically significant (RR 0.87, 95% CI 0.75 to 1.02).

Patients with cleared eczema

Figure 3.2 displays the risk ratios for six studies reporting the number of patients with eczema rated cleared/controlled or excellent.[44,46,54-56,58] Again, it was considered inappropriate to combine these studies in a meta-analysis. In the study by Koopmans and colleagues, the physician's opinion of clearance of lesions shows a significant difference in favour of twice daily treatment. Once-daily treatment reduced the chance of clearance of symptoms by 31% of that with twice-daily treatment (RR 0.69, 95% CI 0.52 to 0.91). However, this is not supported by the patient's opinion of clearance of lesions (RR 0.83, 95% CI 0.64 to 1.07), nor when the data is analysed as illustrated in Figure 3.1. When considering patients in the GSK report whose eczema is assessed by physicians as 'cleared' as in Figure 3.2, rather than success ('cleared', 'good' or 'moderate') as in Figure 3.1, the result, although favouring twice daily use, is no longer statistically significant (once-daily 17% versus twice-daily 23%; RR 0.73, 95% CI 0.44 to 1.23).

A recent study by Berth-Jones and colleagues reported the number of patients aged over 12 years whose atopic dermatitis was controlled (absent or mild) after four weeks with once or twice daily fluticasone propionate cream or ointment.[54] They found no significant difference between once and twice daily application of cream (80% vs 84%, p=0.546) or ointment (77% vs 71%, p=0.249). Another study also found a similar proportion of patients had a target lesion response rated cleared or excellent, as assessed by the physician, after four weeks of once or twice daily fluticasone propionate cream (69% vs 78%, p=ns).[58] Although this study found a statistically significant difference at three weeks (once-daily 57% vs twice-daily 70%, p<0.014), the difference was not statistically significant at one (29% vs 39%) or two (42% vs 62%) weeks.

Other assessments of response rates

In addition to the outcomes included in Figures 3.1 and 3.2 assessed by investigators and patients, Koopmans and colleagues also reported the number of patients with total clearance of lesions. They found that significantly more patients aged over 12 years treated with twice-daily (47%) Locoid Lipocream (0.1% hydrocortisone 17-butyrate) than with once-daily treatment (27%) showed total clearance after four weeks (p=0.02), but not after two weeks (19% vs 12%, p=0.29).[44] However, it is not clear from the study how this outcome was assessed, nor how it differs from the proportion of patients assessed as having clearance of lesions by the investigator (twice daily 70%, once-daily 49%).

When comparing once-daily and three times daily application of the very potent corticosteroid halcinonide cream 0.1%, Sudilovsky and colleagues found that a more favourable comparative response of similar lesions on each side (slightly superior or markedly superior response) was observed with three times daily application.[42] Overall, 31.5% of patients had a better response to three times daily application, 21.5% had a better response to once-daily application, and 47% of patients had an equal response (p<0.05).

Timing of application

The GSK Report[46] (Appendix 8) compared success rates between morning and evening application of active treatment in the once-daily group (67% versus 78%, difference 11.3%, 95% CI -4.6 to 27.2, p=0.17). Despite finding a statistically

significant difference between once and twice daily application (Table 3.4), the difference between once-daily evening treatment and twice-daily application was not statistically significant (78% versus 84%, difference 5.9%, 95% CI -6.6 to 18.4, p=0.33).

Effect of age

The GSK Report found that the percentage of patients who were classed as successes decreased as age increased in both groups (once daily: 0-5 years 80%, 5-15 years 75%, 16+ years 64%; twice daily: 0-5 years 93%, 5-15 years 80%, 16+ years 79%),[46] however the numbers in each age group were small. Subgroup analysis[47] of patients aged 12 years or less produced results similar to the main analysis (Appendix 8), with success rates assessed by the physician of 77% and 91% at the last visit attended with once and twice daily application respectively (difference 13.5%, 95% CI 0.6 to 26.4, p=0.048). The patients' assessment of success also favoured twice daily use (72% versus 91%, 95% CI 5.0 to 32.3, p=0.011). Conversely, subgroup analysis of patients aged 12 years or less from the study by Bleehen and colleagues found no significant differences in success rates between once and twice daily application at the last visit attended (86% versus 89%, difference -3%, 95% CI 15.5 to 9.6, p=0.644),[50] again supporting the main analysis of this study.

Summary

Overall, studies found little difference in the number of patients responding to treatment between once and twice daily application of potent corticosteroids. Some statistically significant differences favouring twice daily treatment were identified, however these were inconsistent between outcome assessors (physicians versus patients) and outcomes selected for analysis. Only one study compared once versus three times daily application of very potent corticosteroids; this found a statistically significant difference in comparative clinical response in favour of three times daily treatment, but no significant difference in the number of patients with at least a good response.

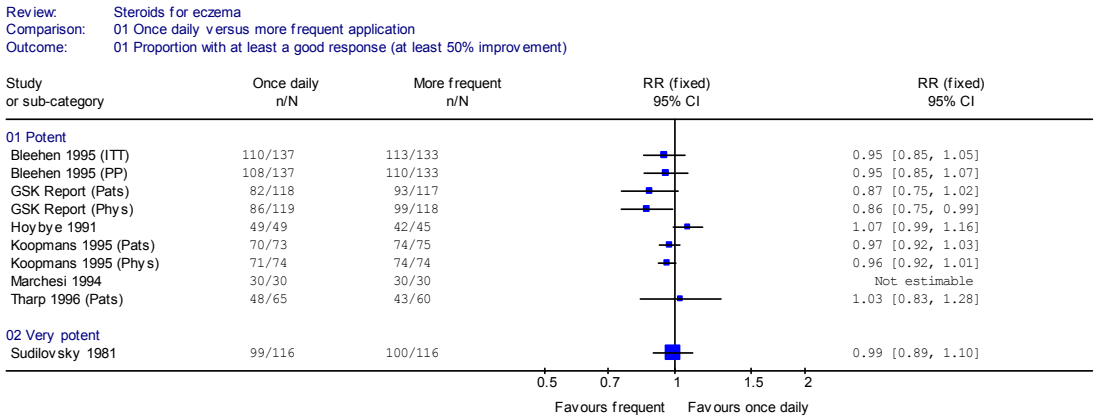
Table 3.4 Number of patients responding to treatment

Study details	Outcome	Once daily	More frequent	Significance
MODERATE				
Richelli et al. 1990 [53]	Not reported			
POTENT				
Berth-Jones et al. 2003 [54] 1. Fluticasone propionate cream 0.05% once daily (n=95). 2. Fluticasone proprionate cream 0.05% twice daily (n=91). 3. Fluticasone propionate ointment 0.005% once daily (n=100). 4. Fluticasone proprionate ointment 0.005% twice daily (n=90).	Patients with controlled atopic dermatitis at end of stabilisation stage (absent or mild)	Cream: 80% (76/95) Ointment: 77% (77/100)	Cream: 84% (76/91) Ointment: 71% (64/90)	p=0.546 p=0.249

Study details	Outcome	Once daily	More frequent	Significance
Duration of treatment: 4 weeks. *Patients:* Age 12-65 years, moderate to severe.				
Bleehen et al. 1995 [43] 1. Fluticasone propionate 0.05% cream once daily and vehicle once daily (n=137). 2. Fluticasone propionate 0.05% cream twice daily (n=133). *Duration of treatment:* 4 weeks *Patients:* Children and adults. At least moderate severity.	Patients with at least a good response (>50% improvement)	ITT: 80% (110/137) PP: 79% (108/137)	ITT: 85% (113/133) PP: 83% (110/133)	95% CI -14.2 to 5.0, p=0.35 95% CI -14.7 to 6.2, p=0.42
	(For subgroup analysis of patients aged 12 years or less, see Appendix 8)			
GSK Report 1995[46] 1. Fluticason propionate 0.005% ointment once daily and placebo once daily (n=123). 2. Fluticasone propionate 0.005% ointment twice daily (n=122). *Duration of treatment:* 4 weeks *Patients:* Children and adults. At least moderate severity.	Number with success (%) (cleared, good, moderate)			Difference (95% CI):
	Investigators' assessment			
	Visit 2:	69% (80/116)	71% (83/117)	2.0%, (-9.8,13.7) p=0.74
	Visit 3:	79% (77/98)	78% (83/106)	-0.3% (-11.6, 11.0) p=0.96
	Visit 4:	74% (70/94)	86% (78/91)	11.2% (-0.1, 22.6) p=0.056
	Visit 5:	78% (64/82)	85% (68/80)	7.0% (-4.9, 18.8) p=0.25
	Last visit:	72% (86/119)	84% (99/118)	11.6% (1.2, 22.1) p=0.031
	Patients' assessment			
	Visit 2:	67% (79/118)	69% (81/118)	1.7% (-10.2, 13.6) p=0.78
	Visit 3:	78% (81/104)	83% (88/106)	5.1% (-5.6, 15.8) p=0.35
	Visit 4:	76% (73/96)	80% (74/92)	4.4% (-7.4, 16.2) p=0.47
	Visit 5:	74% (61/82)	80% (63/79)	5.4% (-7.6, 18.3) p=0.42
	Last visit:	69% (82/118)	79% (93/117)	10.0% (-1.1, 21.1) p=0.079
	(For data displayed by category and for subgroup analysis of patients aged 12 years or less, see Appendix 8)			
Hoybye et al. 1991 [55] 1. Mometasone furoate in fatty cream base (Elocon ®) once daily (n=49). 2. Hydrocortisone 17-butyrate in fatty cream base (Locoid ®) twice daily (n=45). *Duration of treatment:* 3 weeks *Patients:* Adults. Severity score at least 4.5 out of 9.	Global evaluation:			
	Cleared or improved markedly	*88% (43/49)*	*78% (35/45)*	*p=0.28*
	1 (cleared)	10/49	7/45	
	2 (marked improvement)	33/49	28/45	
	3 (moderate improvement)	6/49	7/45	
	4 (slight improvement)	0	0	
	5 (no change)	0	3/45	
	6 (exacerbation)	0	0	
Koopmans et al. 1995 [44] 1. Locoid Lipocream (0.1% hydrocortisone 17-butyrate) once daily and Locobase once daily (n=75). 2. Locoid Lipocream twice daily (n=75).	Overall improvement in skin disease:			
	Investigators' opinion			
	Clearance of lesions	49% (36/74)	70% (52/74)	
	Considerable improvement	35% (26/74)	20% (15/74)	
	Definite improvement	12% (9/74)	9% (7/74)	
	Minimal improvement	4% (3/74)	0 (0/74)	
	No change	0 (0/74)	0 (0/74)	
	Worse	0 (0/74)	0 (0/74)	
	Patients' opinion			

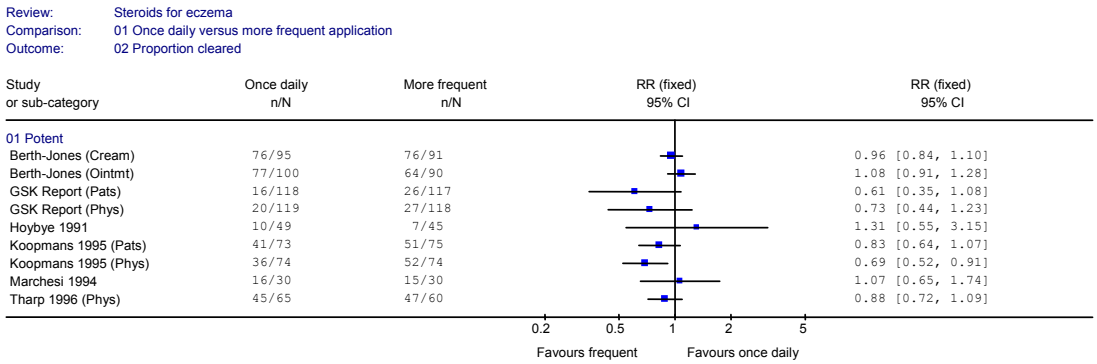
Study details	Outcome	Once daily	More frequent	Significance
Duration of treatment: 4 weeks *Patients:* Aged over 12 years.	Clearance of lesions	55% (41/73)	68% (51/75)	
	Considerable improvement	23% (17/73)	25% (19/75)	
	Definite improvement	16% (12/73)	5% (4/75)	
	Minimal improvement	3% (2/73)	0 (0/75)	
	No change	1% (1/73)	1% (1/75)	
	Worse	0 (0/73)	0 (0/75)	
	Total clearance of lesions:			
	2 weeks	12% (9/73)	19% (14/74)	p=0.29
	4 weeks	27% (20/73)	47% (35/75)	p=0.02
Marchesi et al. 1994 [56] 1. Mometasone furoate ointment 0.1% once daily (n=30). 2. Betamethasone dipropionate ointment 0.05% twice daily (n=30). *Duration of treatment:* 3 weeks *Patients*: Adults. At least moderate severity.	Physicians global evaluation of response to treatment:			
	Cleared	53% (16/30)	50% (15/30)	
	Good improvement	47% (14/30)	50% (15/30)	
	Moderate improvement	(0/30)	(0/30)	
	Slight improvement	(0/30)	(0/30)	
	Unchanged	(0/30)	(0/30)	
	Exacerbation	(0/30)	(0/30)	
Rajka et al. 1993 [57]	Not reported			
Tharp 1996 [58] 1. Fluticasone propionate cream 0.05% once daily and vehicle once daily (n=79). 2. Fluticasone propionate cream 0.05% twice daily (n=79). *Duration of treatment:* 4 weeks *Patients:* Aged over 12 years. Moderate to severe.	Patients' subjective assessment (patients rating treatment excellent or good)			
	Day 8:	74% (56/76)	76% (58/76)	p=ns
	Day 15:	73% (53/73)	84% (61/73)	p=0.01
	Day 22:	72% (50/69)	81% (55/68)	p=0.02
	Day 29:	74% (48/65)	71% (43/60)	p=ns
	Physician's gross assessment (patients with target lesion response rated cleared or excellent)			
	Day 8:	29% (22/76)	39% (30/76)	p=ns
	Day 15:	42% (31/73)	62% (45/73)	p=ns
	Day 22:	57% (39/69)	70% (48/68)	p<0.014
	Day 29:	69% (45/65)	78% (47/60)	p=ns
VERY POTENT				
Sudilovsky et al. 1981 [42] 1. halcinonide cream 0.1% once daily plus placebo twice daily (n=149). 2. halcinonide cream 0.1% three times daily (n=149) *Duration of treatment:* 3 weeks *Patients:* Unclear.	Absolute therapeutic response (excellent or good, at least 50% improvement)	85.3% (99/116)	86.2% (100/116)	p=ns
	Comparative clinical response (markedly or slightly superior):			
	Week 1 (n=149)	Markedly 5	Markedly 11	p=ns
	(equal response: 85)	Slightly 21	Slightly 27	
	Week 2 (n=138)	Markedly 3	Markedly 15	p<0.05
	(equal response: 87)	Slightly 18	Slightly 15	
	Week 3 (n=116)	Markedly 2	Markedly 12	p<0.01
	(equal response: 81)	Slightly 9	Slightly 12	
	Overall (n=149)	Markedly 2	Markedly 12	p<0.05
	(equal response: 70 (47.0%))	(1.3%)	(8.1%)	
		Slightly 30	Slightly 35	
		(20.1%)	(23.5%)	
	Total with better response:	32 (21.5%)	47 (31.5%)	

Figure 3.1 Patients with at least a good response at end of treatment: risk ratios



Note: the patients in the studies by Bleehen et al. (1995), GSK Report and Koopmans et al. (1995) are included twice in the above figure for illustration of different assessments. ITT = intention to treat analysis; PP = per-protocol analysis; Pats = patients' assessment; Phys = physicians' assessment.

Figure 3.2 Patients with controlled or cleared atopic eczema: risk ratios



Note: the patients in the studies by Koopmans et al. (1995) and GSK Report are included twice in the above figure for illustration of the different assessments. Pats = patients' assessment; Phys = physicians' assessment.

3.2.3.2 Severity of signs and symptoms

Studies reporting data on severity scores or percent improvement in severity are summarised in Table 3.5. None of the studies report the use of a validated severity scale, and the clinical relevance of a change in severity is not clear.

Hoybye and colleagues[55] found significantly more improvement in pruritis (p=0.007) with once daily mometasone furorate than with twice daily hydrocortisone 17-butyrate, but not in erythema or infiltration. Rajka and colleagues, whose study comprised of patients with mild to moderate eczema, found once daily application of mometasone furorate resulted in a greater percent improvement in total atopic dermatitis scores than twice daily betamethasone valerate at each assessment.[57] However, it should be noted that both of these studies were judged to be of poor quality. The third study, also of poor quality, that compared once daily mometasone furoate with twice daily application of a different active compound (betamethasone

dipropionate) found no statistically significant differences in percent reduction of signs and symptoms severity.[56]

A greater reduction in scores demonstrated at two weeks (p=0.04) for twice daily Locoid Lipocream was not maintained at four weeks (p=0.08) in the study by Koopmans and colleagues, and although the twice daily group showed more pronounced reductions in rating for erythema at four weeks (p=0.03), this was not the case for the other symptoms assessed.[44]

The GSK report found total severity scores to be similar between once and twice daily application of fluticasone propionate ointment at each visit, although logistic regression analysis of total severity score adjusting for age and baseline total severity score favoured twice daily application at the last visit attended (OR 1.72, 95% CI 1.05 to 2.82, p=0.033).[46] The odds ratio for the treatment effect in the subgroup analysis of patients aged 12 years or less was not statistically significant (OR 1.85, 95% CI 0.88 to 3.89, p=1.03).[47]

None of the other studies comparing potent[43,56,58] or moderate[53] products found a significant difference in severity between once daily or more frequent application. Severity was not reported by Berth-Jones and colleagues[54] or Sudilovsky and colleagues.[42]

Summary

The one study that compared moderately potent corticosteroids found no significant difference in severity of symptoms between once and twice daily application, but was small and of poor quality. Once-daily use of mometasone furorate was found to result in a greater percent improvement in total atopic dermatitis scores compared with twice daily betamethasone valerate in one study, and an improvement in pruritus only in another study compared with twice daily hydrocortisone 17-butyrate. A third study comparing once-daily use of mometasone furoate with a different active compound found no statistically significant differences in percent reduction of severity. Again, these studies were of poor quality. One good quality study favoured twice daily application of fluticasone propionate ointment at the last visit attended only, while other studies found no significant difference or an improvement in one symptom but not others with twice daily application. The validity and reliability of the severity scales used was not reported by any of the studies, and the clinical significance of a change in these severity scores is not clear.

Table 3.5 Severity of signs and symptoms

Study details	Outcome	Once daily	More frequent		Significance
MODERATE					
Richelli et al. 1990 [53] 1. clobetasone 17-butyrate 0.05% lotion once daily at 9pm (n=9). 2. clobetasone 17-butyrate 0.05% lotion twice daily at 8am and 3pm (n=13).	Mean scores for severity of clinical manifestations (eg. Erythema, oedema, exudation, blisters, bullae, scabs, scaling, lichenification), score 0-3 (none to severe) (estimated from figure)		8am/ 3pm	3pm/ 8pm	
		Day 0: 1.21	1.26	1.23	
		Day 1: 1.1	1.09	1.02	
		Day 2: 0.89	0.71	0.66	
		Day 3: 0.7	0.52	0.52	
		Day 4: 0.63	0.48	0.33	
		Day 5: 0.47	0.30	0.31	
		Day 6: 0.43	0.22	0.23	
		Day 7: 0.26	0.28	0.14	

Study details	Outcome	Once daily	More frequent	Significance
3. clobetasone 17-butyrate 0.05% lotion twice daily at 3pm and 8pm (n=8). *Duration of treatment:* 1 week *Patients:* Children.	Mean scores for severity of symptoms (itching, burning, pain), score 0-3 (estimated from figure)	Day 0: 1.0 Day 1: 0.93 Day 2: 0.71 Day 3: 0.6 Day 4: 0.52 Day 5: 0.5 Day 6: 0.52 Day 7: 0.52	1.17 0.95 0.93 0.78 0.64 0.81 0.6 0.64 0.45 0.45 0.33 0.36 0.28 0.36 0.31 0.36	
	States no differences in the degree or speed of recovery in the three patient groups.			
POTENT				
Berth-Jones et al. 2003 [54]	Not reported.			
Bleehen et al. 1995 [43] 1. Fluticasone propionate 0.05% cream once daily and vehicle once daily (n=137). 2. Fluticasone propionate 0.05% cream twice daily (n=133). *Duration of treatment:* 4 weeks *Patients:* Children and adults. At least moderate severity.	Median severity scores of clinical signs and symptoms: erythema, pruritus, thickening, lichenification, vesiculation, crusting (min, max; 25th, 75th percentile), score 0-3 (absent to severe) (estimated from figure)	ITT analysis: Baseline 10.0 (7,16; 9,12) Last visit attended 2.5 (0,16; 1,5) Per-protocol analysis: Baseline 10.0 (7,16; 9,12) Last visit attended 2.5 (0,16; 1,5)	Baseline 10.0 (6,16; 9,12) Last visit attended 2.0 (0,14; 0.5,4) Baseline 10.5 (6,16; 10,12) Last visit attended 2.0 (0,14; 0.5, 4)	
	Assessment of clinical signs and symptoms at last visit attended (proportion of patients judged a success, i.e. had a decrease in severity score compared with baseline)	ITT analysis: 96% Per-protocol analysis: 95%	97% 96%	p=0.72 p=1.00
	(For subgroup analysis of patients aged 12 years or less, see Appendix 8)			
GSK Report 1995[46] 1. Fluticasone propionate 0.005% ointment once daily and placebo once daily (n=123). 2. Fluticasone propionate 0.005% ointment twice daily (n=122). *Duration of treatment:* 4 weeks *Patients:* Children and adults. At least moderate severity.	Total severity score of erythema, pruritus, thickening/lichenification, and scaling, each scored 0-3 (absent to severe). Median (min, max; 25th, 75th percentile)			OR (95% CI)*
	Visit 2:	5.3 (0.0,12.0; 4.0, 7.0)	5.0 (0.0, 10.0; 3.0, 7.0)	1.16 (0.71, 1.90) p=0.55
	Visit 3:	4.0 (0.0, 10.0; 2.5, 5.5)	4.0 (0.0, 10.0; 2.0, 5.5)	1.20 (0.72, 2.02) p=0.48
	Visit 4:	3.5 (0.0, 9.5; 2.0, 5.5)	3.0 (0.0, 9.5; 1.5, 5.0)	1.14 (0.66, 1.98) p=0.64
	Visit 5:	3.0 (0.0, 8.5; 2.0, 5.0)	2.5 (0.0, 11.0; 1.5, 4.5)	1.60 (0.89, 2.86) p=0.11
	Last visit:	3.0 (0.0, 10.5; 1.5, 6.0)	2.3 (0.0, 11.0; 1.0; 4.5)	1.72 (1.05, 2.82) p=0.033
	*Logistic regression model of total severity score on treatment effect adjusting for prognostic factors (age and baseline total severity score): odds ratio for treatment effect (twice/once daily), (95% CI), significance of treatment effect. (For subgroup analysis of patients aged 12 years or less, see Appendix 8)			
Hoybye et al. 1991 [55] 1. Mometasone furoate in fatty cream base (Elocon ®) once daily (n=49). 2. Hydrocortisone 17-butyrate in fatty cream	Improvement in symptoms at 3 weeks:	(Data not reported)		
	Pruritus	States significantly more improvement with once daily momestasone furoate.		p=0.0069
	Erythema	States no difference in improvement between groups.		p=ns
	Infiltration:	States no difference in improvement between groups.		p=ns

Study details	Outcome	Once daily	More frequent	Significance
base (Locoid ®) twice daily (n=45). *Duration of treatment:* 3 weeks *Patients:* Adults. Severity score at least 4.5 out of 9.	Patient evaluation of severity on VAS at 3 weeks	No difference in efficacy between treatments. Data not reported.		p=0.30
Koopmans et al. 1995 [44] 1. Locoid Lipocream (0.1% hydrocortisone 17-butyrate) once daily and Locobase once daily (n=75). 2. Locoid Lipocream twice daily (n=75). *Duration of treatment:* 4 weeks *Patients:* Aged over 12 years.	Ratings of clinical features, score 0-4 (none to very severe) (estimated from figure) Erythema Week 2: 1.5 1.25 Week 4: 0.9 0.6 Induration Week 2: 1.4 1.0 Week 4: 0.8 0.5 Scaling Week 2: 0.7 0.6 Week 4: 0.4 0.25 Pruritus Week 2: 1.0 0.9 Week 4: 0.6 0.25 Excoriation Week 2: 1.0 0.9 Week 4: 0.4 0.3 Overall severity Week 2: 1.4 1.25 Week 4: 0.9 0.7 Total score Week 2: 5.3 4.3 Week 4: 3.0 1.8 Twice daily group showed greater reduction in ratings than once daily group (p=0.04 at two weeks). At 4 weeks p= 0.08. At 4 weeks, twice daily group showed more pronounced reduction in ratings for erythema (p=0.03).			
Marchesi et al. 1994 [56] 1. Mometasone furoate ointment 0.1% once daily (n=30). 2. Betamethasone dipropionate ointment 0.05% twice daily (n=30). *Duration of treatment:* 3 weeks *Patients*: Adults. At least moderate severity.	Percent reduction of signs and symptoms severity score (estimated from figure) Erythema Day 2: 12% 9% Day 3: 27% 21% Day 4: 44% 35% Day 7: 66% 54% Day 14: 83% 80% Day 21: 91% 90% p=ns Induration Day 2: 5% 5% Day 3: 19% 15% Day 4: 34 % 25% Day 7: 61% 54% Day 14: 84% 80% Day 21: 92% 95% p=ns Pruritus Day 2: 20% 32% Day 3: 45% 48% Day 4: 67% 64% Day 7: 88% 83% Day 14: 97% 97% Day 21: 100% 99% p=ns			
Rajka et al. 1993 [57] 1. Mometasone furoate fatty cream 0.1% (Elocon ®) once daily (n=57). 2. Betamethasone valerate cream (Betnovate ®) 0.1% twice daily (n=60).	Percent improvement in total atopic dermatitis scores 8 days: 80% 58% p<0.01 15 days: 93% 75% p<0.01 22 days: 96% 86% p<0.01 End study: 98% 86% p<0.01			

Study details	Outcome	Once daily	More frequent	Significance
Duration of treatment: 3 weeks *Patients*: Aged over 16 years. Mild to moderate severity.				
Tharp 1996 [58] 1. Fluticasone propionate cream 0.05% once daily and vehicle once daily (n=79). 2. Fluticasone propionate cream 0.05% twice daily (n=79). *Duration of treatment:* 4 weeks *Patients:* Aged over 12 years. Moderate to severe.	Severity of symptoms and signs at day 29, score 0-3 (absent to severe) (p value vs baseline)			
	Erythema	0.6 (p<0.001)	0.5 (p<0.001)	
	Pruritus	0.4 (p<0.001)	0.3 (p<0.001)	
	Skin thickening	0.5 (p<0.001)	0.5 (p<0.001)	
	Lichenification	0.4 (p<0.001)	0.4 (p<0.001)	
	Vesiculation	0.1 (p=ns)	0 (p=ns)	
	Crusting	0.2 (p=ns)	0.1 (p=ns)	
	At end of treatment, both treatments had significantly greater improvements compared with vehicle for all signs and symptoms (p≤0.005). No significant differences were found between mean sign and symptom scores for once daily versus twice daily groups at day 29 and at end of treatment (p≥0.07).			
	Mean total severity scores (erythema, pruritus, thickening), score 0-3, (mean percentage change in severity score)			
	Day 8:	(n=76) 3.4 (-51.7%)	(n=76) 3.2 (-55.1%)	
	Day 15:	(n=73) 2.6 (-63.9%)	(n=73) 1.9 (-73.0%)	
	Day 22:	(n=69) 2.1 (-70.7%)	(n=68) 1.5 (-77.9%)	
	Day 29:	(n=65) 1.5 (-79.5%)	(n=60) 1.3 (-81.8%)	
	End of treatment:	1.7	1.4	p=0.9
VERY POTENT				
Sudilovsky et al. [42]	Not reported.			

3.2.3.3 Quality of life and patient preference

Quality of life and patient preference were not reported by any of the included trials.

3.2.3.4 Product usage

Two studies reported product usage.[43,46] Bleehen and colleagues stated that the amount of active treatment used by the once-daily group was roughly half of that used by the twice daily group, however data were not reported.[43] The GSK Report presents data on the approximate mean amount of product used based on the weight of weekly returned used tubes for three groups: morning active treatment plus evening placebo, evening active treatment plus morning placebo, and twice daily active treatment (fluticasone propionate ointment). The average amount used per week decreased throughout the study, from about 32g to 36g in week one to about 21g to 30g in week four[46] (Appendix 8).

3.2.3.5 Other outcomes

In the study by Bleehen and colleagues, sleep was reported to be 'as good as ever has been' or better by 37% of patients with once-daily fluticasone propionate and 55% of patients in the twice-daily application group.[43] For the subgroup analysis of patients aged 12 years or less, these figures were 44% and 66%, respectively.[50]

3.2.3.6 Adverse effects

Moderate corticosteroids
Adverse effects were not reported by Richelli and colleagues.[53] However, they do report that there were no significant differences in serum cortisol and adrenocorticotropic hormone (ACTH) levels before and after clobetasone 17-butyrate administration, and no significant differences between groups.

Potent corticosteroids
Adverse effects were reported in seven of the eight RCTs included in this review concerned with potent corticosteroids. Rajka and colleagues reported adverse effects for all included patients, but not for atopic eczema separately.[57] However, they stated that there was no observed suppression of plasma cortisol levels, nor were there any changes in laboratory values. The remaining studies reported adverse effects to varying levels of detail. Adverse effects did not appear to vary substantially between once and twice daily applications, nor did they appear to be of a severe nature.

The GSK Report described the largest number of adverse effects for the once and twice daily treatments, with 44% and 40% of patients affected and reporting a total of 86 and 75 events, respectively. However, of these, only 21 events in the once daily group and 14 events in the twice daily group were possibly, probably or almost certainly related to the study medication, fluticasone propionate ointment, and were mainly skin related disorders, including exacerbation of eczema, pruritus and redness of skin. The three serious adverse events that occurred were thought to be unrelated to the study medication.[46]

Similarly, when comparing once and twice daily application of fluticasone propionate cream, Bleehen and colleagues found 33.6% and 33.8% of patients affected and reporting a total of 68 and 64 events, respectively. Again, only 26 events in the once-daily group and 24 events in the twice daily group were possibly, probably, or almost certainly, related to study medication. The most frequent adverse effect in this study was exacerbation of eczema. Only two serious adverse events were reported; one in each group. These however were not thought to be related to the study drug. [43]

Tharp and colleagues investigated the same products and frequency of use as Bleehen and colleagues, but found fewer adverse effects, with 10%, 5% and 4% of patients aged over 12 years reporting adverse effects for the vehicle, once daily and twice daily applications of fluticasone propionate cream 0.05%, respectively. None of the adverse events were judged to be serious or unexpected.[58]

The most common adverse event in the study by Berth-Jones and colleagues was ear, nose and throat infection, but the treatment groups were not specified.[54] Four patients had adverse events described as serious, namely erysipelas, exacerbation of asthma, and two flares of eczema, but again it is not clear which treatment group these occurred in. Three patients had visual signs of atrophy related to the study treatment (fluticasone propionate ointment or cream), although it is noted that two of these had a previous history of skin changes, and therefore only one report was newly observed.

Koopmans and colleagues had a similarly low level of reported adverse effects, with 5.3% of patients in each treatment group reporting an adverse reaction to Locoid Lipocream. Folliculitis occurred in both groups, while the once daily treatment group also reporting burning, itching and stinging sensations.[44]

In the study by Hoybye and colleagues, treatment-related side effects were reported to be few and similar between once-daily mometasone furoate and twice-daily hydrocortisone 17-butyrate, however data were not presented. Reported side effects included stinging, burning, itching, dryness, acne, folliculitis and hair growth. None of the patients (adults) showed any evidence of skin atrophy.[55]

Marchesi and colleagues stated that neither systemic nor local reactions occurred. Furthermore, in all patients checked for blood tests, values varied within a very narrow range. Both treatment groups reported telangiectasias of mild severity in the last two weeks of treatment with four (13.3%) cases in the once-daily mometasone furoate group and five (16.7%) cases in the twice-daily betamethsaone dipropionate group. Only one patient, belonging to the twice-daily group, reported loss of skin marks and reduced elasticity.[56]

Subgroup analysis of patients aged twelve years or less found 49%[47] and 36.5% [50] of patients in the once daily group and 40%[47] and 35%[50] in the twice-daily group reported adverse events with fluticasone propionate ointment[47] and cream,[50] respectively. As in the main analyses,[43,46] most of these events were unrelated or unlikely to be related to the study medication (Appendix 8).

Very potent corticosteroids

Sudilovsky and colleagues state that side-effects with halcinonide cream 0.1% were generally of a mild nature, the most common being burning, puritus and erythema, with no differences in incidence between once daily and three times daily regimens, and that no systemic effects were observed. However, data were not presented.[42]

Summary of adverse effects

The quality and extent of reporting of adverse effects was variable between studies. Actual numbers for each group were reported in only six of the ten studies. There appears to be little difference in the frequency or severity of adverse events between once daily and more frequent application of topical corticosteroids, however data are limited. No studies reported data on long-term adverse events.

Table 3.6 Adverse events

Study details	Adverse Effects		Once daily	Twice daily
MODERATE				
Richelli et al. 1990 [53] 1. clobetasone 17-butyrate 0.05% lotion once daily at 9pm. 2. clobetasone 17-butyrate 0.05% lotion twice daily at 8am and 3pm. 3. clobetasone 17-butyrate 0.05% lotion twice daily at 3pm and 8pm. *Patients:* Children.			**(n=9)**	**(n=13) / (n=8)**
	Adverse effects not reported. No significant differences in serum cortisol and ACTH levels before and after clobetasone 17-butyrate administration in any of the 3 groups ($p>0.05$), and no significant differences between groups.			
POTENT				
Berth-Jones et al. 2003 [54] 1. Fluticasone propionate cream 0.05% once daily 2. Fluticasone proprionate cream 0.05% twice daily 3. Fluticasone propionate ointment 0.005% once daily 4. Fluticasone proprionate ointment 0.005% twice daily *Patients:* Age 12-65 years, moderate to severe.	**No. of patients**	cream	**(n=95)**	**(n=91)**
		ointment	**(n=100)**	**(n=90)**
	Ear, nose and throat infection (most common event): 9 (group not specified). Serious adverse events: 4 (1 episode of erysipelas, 1 exacerbation of asthma, 2 flares of eczema, groups not specified). Visual signs of atrophy related to study treatment*:			
	Telangiectasia:	cream	0	1
		ointment	1	0
	Striae:	cream	0	0
		ointment	1	0
	*2 of these patients had a previous history of skin changes, and therefore only one report was newly observed (group not specified).			
Bleehen et al. 1995 [43] 1. Fluticasone propionate 0.05% cream once daily and vehicle once daily. 2. Fluticasone propionate 0.05% cream twice daily. *Patients:* Children and adults. At least moderate severity.	**No. of reports**		**(n=137)**	**(n=133)**
	Digestive system disorders		2	7
	Diseases and symptoms of the nervous system		2	7
	Diseases of the blood		0	1
	Diseases of the ear		1	4
	Diseases of the eye		0	1
	Diseases of the musculoskeletal system		1	0
	Diseases of the respiratory system* (mainly acute nasopharyngitis, asthma, upper respiratory tract infection, chest infection, coryza, seasonal allergic rhinitis)		21	18
	Infectious and parasitic diseases		2	1
	Injury and poisoning		2	1
	Kidney and urinary system disorders		0	1
	Mental disorders		1	1
	Neoplasms		1	0
	Non-specific symptoms and abnormal findings		1	1
	Skin disorder		34	21
	- Exacerbation of eczema:		7	2
	- Skin irritation following drug admin:		5	2
	- Exacerbation of itching:		4	1
	Total number of reports		*68*	*64*
	Total number of patients (%)		*46(33.6)*	*45(33.8)*
	Events possibly, probably, or almost certainly related to study medication (mostly skin disorders)		26	24
	Deaths, pregnancies, or adverse events of special interest		0	0

Study details	Adverse Effects	Once daily	Twice daily
	Serious adverse events, due to inpatient hospitalisation, unrelated to study drug	1	1
	*Diseases of respiratory system: 138 patients (69 in each group) had concomitant disease of respiratory system on entering study. Only 1 case (sore throat) was rated as being even possibly related to study medication.		
GSK Report 1995[46] 1. Fluticason propionate 0.005% ointment once daily and placebo once daily. 2. Fluticasone propionate 0.005% ointment twice daily. *Duration of treatment:* 4 weeks *Patients:* Children and adults. At least moderate severity.	**No. of reports**	**(n=123)**	**(n=122)**
	Digestive system disorder	4	6
	Diseases and symptoms of the nervous system	13	7
	Diseases of the ear	1	1
	Diseases of the eye	0	1
	Diseases of the musculoskeletal system	2	2
	Diseases of the respiratory system (most common: acute nasopharyngitis, viral infection of upper respiratory tract, cough, chest infection, sore throat)	27	25
	Infectious and parasitic diseases	4	2
	Injury and poisoning	3	5
	Kidney and urinary system disorders	0	1
	Metabolic and immunity disorders	0	1
	Skin disorder	32	24
	Including: - exacerbation of eczema	13	6
	- pruritus	6	4
	Total number of reports	*86*	*75*
	Total number of patients (%)	*54 (44)*	*49 (40)*
	Serious adverse events (all unrelated to study medication)	1	2
	Relationship to study medication (no. of reports)		
	Unrelated	44	47
	Unlikely	21	14
	Possibly	6	8
	Probably	9	3
	Almost certain	6	3
	Total number of reasons	*86*	*75*
	Total number of patients (%)	*54 (44)*	*49 (40)*
	Possibly, probably or almost certainly related to study medication: mainly skin related disorders, including exacerbation of eczema, pruritus and redness of skin. For subgroup analysis, see Appendix 8.		
Hoybye et al. 1991 [55] 1. Mometasone furoate in fatty cream base (Elocon ®) once daily. 2. Hydrocortisone 17-butyrate in fatty cream base (Locoid ®) twice daily. *Patients:* Adults. Severity score at least 4.5 out of 9.		**(n=49)**	**(n=45)**
	States that treatment-related side effects were few, and these were similar in both groups. Reported side-effects were stinging, burning, itching, dryness, acne, folliculitis and hair growth. None showed evidence of skin atrophy.		
Koopmans et al. 1995 [44] 1. Locoid Lipocream (0.1% hydrocortisone 17-butyrate) once daily and Locobase once daily. 2. Locoid Lipocream twice daily. *Patients:* Aged over 12 years.	**No. of patients (%)**	**(n=75)**	**(n=75)**
	Total number reporting adverse events	4 (5.3)	4 (5.3)
	Folliculitis in all skin areas after 1 week of treatment; treatment stopped	1 (1.3)	0
	Folliculitis but treatment continued	0	4 (5.3)
	Burning, itching and stinging sensations; treatment continued	3 (4)	0
Marchesi et al. 1994 [56]	**No. of patients (%)**	**(n=30)**	**(n=30)**

Study details	Adverse Effects		Once daily	Twice daily
1. Mometasone furoate ointment 0.1% once daily. 2. Betamethasone dipropionate ointment 0.05% twice daily *Patients*: Adults. At least moderate severity.	Telangiectasias of mild severity in last 2 weeks of treatment		4 (13.3)	5 (16.7)
	Loss of skin marks and reduced elasticity		0	1 (3.3)
	Neither systemic nor local reactions occurred. In all patients checked for blood tests, values varied within a very narrow range.			
Rajka et al. 1993 [57] 1. Mometasone furoate fatty cream 0.1% (Elocon ®) once daily 2. Betamethasone valerate cream (Betnovate ®) 0.1% twice daily *Patients*: Aged over 16 years. Mild to moderate severity.			**(n=57)**	**(n=60)**
	Not reported for atopic dermatitis separately. No suppression of plasma cortisol levels was observed, nor were there significant changes in laboratory values.			
Tharp 1996 [58] 1. Fluticasone propionate cream 0.05% once daily and vehicle once daily. 2. Fluticasone propionate cream 0.05% twice daily. *Patients:* Aged over 12 years. Moderate to severe.	**No. of patients (%)**	**Vehicle (n=78)**	**(n=77)**	**(n=77)**
	Burning	4 (5)	2 (3)	0
	Dryness	0	2 (3)	0
	Pruritus	5 (6)	0	1 (1)
	Erythema	1 (1)	0	0
	Stinging	2 (3)	0	1 (1)
	Irritation	0	0	1 (1)
	Total	8 (10)	4 (5)	3 (4)
	None of the adverse events was judged to be serious or unexpected.			
VERY POTENT				
Sudilovsky et al. 1981 [42] 1. halcinonide cream 0.1% once daily plus placebo twice daily 2. halcinonide cream 0.1% three times daily *Patients:* Unclear.			**(n=149)**	**3x daily (n=149)**
	Side-effects generally of a mild nature, the most common being burning, puritus and erythema, with no differences in incidence between once daily and three times daily regimens. However, not reported for eczema and psoriasis separately. No systemic effects were observed.			

4 ECONOMIC ANALYSIS

4.1 Methods for economic analysis

The aim of this section is to assess the cost-effectiveness of once-daily versus more frequent use of topical corticosteroids (same potency) in the treatment of atopic eczema. The *a priori* methods for systematically reviewing the evidence of cost-effectiveness are described in the research protocol (Appendix 2).

Systematic review

A systematic literature search was undertaken to identify economic evaluations comparing once-daily versus more frequent use of topical corticosteroids in atopic eczema. Methodological details of this search are presented in Appendix 3. Manufacturers' submissions to NICE were reviewed for additional studies.

Further systematic searching of the literature was undertaken to identify information related to costs associated with topical corticosteroids and the quality of life of patients with atopic eczema.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by an information scientist and thereafter further screening was undertaken by a health economist. The full text of relevant papers was obtained and inclusion criteria applied.

Studies were eligible for inclusion if they reported on the cost-effectiveness of once-daily versus more frequent use of same-potency topical corticosteroids, excluding compound preparations.

4.2 Results of literature search: cost-effectiveness

Economic evaluations

No published economic evaluations were identified which compared frequency of use of same potency topical corticosteroids. Recent reviews reported by Schiffner and colleagues[59] and Lamb and Rademaker[39] support this finding.

Economic impact of atopic eczema

A number of studies were identified from the literature search to inform on the burden of illness and general costs associated with atopic eczema, indicating a substantial cost burden imposed on individuals and society as a result of the condition.[7,38,60]

Emerson and colleagues[38] in a study involving children aged 1-5 years (n=290) with atopic eczema, estimate annual NHS costs (1995-6 cost presented), across the UK, to be £30 million for this patient group. Total annual costs were estimated at £47 million, including non-NHS costs. The total mean disease cost, over the 12-month study period, was £79.59 per patient, with the total NHS cost per patient at £50.65 per year (£28.62 for NHS consultations, plus £22.02 for NHS prescriptions). Emerson and colleagues estimate that NHS prescription costs for atopic eczema in those aged

1-5 years in the UK are in the region of £13 million, but less than 25% of the prescription costs are attributed by the authors to topical corticosteroids; the majority of the NHS prescribing costs (76%) for this patient group are found to be on emollients and bath preparations.

Herd and colleagues[60] extrapolate the findings from a study (n=155) in rural Scotland to present estimates of the total UK expenditure on atopic eczema, finding total expenditure could be £465 million; with £125 million of this falling on the NHS. Herd and colleagues report an estimated mean annual cost in their sample of £97, of which £63 is attributed to treatments (prescriptions), with most (over 60%) of the expenditure on treatments/prescriptions being on items other than topical corticosteroids (e.g. emollients, bath additives, bandages). The study reports a mean health care cost £16.20 over a two month follow-up period, with health service costs in a hospital cohort (n=10) at £415 per patient, in the same two month follow-up period.

Verboom and colleagues[7] report findings from a cost of illness study for atopic eczema in the Netherlands. The retrospective cohort study reports the total mean health care cost per patient at US$71, for a mean follow-up period of 11-months, with this comprising mainly of GP costs (US$32) and medication costs, with US$21 attributable to corticosteroids. Where patients were referred to a specialist (7.8% of cases), the mean costs were US$186 per patient. Costs presented are 1999 US$, with Dutch costs converted to US dollars using the Consumer Price Index and the Purchasing Power Parity, for the Netherlands.

4.3 Estimation of net benefits

In the included trials the clinical-effectiveness of comparisons have been reported using response rates, severity of symptoms, and an assessment of adverse effects. None of the included studies reported on other quality of life or patient preference outcomes. One study[43] did report potential differences in sleep disturbance. Bleehen and colleagues[43] reported sleep to be 'as good as ever has been' or better by 37% of patients with once-daily fluticasone propionate and 55% of patients in the twice-daily application group.

The reported review of the comparative clinical effectiveness (Section 3) has not identified any clear differences in outcomes between once-daily and more frequent application of topical corticosteroids; with only one study (GSK)[46] indicating a significant difference in response rates between different regimens (i.e. where response is based on 'at least a good response or 50% improvement'). The GSK study reports a significant difference between once-daily and twice-daily application of fluticasone propionate ointment (Cutivate®), favouring the twice-daily use of the product (see Section 3.2). One further study[42] reports a significant difference in clinical response, whilst finding no difference in absolute therapeutic response (at least a good response). The findings on severity of symptoms are very similar, with one good quality study (GSK)[46] favouring twice-daily frequency on an overall severity measure, two studies regarded as poor quality favouring once-daily treatment on severity of certain symptoms, and four other studies reporting no difference (see Section 3.2). Furthermore, we have warned above over the subjective nature of

outcome measures used in the reported trials, and the difficulties translating differences in severity scores into clinically meaningful outcomes.

There seems to be no basis upon which to draw firm conclusions over the relative merits of once-daily versus more frequent use of topical corticosteroids. As there are no clear differences reported between comparators, the economic analysis becomes a case of 'cost-minimisation analysis'; essentially a search for the least cost alternative where the principal is an efficiency comparison based on the cost per patient treated.

It may be that due to trial design, or quality of the reporting of trials, important differences in outcomes, other than those reported, have not been captured. Given the findings from the clinical review above it is assumed for the purposes of the economic analysis that the consequences of once-daily and more frequent application of topical corticosteroids are equivalent.

4.4 Estimation of net costs

The product costs associated with topical corticosteroid treatment are dependent on the product prescribed, the recommended frequency of application (i.e. once-daily or more frequent use), and the quantity of product used on each application. Each of these items will vary by patient, therefore it is difficult to assess the typical intervention cost for once-daily and more frequent use of topical corticosteroids.

Product costs

Table 4.1 reports the estimated cost per 30mg/30ml for topical corticosteroids eligible for inclusion in this review, using prices listed in the BNF (applying the largest pack size available). These costs are net costs and are subject to pharmacy handling costs (e.g. a dispensing fee is estimated at £0.946 per item[61]). There are wide variations in the cost of products available. Of note is the relatively high cost of the newer 'once-daily' topical corticosteroids, fluticasone propionate cream (Cutivate®) and mometasone furoate (Elocon®), at £4.59 and £4.88 respectively per 30g/30ml, with comparator potent products such as betamethasone valerate (Betnovate®) or hydrocortisone butyrate (Locoid®) costing £1.31 and £1.88 respectively per 30g/30ml.

Table 4.1 Product costs, topical corticosteroids (eligible for inclusion in the review), by BNF potency, with BNF list price for 30mg/30ml

Potency	BNF Chemical Name	Product Name	Cost per 30g/30ml **
Mild	Hydrocortisone (Generic*)	Hydrocortisone cream/ointment 0.5%	£0.60
	Hydrocortisone (Generic*)	Hydrocortisone cream/ointment 1%	£0.72
	Hydrocortisone (Generic*)	Hydrocortisone cream/ointment 2.5%	Not listed
	Hydrocortisone (Proprietory)	Efcortelan cream/ointment 0.5%	£0.66
	Hydrocortisone (Proprietory)	Efcortelan cream/ointment 1%	£0.81
	Hydrocortisone (Proprietory)	Efcortelan cream/ointment 2.5%	£1.83
	Hydrocortisone (Proprietory)	Mildison Lipocream 1%	£2.19
	Hydrocortisone (Proprietory)	Dioderm cream 0.1%	£2.69
	Fluocinolone Acetonide	Synalar cream 1/10, 0.0025%	£0.89
Moderate	Alclometasone Dipropionate	Modrasone cream/ointment 0.05%	£1.69
	Betamethasone Valerate	Betnovate RD cream/oint 0.025%	£1.08
	Clobetasone Butyrate	Eumovate cream/oint 0.05%	£1.70
	Desoxymethasone	Stiedex LP oily cream 0.05%	£2.46
	Fluocinolone Acetonide	Synalar cream/oint 1/4, 0.00625%	£0.94
	Fluocortolone	Ultralanum cream/oint Plain	£1.77
	Flurandrenolone	Haelan cream/oint 0.0125%	£1.63
Potent	Beclomethasone Dipropionate	Propaderm cream/oint 0.025%	£1.74
	Betamethasone Dipropionate	Diprosone cream/oint/lotion 0.05%	£2.05
	Betamethasone Valerate	Betnovate cream/oint/lotion/scalp applic 0.1%	£1.31
	Betamethasone Valerate	Bettamousse foam 0.12%	£2.25
	Betamethasone Valerate	Betacap scalp applic 0.1%	£1.27
	Betamethasone Valerate (Generic)	Betamethasone valerate cream/oint 0.1%	£1.40
	Fluocinolone Acetonide	Synalar cream/ointment 0.025%	£1.34
	Fluocinonide	Metosyn FAPG cream/oint 0.05%	£1.19
	Fluticasone Propionate	Cutivate cream/oint 0.05%	£4.59
	Hydrocortisone Butyrate	Locoid Lipocream 0.1%	£1.97
	Hydrocortisone Butyrate	Locoid cream/oint 0.1%	£1.88
	Hydrocortisone Butyrate	Locoid Crelo 0.1%	£2.25
	Mometasone Furoate	Elocon cream/oint/scalp lotion 0.1%	£4.88
Very Potent	Clobetasol Propionate	Dermovate cream/oint 0.05%	£2.48
	Diflucortolone Valerate	Nerisone Forte oint/oily cream 0.3%	£2.09
	Diflucortolone Valerate	Nerisone cream/oint/oily cream 0.1%	£2.09
	Halcinonide	Halciderm_cream 0.1%	£3.40

* Includes generic hydrocortisone products

** using largest pack sizes available (e.g. where 100mg is the largest pack size the cost is calculated using the 100mg price multiplied by 0.30)

Quantity of topical corticosteroid used

Data on the quantity of topical corticosteroid used, by frequency, is not generally reported in the clinical trials included in the review of clinical effectiveness (Section 3). Only two studies refer to product usage. Bleehen and colleagues[43] report that the amount of active treatment used by the once-daily group was roughly half of that used by the twice daily group, however data were not reported. The GSK study[46] presents data on the estimated amount of topical corticosteroid used per week, over a 4-week period, in the comparison of fluticasone propionate ointment once daily, plus placebo

once daily, versus fluticasone propionate ointment twice-daily. As part of the study protocol patients returned the tubes containing unused topical corticosteroid each week, estimates are based on the difference in weight between new tubes and those returned. Overall, the estimated mean weekly amount of product used across all comparator groups (all patients following a twice-daily regimen) is 28.3g (ranging from 32g to 36g in week one to about 21g to 30g in week four.

Outside of the present review of clinical effectiveness we have identified a small number of studies that refer to the amount of product used by patients with atopic eczema.

Reidhav & Svenson[62] report findings from an RCT comparing betamethasone versus mometasone furoate cream once daily, comprising 30 patients with atopic dermatitis, aged 15-66 yrs, (median 26.4). Each patient was treated with one preparation on the left and the other preparation on the right side of the body, by random allocation, with emollient permitted in addition to study preparations. The study reports that after 4-weeks 34.1g of betamethasone and 31.4g of mometasone furoate had been used per patient, a total of 65.5g over 4-weeks on a once daily regimen (analysis was subject to some cases of missing data reported).

Furue and colleagues[63] report a study in a group of Japanese patients with atopic eczema (Japanese patients have to pay 20-30% of total costs), finding the mean clinical dose (and inter-quartile range) of topical corticosteroids during 6-months of treatment in infants to be 25g (42.8-89.5), in children to be 45g (80-135), and in adolescents and adults to be 95g (180-304). Findings are not presented by frequency of application (i.e. once-daily, twice-daily).

Thomas and colleagues[64] report findings from an RCT of 18-weeks duration, comparing short bursts of a potent topical corticosteroid versus prolonged treatment with a mild preparation for children aged 1-15 years, with mild to moderate atopic eczema. The mild treatment arm used 1% hydrocortisone ointment twice-daily for 7 days, and over an 18 wk period the authors report an average of 68g of hydrocortisone used.

Ellis and colleagues[30] when comparing the cost-effectiveness of topical corticosteroids (high potency) with tacrolimus ointment (topical immodulator), using a Markov modelling approach, assumed patients used 17.5g per week of topical corticosteroids (they used the input of a physician panel to assist with the construction of their model).

Information to guide us on the amount of product used by patients is varied and it is difficult to draw conclusions due to differences in study duration (i.e. 4-weeks versus 18-weeks), patient groups, and products used. It is clear from the general literature on the treatment of atopic eczema that product use varies by severity of disease, patient group (child versus adult), and setting (hospital versus community).

Although it would seem reasonable to assume that the amount of topical corticosteroid used by patients on a once-daily regimen is less than that used for more frequent applications (especially where we refer to the same product), it is not possible to predict with any certainty whether the quantity of medication used can be

judged on a 'pro-rata' basis according to frequency of application. Furthermore, topical corticosteroids are applied when patients experience 'flare-ups', not continuously over time, therefore, where indications on quantity of product are reported (e.g. over a 4-week period) it is not simply a case of using a mean quantity of product per week and extrapolating over a 52-week period.

NHS cost of once-daily application of topical corticosteroids

Should NICE recommend that 'once-daily' application of topical corticosteroids is preferred to more frequent use of topical corticosteroids (i.e. once-daily becomes the 'new intervention'), the NHS costs associated with prescribing should not increase where the same product is used, or where a product with a similar cost per unit (gram/ml) is prescribed, for once-daily application. However, this may not be the case. Clinicians responding to such guidance may prefer to prescribe products that are specifically marketed for once-daily application, and these products may be more expensive than traditional products used for more frequent application. In some cases same potency products may be more costly overall on a once-daily regimen than the former twice-daily regimen, with an associated additional cost to the NHS. For example, where fluticasone propionate cream (Cutivate®) or mometasone furoate (Elocon®) once-daily is substituted for betamethasone valerate, betamethasone dipropionate or hydrocortisone butyrate twice-daily, the once-daily regimen would be expected to be more costly than the twice-daily regimen. This scenario is also possible in mild potency products where generic hydrocortisone is substituted for proprietary brands of hydrocortisone (e.g. Mildson® or Dioderm® cream), although it is difficult to gauge the likelihood of such a substitution.

Two further complications are relevant to the consideration of NHS costs. Firstly, not all prescription costs fall on the NHS, many adults are subject to a prescription charge of £6.30 per item. In a large number of cases this charge will be greater than the ingredient cost for the prescription (e.g. for milder hydrocortisone products), and in most other cases the prescription charge will offset a large proportion of the prescription cost. However, the Department of Health report that 85% of community dispensed prescriptions were dispensed free of charge in 2002.[35] Secondly, when considering changes in prescribing behaviour we must consider the impact of specific marketing authorisation for different products. The BNF indicates that most products are for use 1-2 times daily (see Table 2.3), and we would expect the BNF to be the dominant guiding instrument for the general practitioner. Presently, there are only a small number of products specifically licensed for use once daily (see Table 2.3). However, in this report we assume that in practice all listed products can be prescribed for once-daily use.

4.5 Cost effectiveness

The approach taken in this report to the cost-effectiveness of once-daily versus more frequent use of topical corticosteroids is that of cost-minimisation analysis; where outcomes for the comparators are assumed to be equivalent and the objective becomes the selection of the least cost alternative. However, selecting the least cost alternative

is not purely a case of considering the frequency of application, as discussed above it is important to consider the product costs associated with comparisons of different treatment regimens. It seems reasonable to consider that where the same product is used for once-daily compared to more frequent use, the once-daily regimen will present as the least cost option, as a reduction in the amount of topical corticosteroid applied will offer cost savings (an NHS saving where the NHS is responsible for prescription costs), although the magnitude of the savings is subject to uncertainty. Yet, where different products are considered in different treatment regimens (by frequency) the relative product costs must be considered in the assessment of the least cost alternative.

Table 4.2 illustrates the cost-minimisation approach using the studies included in the review of clinical effectiveness (Section 3.2), based on findings on response rates for 'at least a good response or 50% improvement' (Section 4.3 above discusses other differences identified in the clinical review). Where the same product has been compared across differing frequency of application the once-daily treatment option would be expected to dominate in the cost-minimisation analysis, and this is the case in six of the ten comparisons in the clinical review. However, in three of the ten comparisons (Hoybye et al,[55] Rajka et al,[57] and Marchesi et al[56]) the twice-daily treatment regimen dominates as costs are expected to be less for the products in these regimens (i.e. cost per gram/ml in the once-daily regimen is greater than twice that of the twice-daily regimen), with no difference expected in outcomes (although we have discussed above differences in severity scores for two studies[55,57]).

Where studies report an effectiveness difference (greater number or patients responding to treatment) a judgement is required over the cost-effectiveness of treatment. This is the case in the study reported by GSK[46] which indicates that twice-daily use of fluticasone propionate ointment offers an improved outcome, over once-daily use of the same product (72% success in the once-daily group compared to 84% success in the twice-daily group), therefore a decision is required over the balance of costs and benefits associated with the difference between the two treatment groups.

Table 4.2 Summary of comparisons and related cost-minimisation analysis

Study	Once daily	More frequent	Cost-minimisation analysis outcome (least cost alternative)
MODERATE			
Richelli et al. 1990 [53]	Clobetasone 17-butyrate 0.05% lotion at 9pm.	Clobetasone 17-butyrate 0.05% lotion 1.at 8am and 3pm 2. at 3pm and 8pm	Once daily
POTENT			
Bleehen et al. 1995 [43]	Fluticasone propionate cream 0.05% once daily Vehicle once daily	Fluticasone propionate cream 0.05% twice daily	Once daily
Tharp 1996 [58]	Fluticasone propionate cream 0.05% once daily Vehicle once daily	Fluticasone propionate cream 0.05% twice daily.	Once daily
Berth-Jones et al. 2003 [54]	1. Fluticasone propionate cream 0.05% once daily 2. Fluticasone propionate ointment 0.005% once daily	1. Fluticasone propionate cream 0.05% twice daily 2. Fluticasone propionate ointment 0.005% twice daily	Once daily Once daily **
GSK Report 1995[46]	Fluticasone propionate ointment 0.005% once daily (Cutivate®) Placebo once daily	Fluticasone propionate ointment 0.005% (Cutivate®) twice daily	Judgement/Decision
Hoybye et al. 1991 [55]	Mometasone furoate in fatty cream base (Elocon ®) once daily	Hydrocortisone 17-butyrate in fatty cream base (Locoid ®) twice daily	Twice daily
Rajka et al. 1993 [57]	Mometasone furoate fatty cream 0.1% (Elocon ®) once daily	Betamethasone valerate cream (Betnovate ®) 0.1% twice daily	Twice daily
Marchesi et al. 1994 [56]	Mometasone furoate ointment 0.1% once daily	Betamethasone dipropionate ointment 0.05% twice daily	Twice daily
Koopmans et al. 1995 [44]	Locoid Lipocream fatty cream (0.1% hydrocortisone 17-butyrate) once daily Locobase once daily	Locoid Lipocream fatty cream twice daily	Once daily
VERY POTENT			
Sudilovsky et al. [42]	Halcinonide cream 0.1% once daily Placebo twice daily	Halcinonide cream 0.1% three times daily	Once daily*

* Note that although no difference is reported in overall therapeutic response, a difference in clinical response was noted.

** Note that fluticasone propionate ointment is not licensed for once-daily use

When considering the trial results reported in the GSK study,[46] the benefit in this study of using twice-daily application is reported in terms of the number of patients that are classified as being a treatment success. Above (Section 3) we have discussed the methodological uncertainty over the outcome measures used in the published trials generally (i.e. their subjective / categorical nature). Regardless of such uncertainty, we can offer a very simple analysis to estimate the difference in treatment cost per 1,000 patients (product costs only) and the difference in the number of patient flare-ups classed as a treatment success or failure (at least a good response or 50% improvement). Figure 4.1 details a simple analysis using assumptions on cost and effectiveness data from the GSK study. This simple analysis estimates the additional cost per additional flare-up regarded as a treatment success to be very small. However, what is difficult to ascertain is the consequences of being classed as a treatment failure or 'non-responder', i.e. the difference between success and failure on the different treatment/frequency regimen. For example, where a patient is classed as a treatment failure, does this mean that the flare-up takes a longer period to clear (e.g. an extra week), or that the patient needs to visit the GP to change the treatment plan. Expert opinion suggests that where patients do report limited response to treatment, it will entail either a change in prescription (to a different product of the same potency, or a step up prescription to a more potent product, or a combination of treatment options), or a possible referral to a dermatology clinic. One expert comments that the consequences of treatment failures are the need to visit the GP (or Dermatologist) for a change in treatment plan, and where treatment failure leads to infection there will be treatment with antibiotics, all of which generally impacts on quality of life for the patient (plus family/carers where affected) with lost school and/or work time a common result.

Generally, given the relatively small cost associated with topical corticosteroid treatment, the balance of costs and benefits (for once-versus more frequent use) would lead to an assessment of an acceptable cost-effectiveness profile for any treatment regimen that demonstrated a meaningful difference in treatment outcome (e.g. greater number of patients classed as a meaningful treatment success). Furthermore, any difference in product costs would be largely offset by the opportunity cost of additional visits to the GP (regardless of other NHS on-costs), where treatment is regarded as a failure.

Also of note is the fact that the GSK trial aimed to demonstrate equivalence of once daily versus twice daily, and although a significant difference in favour of twice daily is reported by the authors, the trial concludes that once-daily should be the preferred treatment option, with the reduction in effectiveness being an acceptable trade-off in the context of the potential benefits of related to increased compliance associated with a once-daily treatment regimen.[46]

Figure 4.1 A simple analysis of costs and benefits in relation to the findings in the GSK study[46]

Group A: Twice-daily treatment group (fluticasone propionate ointment)

- Assume for each flare-up treatment comprises 30g product per week for 4-weeks.
- Assume 4 Flare-ups per patient per year.
- Assume all prescription costs fall on the NHS.
- Assume product cost is £4.59 per 30ml [net ingredient cost only]
- Cost per 1,000 patients = £7,344 per year
- Total number of flare-ups per 1,000 patients = 4,000 per year
- Number of flare-ups classed as treatment success (84%) = 3,360 per 1,000 patients

Group B: Once-daily treatment group (fluticasone propionate ointment)

- Assume for each flare-up treatment comprises 15g product per week for 4-weeks.
- Assume 4 Flare-ups per patient per year.
- Assume all prescription costs fall on the NHS.
- Assume product cost is £4.59 per 30ml [net ingredient cost only]
- Cost per 1,000 patients = £3,672 per year
- Total number of flare-ups per 1,000 patients = 4,000 per year
- Number of patients classed as treatment success (72%) = 2,880 per 1000 patients
- Assume no further cost associated with treatment failure.

Difference =

£3,672 in extra costs, per 1,000 patients.
480 additional flare-ups classed as treatment success, per 1,000 patients.

Cost per treatment success is: £7.65 per additional successful flare-up

Where the difference between treatment success and failure was assumed to result in a further week of treatment per patient, the above simplistic result could be related to cost per treatment free week.

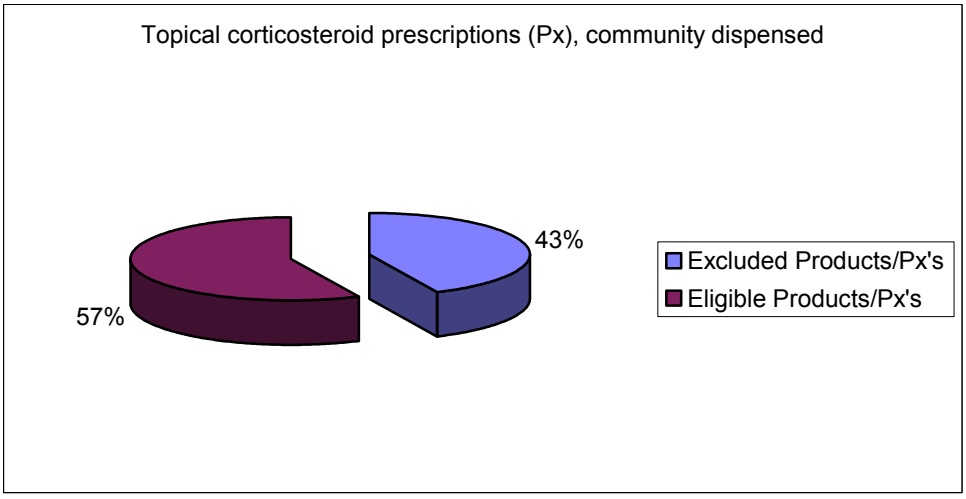
4.6 Potential cost-savings from once-daily versus more frequent application of same potency topical corticosteroids

In order to estimate potential cost-savings from a general move to once-daily application of topical corticosteroids, compared to more frequent use, it is necessary to give some consideration to current prescribing practice, and to make some assumptions surrounding the reduction in the quantity of the product (cream, ointment, etc.) used per patient.

As stated above, data from the Department of Health analysis of prescribing data offers an overview across all community dispensed prescribing of topical corticosteroids. This data highlights that in 2002 over 12.4 million prescriptions for topical corticosteroids were dispensed at an overall net ingredient cost in excess of £45 million. Over 5.3 million (43%) of these prescriptions, amounting to £23.7 million (51.9% of the total costs) were related to products that are not included in the

scope of this review (compound preparations and antimicrobial preparations), see Fig 4.2.

Figure 4.2 Topical corticosteroids (BNF Chapter 13.4) prescribed in the community in 2002, according to eligibility for inclusion in the present review of clinical and cost-effectiveness



Figures 4.3 and 4.4 below show the differences between the prescribing patterns by potency for the overall prescribing activity for topical corticosteroids and the prescribing patterns for those products eligible for inclusion in this review. The profile of these two groups of products by potency differs, with the profile for the grouping of eligible products reflecting a greater proportion of potent product prescriptions.

Figure 4.3 Proportions of prescriptions by potency for 'all' 2002 community dispensed topical corticosteroid prescriptions and for those products eligible for inclusion in the present review

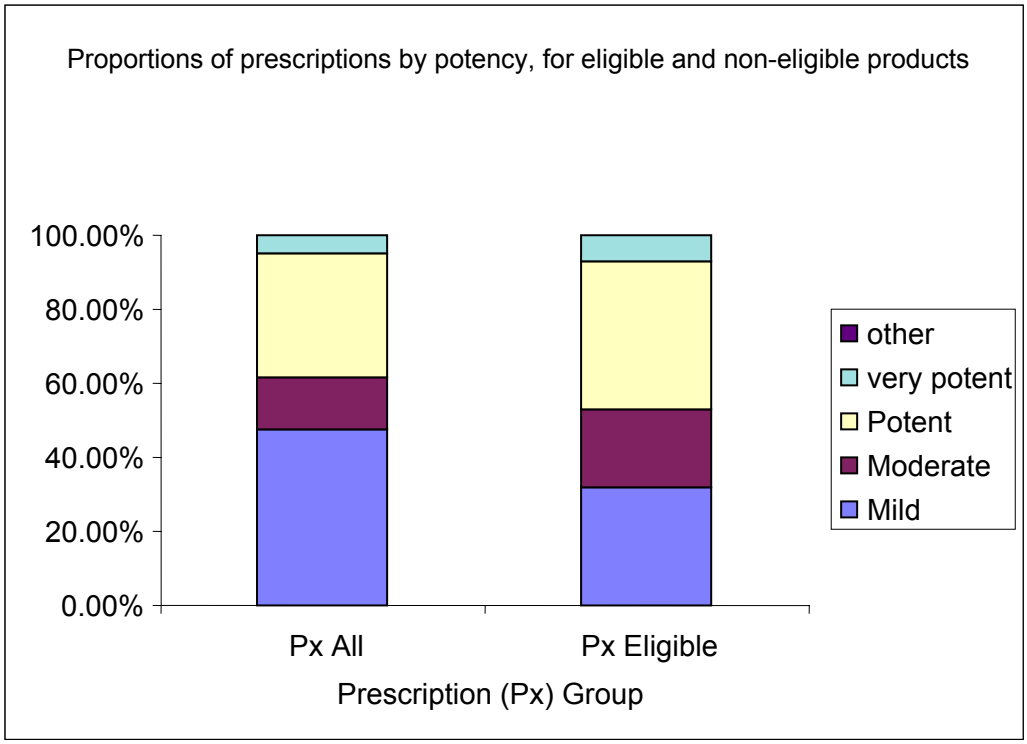
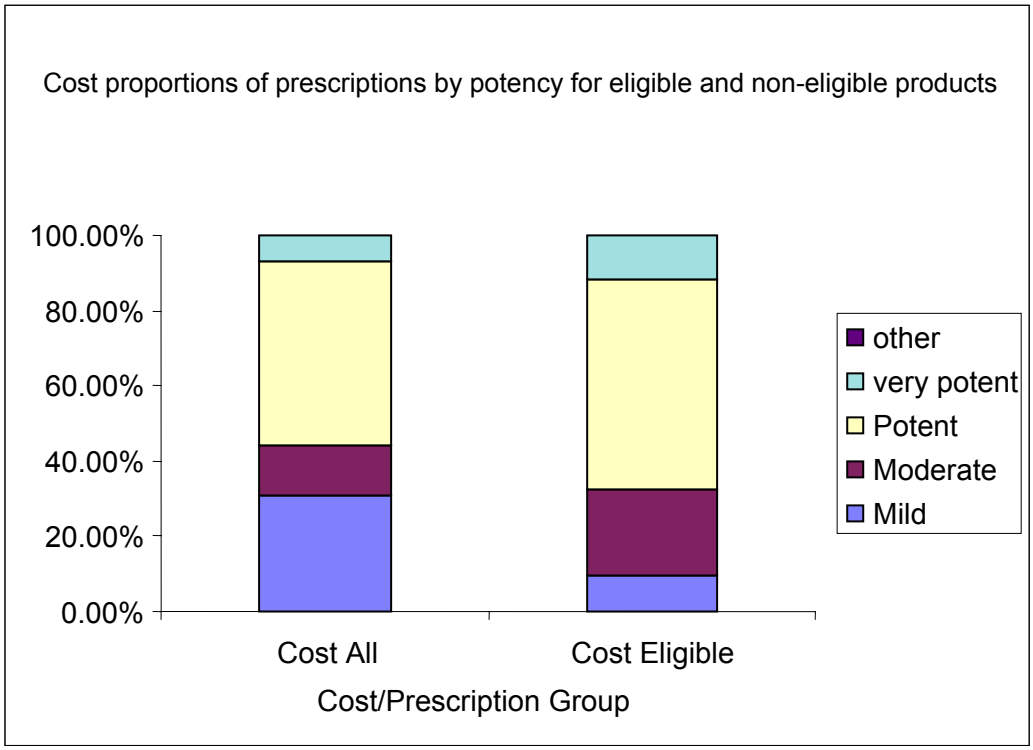


Figure 4.4 Cost proportions of prescriptions by potency for 'all' 2002 community dispensed topical corticosteroid prescriptions and for those products eligible for inclusion in the present review



From the 2002 prescribing data available, we can make some general aggregate estimates on potential cost-savings. Products eligible for inclusion in the present review comprised over 7 million prescriptions at almost £22 million. When removing the newer 'once-daily' topical corticosteroids (assuming they are prescribed once-daily at present) from this total we have figures of 6.43 prescriptions at £17.4 million. One crude assumption could be a 50% (or 25%) reduction in the cost associated with these 6.43 million prescriptions, offering an 'extreme case' scenario of NHS cost-savings at circa £8.7 million (£4.35 million with a 25% reduction), and this together with a potential saving from a change in prescribing of once-daily products to a less costly once or twice-daily product, where prescribing changes were appropriate, would seem to be the most optimistic estimate. Such an extreme case scenario assumes all prescriptions are for treatment of atopic eczema, and this is not the case.

If we assumed that only 25.8% of the £17.4 million total were for atopic eczema[5] that would offer potential cost savings of circa £2.24 million assuming a 50% reduction in the quantity of products used (£1.12million with a 25% reduction). Furthermore, the extreme case scenario assumes that all costs for prescriptions fall on the NHS and this is not the case, with many of those patients of working age being liable for payment of a prescription charge, which in many instances may be greater than the ingredient cost. However, the Prescription Cost Analysis, for the Department of Health, reports that for all community dispensed prescriptions in 2002, over 85% were dispensed as 'free' prescriptions.[35]

We are also unable to make an informed judgement over the differences in product use by treatment frequency. Furthermore, the packaging of products (usually either in 30mg/ml, 50mg/ml or 100mg/ml containers), is thought to lead to waste in many prescribed items (i.e. unused product due to the size of the packaging used in the prescription). Even if we were able to draw conclusions surrounding the relative effectiveness of once-daily use of same potency topical corticosteroids, compared to more frequent use, we really are unable to say with any certainty the magnitude of cost savings to the NHS as a result.

At a more micro level, it is possible to make some assumptions over the quantity of topical corticosteroid used per patient, and to consider potential cost savings based on estimates of patient numbers. There is insufficient data for an informed estimate on the quantity of product used on either once-daily or more frequent application of topical corticosteroids, so these assumptions are, once again, largely 'guesses'. Table 4.3 presents some scenario analyses for potential NHS cost-savings using this crude 'bottom-up' approach. Table 4.3 demonstrates that potential cost-savings per patient are relatively small, yet patient numbers for atopic eczema are large.

Assumptions on quantity used are fairly arbitrary and are based on the small amount of literature identified to inform on this issues. We assume for a twice-daily treatment regimen that where patients experience a 'flare-up' they apply an average of 30g of topical corticosteroid per week, over a 4-week period (120g per flare-up). This assumption is based on data reported in the study reported by GSK,[46] where estimates of product use were calculated as part of the trial protocol, based on the weights of the weekly returns of unused product. The study by Reidhav[62] also supports the assumption, as the authors report that once-daily treatment for each flare-up involved 65g of topical corticosteroid over a 4-week period.

In Table 4.3 we use scenarios of two and four flare-ups per year, with a once-daily treatment regimen assumed to result in (i) a 50% reduction in the amount of topical corticosteroid used and (ii) a 25% reduction. Crude analysis presents potential cost savings to the NHS assuming a patient group of 100,000, 200,000 and 300,000 people, where all patient prescription costs are assumed to be met by the NHS (net ingredient costs included only), and considerations of pack size (i.e. wasted product) have not been taken into account. Information from GSK indicates that in 2002/3 over 300,000 patients received a prescription for a plain steroid (i.e. not including compound preparations) for atopic eczema, across the UK, with approximately 137,000 of these receiving one or more prescriptions for a steroid in a potent class.[65]

Estimates of potential cost savings range from circa. £300,000 to over £3.5 million, however, the reader is reminded of the crude basis on which these estimates are made.

Table 4.3 Estimates of potential cost-savings to the NHS associated with a move to once-daily application of topical corticosteroids

Selected Products	Product/Cost per 30mg/ml	Twice -daily application, quantity of product per year (grams/ml) assuming:		Once -daily application, quantity of product per year (grams/ml) assuming:				Potential saving per patient per year			
				Option 1	Option 2	Option 3	Option 4				
		2 Flare-ups per year	4 Flare-ups per year	2 Flare-ups per year, and od at 50% quantity of bd	2 Flare-ups per year, and od at 75% quantity of bd	4 Flare-ups per year, and od at 50% the quantitiy of bd	4 Flare-ups per year, and od at 0.75% the quantitiy of bd	OPTION			
(Most commonly prescribed, see Fig. 2.3)		240	480	120	180	240	360	1	2	3	4
Very Potent: Dermovate 0.05%	£2.48	£19.84	£39.68	£9.92	£14.88	£19.84	£29.76	£9.92	£4.96	£19.84	£9.92
Potent: Betamethasone valerate 0.1% (generic)	£1.40	£11.20	£22.40	£5.60	£8.40	£11.20	£16.80	£5.60	£2.80	£11.20	£5.60
Potent: Betamethasone valerate 0.1% (proprietary)	£1.31	£10.48	£20.96	£5.24	£7.86	£10.48	£15.72	£5.24	£2.62	£10.48	£5.24
Potent: Locoid Lipocream 0.1%	£1.97	£15.76	£31.52	£7.88	£11.82	£15.76	£23.64	£7.88	£3.94	£15.76	£7.88
Moderate Potency: Eumovate 0.05%	£1.70	£13.60	£27.20	£6.80	£10.20	£13.60	£20.40	£6.80	£3.40	£13.60	£6.80
Moderate Potency: Betnovate RD 0.025%	£1.08	£8.64	£17.28	£4.32	£6.48	£8.64	£12.96	£4.32	£2.16	£8.64	£4.32
Mild Potency: Hydrocortisone 1% (generic)	£0.72	£5.76	£11.52	£2.88	£4.32	£5.76	£8.64	£2.88	£1.44	£5.76	£2.88
Mean Cost Saving per patient								£6.09	£3.05	£12.18	£6.09
Potential Patient Numbers		=	100,000	patients		Crude cost-savings (estimate):		£609,143	£304,571	£1,218,286	£609,143
		=	200,000	patients		Crude cost-savings (estimate):		£1,218,286	£609,143	£2,436,571	£1,218,286
		=	300,000	patients		Crude cost-savings (estimate):		£1,827,429	£913,714	£3,654,857	£1,827,429

4.7 Other issues

It has been suggested that once daily use of topical corticosteroids, compared to more frequent use of same potency products, would offer advantages in terms of improved compliance, reduced fear of using topical corticosteroids, quality of life benefits associated with a reduction in the use of steroids, and a reduction in the time required for daily skin care.[1] This review has not found evidence to suggest such benefits from once-daily use, however, this may be due to the limited literature, therefore a brief commentary on these issues is offered below.

Quality of Life

The evidence on the clinical effectiveness of once-daily versus more frequent use of topical corticosteroids does not offer any indication on differences in quality of life for patients according to the frequency of use of same potency products.

Generally, the literature to inform on the quality of life issues associated with atopic eczema is not extensive. Schiffner and colleagues in a recent review of the literature related to atopic eczema and quality of life, report that quality of life studies in this area are scarce.[59] However, a number of studies have shown that patients with atopic eczema have inferior quality of life (as shown by generic health status measures e.g. SF-36) compared to individuals in the general population.[22,66]

A survey in Uppsala, Sweden, has reported health status and health state utilities for patients with skin disease, including atopic eczema.[67] Lundberg and colleagues[67] report health status as measured by the SF-36 and by the Dermatology Life Quality Index (DLQI), together with the results from patients' own ratings of their current health state, using a visual analogue rating scale, the time trade-off and the standard gamble techniques for health state valuation. Table 4.4 presents findings from this study for patients with atopic eczema with or without concomitant disease (n=132), and for those patients with atopic eczema only (n=34). The most common concomitant diseases were asthma, allergy, cardiovascular disease and diabetes. Patients were interviewed whilst attending a hospital dermatology outpatient clinic, and the mean age for atopic eczema patients was 34.8 years (SD:12); 29% were male.

Table 4.4 Health State Utilities for atopic eczema reported in Lundberg et al[67]

		Health State Utilities		
Patient Group	N	Rating Scale	Time Trade-off	Standard Gamble
Atopic eczema only	34	0.77 (0.034)	0.95 (0.022)	1.00 (0.002)
Atopic eczema - total	132	0.73 (0.017)	0.93 (0.010)	0.98 (0.006)

Note: health state utilities reflect a single index measure of the value placed on health states by respondents, with 0 usually regarded as death and 1 as full health

In general, the limited literature reports that atopic eczema can have a considerable impact on quality of life.[22,27,66-68] Those suffering with atopic eczema can find that their sleep, work and social relationships are all affected by their disease,[68] impacting on everyday functioning in daily life.[66] Given that the condition affects so many in

childhood, it adds to the difficulties of parenting,[69] and can have a strong negative impact on family life.[70]

Fear associated with use of topical corticosteroids

Related to quality of life are concerns that patients may have over the use of topical corticosteroids. The literature review by Schiffner and colleagues[67] reports that it is not uncommon for patients to express anxiety about using topical corticosteroids. This anxiety is often due to the fear of side-effects, with skin atrophy (thinning) and non-specific long-term effects reported as the main reasons for fears surrounding use of topical corticosteroids.[71] Patients often have a limited understanding over the variations in strength between different preparations, and the differences associated with preparations of varying potency.[71-73] Yet, some of the side-effects that patients worry about are unlikely to occur with standard topical corticosteroid treatment, and studies have characterised the fear of these side-effects as an irrational fear, or phobia, of topical corticosteroids. This steroid phobia is thought to have been accentuated by the common misconception that topical corticosteroids are analogous to anabolic steroids or oral steroids.[71]

Anxiety and phobia associated with use of topical corticosteroids in atopic eczema is an important cause of poor patient adherence, and an important issue to consider in the management of the condition. In the above review of clinical effectiveness of once-daily versus more frequent application of topical corticosteroids (Section 3) we have found no evidence on adherence/compliance and/or anxiety by frequency.

Small experimental studies by Charman and colleagues[71] and Beattie and Lewis-Jones[73] indicate that there is confusion among patients over the products being used and the potential side-effects of treatment. The consequences of poor compliance and under-treatment of atopic eczema (e.g. sleep loss, psychological distress, family disruption) may be more harmful that the risk of side-effects from treatment.[31] Therefore, patient education over treatment and its consequences, both under-treatment and over-treatment, is a key element in the management of atopic eczema.

The trials included in this review do not answer patient concerns over skin atrophy. As skin atrophy is a rarer consequence of treatment, occurring in the longer term, the short-term nature of the included trials (up to four weeks) does not allow consideration of this important adverse effect of treatment. Indeed, RCTs may not be the best source of information on the occurrence of skin atrophy.

Compliance/Adherence

Compliance problems are common in atopic eczema. The main reasons for non-compliance with treatment advice are a poor understanding of the nature of the condition, fear of topical corticosteroids, and the time and cost associated with treatment of the atopic eczema.[72] In the above review of clinical effectiveness of once-daily versus more frequent application of topical corticosteroids (Section 3) we have found no evidence of any difference in compliance by frequency.

Non-compliance (poor adherence) is a common cause of treatment failure in atopic eczema,[73] and although compliance is regarded as a complex phenomenon involving many psychosocial factors,[74] the acceptability of prescribed products to patients is an important factor in the patients adherence to treatment advice. A recent

questionnaire-based study[73] in parents/carers of children attending a paediatrics outpatient clinic (n=100) found that the most important reason for poor adherence with topical corticosteroid therapy was the lack of knowledge about treatment. The authors suggest that to achieve optimal topical treatment for atopic eczema, patients and carers require adequate information and training in how and when to use topical therapies.

Where consideration is given to the treatment regimen, both product and product frequency, compliance should be a prominent factor. As well as information and training on the use of products, the provision of clear and simple information about the benefits and risks of topical corticosteroids is required for patient compliance and the safe use of corticosteroids.[31]

5 IMPLICATIONS FOR OTHER PARTIES

As atopic eczema often occurs in childhood the implications of treatment in many patients are at a family level, with parents and guardians taking an active role in the management of childhood atopic eczema. Where adults are affected by atopic eczema, it can also impact on social relations, both family and carers, and beyond.

The issues discussed above related to quality of life, fear associated with the use of topical corticosteroids and the related issue of compliance will all be important to parents of children with atopic eczema. As well as any potentially direct impacts on patients, indirect impacts on parents may also be important (e.g. the impact at a family level on quality of life).

From the limited literature available, it is difficult to determine the implications of a treatment change to once-daily use of topical corticosteroids from more frequent use. None of the included trials addresses these issues. The sparse literature on quality of life indicates that treatment for atopic eczema generally can have an impact on broader family and social relations. However, in the context of differing regimens for frequency of use of corticosteroids, it is not possible to infer any impact, other than by conjecture, on reductions in daily treatment times, reductions in the fears held over use of products by parents on children, and on the potential improvements in compliance, as none of these issues are covered in the literature on differing frequency of use for topical corticosteroids. An important outcome to patients is the speed of recovery (from flare-ups) and the published trials do not offer information on this issue.

The literature reporting on the costs associated with atopic eczema at a patient level emphasises that patients themselves incur substantial private expenditure on the treatment of atopic eczema. We would not expect this expenditure to differ significantly on the basis of once-daily versus more frequent use of topical corticosteroids.

6 FACTORS RELEVANT TO NHS

We are not aware of any issues arising in this report that are relevant to the NHS with respect to National Service Frameworks, health targets, or legal issues, nor do we see any implications of this report for issues of fair access or equity more broadly.

7 DISCUSSION

7.1 Clinical effectiveness

One published systematic review and ten RCTs were included in this systematic review, one comparing moderate, eight comparing potent and one comparing very potent corticosteroids. Most of the included studies were poor quality, therefore the strength of the evidence and the conclusions that can be drawn are limited.

Generally, there is a huge variation in the outcome measures used in the area of atopic eczema,[12] and in this review primary outcome measures were found to be subjective and varied between studies.

Overall assessment of response to treatment by physicians and/or patients was a common approach, but response to treatment was defined differently across studies. From the data available in the included studies, two such outcomes were considered in the present review: (i) the number of patients with at least a good response or 50% improvement, and (ii) the number of patients rated cleared or controlled, although neither of these outcomes was considered to be a good measure of treatment effect. Numbers responding to treatment tended to be similar between once daily and more frequent application of potent or very potent corticosteroids. Although some statistically significant differences favouring more frequent application were identified, these were inconsistent between outcome assessors, depending on whether they were assessed by the physician or patient, and varied according to the outcome selected for analysis. Number responding to treatment was not reported by the study comparing moderate corticosteroids.

When considering severity of signs and symptoms, two studies favoured once-daily application of mometasone furorate when compared with twice daily application of a different active compound, but again results were inconsistent between symptoms, and a third study found no statistically significant differences. These studies were of poor quality. No RCTs comparing once-daily versus twice daily application of mometasone furoate were identified, although it is of note that that this product (Elocon®) is marketed as a once-daily product. Twice daily application of fluticasone propionate ointment was found to significantly improve symptoms at the last visit attended only by one good quality study, but other studies either found no significant differences or an improvement in one symptom but not others with twice-daily treatment. However, none of the studies reported the use of validated severity scales and the level of detail in the reporting of disease severity is disappointing. The literature on the assessment of disease severity in atopic eczema emphasises that there are a large number of severity scales available for use in trials, most of which are inadequately tested, and that in general the clinical relevance of a change in severity score is not easily understood.[9,12]

No RCTs or CCTs of mild potency corticosteroids were included in the review. One small CCT was identified that evaluated the effectiveness of an emollient as an adjunct to corticosteroid treatment for mild to moderate atopic dermatitis in children, comparing once and twice daily application of a mild corticosteroid.[75] However, this

study was excluded as the emollient was used in the once-daily group only and the treatment groups were not considered to be comparable. The study found no significant differences in rates of improvement or reductions in mean lesion size, and inclusion of the CCT would not have changed the conclusions of this systematic review.

Quality of life outcomes and/or measures of patient preference were not reported by any of the included trials. It is generally thought that a reduction in the use of topical steroids will offer patient benefits and greater convenience for patients, but no information has been reported on these issues. Other potentially useful outcomes, such as speed of recovery, were not reported.

The extent of reporting of adverse effects varied between studies. The number and severity of adverse events tended to be similar between once-daily and more frequent application, but data are limited. None of the studies reported data on late onset or long-term adverse events, such as skin atrophy. It is the possible occurrence of these long-term effects that is of concern to some patients, leading to issues of fear of use and non-compliance.

7.2 Cost-effectiveness

No literature has been identified to inform on the cost-effectiveness of once-daily versus more frequent use of topical corticosteroids. Based on the evidence available to inform on the clinical effectiveness of once-daily versus more frequent use of same potency products, there is no basis upon which to favour either option, as outcomes are very similar. For the purposes of economic analysis, outcomes are therefore assumed to be similar and from an efficiency point of view the decision on frequency becomes one of 'cost-minimisation', with the least cost option being the most cost-effective.

The wide range of topical corticosteroid products available and the varied price levels of products creates a situation where a judgement on the least cost alternative can only be based on a comparison of two particular prescribing options i.e. where products are known and specified. We have provided a cost-minimisation judgement against nine of the ten included clinical trials included in this review, with once-daily being favoured on six occasions and twice-daily use being favoured on three occasions. Where there is an extra benefit associated with twice-daily use of a product, compared to once-daily, and this comes at an extra cost, a judgment is required on the cost-effectiveness of the additional expenditure; this is the case in the trial reported by GSK.[46] In this instance we have concluded that, where a treatment success (i.e. successfully treated flare-up) is of value to the NHS (regardless of the magnitude of that value) the additional expenditure associated with twice-daily use of topical corticosteroids will be regarded as a cost-effective use of resources. However, at the present time there is little information in the literature to help inform on the consequences of a patient being classed as a non-responder to treatment.

The availability of specifically marketed once-daily topical corticosteroids, which are priced at a much higher level than other generic and proprietary products, makes a once-daily regimen more costly when these products are used. Therefore, it is not

possible to make a general statement that once-daily treatment is less costly than more frequent use of topical corticosteroids. Furthermore, limited information is available on the quantity of product used by frequency of use, and prescribing information is not readily available to advise on the prescribing patterns amongst patients with atopic eczema, therefore it is not possible, with any certainty, to estimate specific cost impacts from changes in prescribing behaviour.

However, where a prescribing practice of twice daily use of topical corticosteroids can appropriately be altered to once-daily use of same potency products which are at the same price level, some cost-saving can be expected. Such cost-savings will be relatively small at the patient level, and issues related to pack size and product waste, can easily erode any potential cost-saving. However, given the large patient group there may be opportunities for significant savings to the NHS on products prescribed. In some illustrative estimates of cost-savings we report potential savings of between £300,000 and £3.5million, where savings in the quantity of topical corticosteroid used are assumed across a patient group of between 100,000 and 300,000 persons. However, these estimates are based on a number of convenient assumptions. Many patients receive only one prescription per year, and pack size will determine the quantity dispensed. Furthermore, where patients are liable to pay a prescription charge the impact on the NHS of savings in prescribing costs is not clear.

7.3 Strengths and limitations of the review

The systematic review has the following strengths:

- The systematic review is independent of any vested interests.
- The systematic review brings together the evidence for the effectiveness of once daily versus more frequent application of same potency corticosteroids for atopic eczema applying consistent methods of critical appraisal.
- The review was guided by the principles for undertaking systematic reviews. Before undertaking the review the methods were set out in research protocol (Appendix 1), which was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods used to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.

In contrast, there were certain limitations placed upon the review:

- Owing to time constraints placed upon the review there was a lack of follow-up with authors of studies to clarify methodological details and results from the primary studies.
- The review was limited to published and unpublished systematic reviews of RCTs, as well as reports of RCTs (and CCTs if appropriate). Abstracts and conference proceedings were excluded from the review as these usually fail to provide adequate details of the methods of the study and their results. However, full reports of three identified abstracts were provided by industry, and no further abstracts were identified by the searches.
- Inclusion was limited to English language due to time constraints.

- Included trials are of a short-term nature (up to 4-weeks follow up) and this does not inform on the long-term consequences of treatment for atopic eczema.
- Economic analysis has been severely restricted due to the absence of literature to inform on the relative cost-effectiveness of different treatment options (i.e. frequency of use). An assessment of the cost implications of moving to once-daily use of topical corticosteroids has been limited by the absence of data on quantity of product used and prescribing practices.

Other issues

- This systematic review updates and expands on a previous systematic review,[1] with broader eligibility criteria allowing the inclusion of additional studies (i.e. comparisons of different products of the same potency) in the present review.
- The results of this systematic review appear to concur with findings of the previous systematic review,[1] despite the inclusion of additional studies.
- Within the review, studies were considered according to the potency of the corticosteroids they assessed. Most studies compared once-daily versus more frequent application of the same product, while three RCTs concerned with potent corticosteroids compared different products of the same potency. There was insufficient data to consider these separately.
- Results were based on data from available patients rather than numbers randomised, as it was assumed that missing data could be due to either exacerbation or clearance or eczema. However, numbers and reasons for withdrawals and dropouts are clearly noted on the data extraction forms in the Appendices.
- Most of the trials included patients with moderate to severe atopic eczema. This group of patients are not representative of the majority of patients with atopic eczema, who have mild symptoms.
- Outcome measures used in the included RCTs displayed clinical/methodological heterogeneity, with subjective measures of treatment outcome. Inadequate blinding of patients or outcomes assessors in six of the ten RCTs is likely to have introduced bias. Severity scales used by the studies were not shown to be valid, and their clinical meaning is not clear. Pooling of the outcome data was not appropriate as the studies were considered to be too dissimilar, for example differences in product and comparators used, patient group, outcomes and method of assessing outcomes, and duration of follow-up.
- Due to the short duration of the studies (up to four weeks), no data on long-term adverse events and consequences of treatment were available. The fluctuating nature of the disease is also unaccounted for by these relatively short trials. Experts have indicated that the trials do not inform on 'real life' experiences.

7.4 Need for further research

Further research is needed on the clinical effectiveness of a broader range of same potency topical corticosteroids by frequency of use. Trials involving mild, moderate and very potent products are very limited at the moment and further information is needed on the relative merits of treatment frequency in these potency groups (e.g. comparisons on differing frequency of hydrocortisone, betamethasone valerate,

clobetasol propionate). Within the potent products, the trial literature is dominated by comparisons of differing frequency of use of fluticasone propionate (four of the eight trials included), and comparisons of mometasone furoate with more traditional twice-daily treatment options (three of the eight trials included). Trials to establish whether once-daily use of the older/cheaper generic products are equivalent to more frequent use would be helpful.

In the context of the clinical question of frequency of use of topical corticosteroids, further research is required to establish the impact on quality of life, compliance, and phobia of topical steroids, of once-daily use versus more frequent use of products. Long term follow-up is required to assess adverse effects such as skin atrophy.

8 CONCLUSIONS

The literature to inform on the clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids is limited. The RCTs included in this review are predominantly for potent topical corticosteroids, and there is an absence of trial data on mild potency products, therefore the generalisability of findings is limited.

From the available evidence, the clinical effectiveness of once-daily and twice daily use of same potency topical corticosteroids appears similar; although point estimates indicating a small difference in favour of more frequent use cannot be ignored. Given the apparent similarities in clinical effectiveness, the cost-effectiveness of the treatment options is based on the selection of the least cost alternative, and this is driven by the relativities in product prices, as well as the frequency of treatment, therefore there is no basis upon which to favour either once-daily or twice-daily application of topical corticosteroids, at a general level.

There are no published empirical data to assess the patterns of prescribing with respect to frequency of application, but it is generally accepted that a twice-daily regimen is the most widespread approach to the use of topical corticosteroids in atopic eczema. A move to once-daily application of topical corticosteroids could result in cost savings on the NHS prescribing budget, but any difference at a patient level would be very small (circa £2-£10 for most patients), and there are a number of factors that could erode any such savings, we are therefore unable to estimate potential NHS cost savings with any confidence. Indeed, given the availability of relatively expensive topical corticosteroids which are specifically marketed, and licensed, for once-daily use, a general move to once-daily use could result in significant additional costs falling on the NHS.

An important issues for patients is the fear of long term side effects, unfortunately the literature reviewed has not informed on this issue, with trials usually taking a short-term perspective (up to four weeks).

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Previous publications (inside back cover)
List of unit's publications to date (most recent ones first, number determined by space).

Appendix 1 Outline of studies examining the prevalence and incidence of atopic eczema in the UK

Authors	Setting	Design	Subjects	Prevalence	Cumulative incidence/prevalence
Taylor et al 1984[76]	3 cohort studies in Britain. Included all children born within a (different) specified 7 day period in 1946, 1958 and 1970.	Structured interview in home by health visitor (parental recall)	4624 children aged 6 (1946 cohort) 14498 children aged 7, (1958 cohort) 12982 children aged 5 (1970 cohort)		Cumulative incidence rates 5.1% (1946 cohort) 7.3% (1958 cohort) 12.2% (1970 cohort)
Ninan and Russel 1992[77]	Aberdeen, Scotland	Questionnaires based on parental recall	2510 children aged 8-13 in 1964 (91.5% response rate) 3403 children aged 8-13 in 1989 (85% response rate)	5.3% in 1964 12% in 1989	
Kay et al 1994[14]	All children aged 3 to 11 years were identified from a socially and ethnically mixed General practice in England	Structured interviews carried out with parent(s) and where possible with child. Medical notes also consulted	1077 children aged 3-11 years from an identified (from GP register) population of 1104 (97.6% response rate)	10-14% in boys aged 3-11 15% in girls aged 3-5 8% in girls aged 9-11	20% in boys (12% in last year) 19% in girls (11% in last year) (up to age 11 inclusive)
Williams et al 1994[18]	National Child Development Study (England, Wales, Scotland) All children born from 3-9 March 1958 inclusive	Comparison of structured questionnaire (parental reports) and visible eczema determined by medical officers during physical examination	8279 children born 3-9 March 1958. Followed up at ages 7,11 and 16 (87% response rate)	Prevalence according to medical officers examination at ages 7, 11 and 16 according to social class: (I) 6.7% (95% CI 4.6,9.4) (II) 6.8% (95% CI 5.5,8.4) (IIINM) 5.8% (95% CI 4.3,7.6) (IIIM) 5.3% (95% CI 4.6,6.1) (IV) 3.7% (95% CI 2.8,4.8) (V) 5.4% (95% CI 3.5,7.9) (p<0.001)	Cumulative incidence (by age 16) according to social class: (I) 13.1% (95% CI 10.0,16.2) (II) 12.4% (95% CI 10.5, 14.2) (IIINM) 12.5% (95% CI 10.4,14.8) (IIIM) 11.1% (95% CI 10.1,12.1) (IV) 8.6% (95% CI 7.2,10.2) (V) 8.8% (95% CI 6.4,11.9) (p<0.001)
Williams et al 1995[19]	London - 3 junior schools	Cross sectional prevalence survey. Presence of atopic dermatitis determined by (1) parental recall (2) dermatologists examination (3) examination by independent observer	693 junior school children	Prevalence (assessed by dermatologist) 16.3% in black Caribbean children, 8.7% in white children (increased risk also present when assessed by parental recall and independent observer)	
Neame et al 1995[17]	(1) Obligatory routine surveillance clinics required to attend at 6 weeks and 8, 18 and 42 months. All parents asked at 18 and 42 month assessment over specified time period. (2) Social services day nurseries in Leicester	Comparison of: (1) parental recall (2) GP records (3) examination by trained observer for estimation of prevalence	322 children aged 1-4 255 from surveillance clinics (98.5% response rate) 67 from day nurseries (38.1% response rate)	(3) examination by trained observer 14% (95% CI 10,18) (point prevalence)	(1) parental recall 27% (95% CI 22,32) (cumulative incidence - "ever had") (2) GP records 32% (95% CI 28,36) (cumulative incidence - "ever had")

Authors	Setting	Design	Subjects	Prevalence	Cumulative incidence/prevalence
Herd et al 1995[16]	Scotland – semi-rural community setting.	Records from one general practice. Access to infants via direct contact made to every family on GP register with a child aged < 2 years. Plus cluster sample of registered patients.	GP of 9,786 patients. Sampled 2,365 (24%) of patients.	One-year period prevalence (SE), by age(yrs): <2 9.8% (0.5) 2-11 8.1% (1.5) 12-15 2.2% (0.8) 16-24 2.1% (0.5) 25-40 2.0% (0.7) Over 40 0.2% (0.15) Overall 1-yr period prevalence for age-standardised (Scottish population) was 2.3%	
Butland et al 1997[78]	England, Scotland and Wales. National Child Development Study (1958 cohort). All children born from 3-9 March inclusive. British cohort Study (1970 cohort). All children born from 5-11 April inclusive	Prospective birth cohort studies. Structured interviews	11195 (62%) at age 16 from 1958 cohort. 9387 (54%) at age 16 from 1970 cohort	Prevalence 3.1% (1958) cohort) 6.4% (1970 cohort) (prevalence ratio 2.04 (95% CI 1.79, 2.32)	
Emerson et al 1998[20]	Four urban and semi-urban general practices in Nottingham, UK	Cross-sectional survey of all children aged 1-5 years listed on the 4 GP registers. Questionnaire, followed by interview and examination.	Questionnaire responses from 1523 (86.5%) of 1760 patients.	12-month period prevalence of atopic eczema was: 16.5% (95% CI:14.7-18.2%) 22% in children aged 1-2 yrs, 19% in 3-4 yrs 15% in 4-5 yrs	

Source: Sections of this table are reproduced from Fennessy and colleagues 2000[13]

Appendix 2 Methods from research protocol

Full title of research question

The clinical and cost-effectiveness of once daily versus more frequent use of same potency topical corticosteroids for people with atopic eczema.

Clarification of research question and scope

- The terms atopic eczema and atopic dermatitis are used synonymously. In this review we will use the term atopic eczema (unless citing directly from the published literature), which is more commonly used in the UK.
- Atopic eczema is a multi dimensional phenomenon, and there are variations in the criteria used for diagnosis of the condition. This review will employ the diagnostic criteria set out by Williams et al (1994), for general guidance. However, as these criteria have only recently been applied in trials, diagnostic criteria reported by included studies will be described.
- For the definition of disease severity (i.e. subsets of atopic eczema) there are a number of scoring systems which have been used to categorise disease into mild, moderate or severe disease (e.g. SCORAD). None of these scoring systems are accepted as a 'gold standard' and there is uncertainty and debate over their use. Where studies which have employed severity scoring systems are referenced in this review the scoring system will be stated, and guidance given as to the nature of the scoring system.
- Topical corticosteroids are the mainstay of treatment for atopic eczema. The BNF (March, 2003) lists, under topical corticosteroids for eczema (section 13.4), more than 50 products (comprising over 80 different preparations/formulations), from over 20 manufacturers. Some products have added ingredients (e.g. salicylic acid or antimicrobials), and there are a number of products which are available over-the-counter (OTC).
- This review will include topical corticosteroids reported in section 13.4 of the BNF (March, 2003), excluding compound preparations (i.e. antimicrobials, preparations containing added ingredients).
- Where included studies report on the clinical and cost-effectiveness of OTC products, findings will be presented separately; such products do not incur NHS expenditure, and their use is not generally under the direct guidance of a clinician.
- Topical corticosteroids are classified according to their potency, or strength, and are mild, moderate, potent or very potent. In this review we will use the classification of potency for each preparation as listed in the BNF (45).
- Most products are recommended for use 1-2 times daily (BNF), however, the frequency of application seems to have developed empirically (Lagos & Maibach, 1998) and twice daily application is the most common approach. This review will compare the use of topical corticosteroids once daily with more frequent use of products of the same potency.
- Early appraisal of some literature in this area indicates that the evidence-base, from randomised controlled trials/controlled clinical trials, comparing topical corticosteroids of the same potency is concentrated on products that are either potent or very potent (Hoare et al, 2001), whilst a large proportion of the patient group (60-70%) are expected to be treated with mild or moderate potency products.

Report methods

- The review will be undertaken as exhaustively as time allows following the general principles outlined in NHS CRD Report 4 (2nd Edition).
- This research protocol may be updated as the research programme progresses. Any changes in the protocol will be notified to the NCCHTA and NICE.

Search strategy

- Electronic databases that will be searched include: Cochrane Systematic Reviews Database; Cochrane Controlled Trials Register; NHS CRD (University of York) databases (including DARE, NHS EED and HTA database); Medline (Ovid); EMBASE; National Research Register; Science Citation Index; BIOSIS; EconLit; MRC Trials database; Early Warning System; and Current Controlled Trials. These will be searched for the periods covered by the databases, and will be limited to English language.
- Bibliographies of included studies and other related papers will be assessed for relevant studies.
- Experts will be contacted for advice and peer review, and to identify additional published and unpublished references and any ongoing studies.
- Industry submissions to NICE will be checked for the completeness of ascertainment of our searches.

Inclusion and exclusion criteria

Intervention

- Studies comparing once daily versus more frequent application of topical corticosteroids of the same potency will be included. Studies comparing corticosteroids with different potencies will be excluded. The review will include topical corticosteroids reported in section 13.4 of the BNF (March, 2003), excluding compound preparations (i.e. antimicrobials, preparations containing added ingredients).

Participants

- The review will include children and adults with atopic eczema (atopic dermatitis). Patients with other types of eczema such as contact dermatitis, seborrhoeic eczema, varicose eczema and discoid eczema will be excluded from the review. The review will use as a general guide the diagnostic criteria for atopic eczema set out by Williams et al (1994). Where uncertainty exists over the classification of disease in published studies, a clinical advisor will determine the appropriateness of the inclusion of the study in the review.

Design

- Systematic reviews and meta-analyses of RCTs as well as individual RCTs will be included. The review will consider products by potency grouping and where no RCT evidence is identified for a potency group the inclusion of controlled clinical trials (with concurrent controls) will be considered. Reports published only as abstracts and non-English language studies will be excluded. Published abstracts that would otherwise meet the inclusion criteria will be listed for information.

Outcomes

- Studies will be included if they report one or more of the following as primary outcomes; overall response to treatment (e.g. using severity scores), impact on

clinical features of the condition (e.g. erythema, induration, pruritus, excoriation, thickening), relapse/flare-up rate, side-effects, compliance, tolerability, patient preference measures, and quality of life.

Inclusion and exclusion criteria will be applied by one reviewer and checked by a second. Any disagreement will be resolved through discussion.

Inclusion criteria for papers on cost-effectiveness

- All studies that present findings on the cost-effectiveness of once daily versus more frequent application of topical corticosteroids of the same potency will be included. Studies comparing products with other active ingredients (e.g. antimicrobials) will be excluded.

Data extraction strategy

- Data extraction will be undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved though discussion.

Quality assessment strategy

- The quality of included systematic reviews will be assessed using criteria recommended by NHS CRD (University of York) (Appendix 4).
- Quality assessment of RCTs will be undertaken in accordance with chapter II.5 of CRD Report 4 (2nd Edition) (Appendix 5).
- Quality criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved though discussion.
- The quality of economic evaluations will be assessed for their internal validity (i.e. methods used), and external validity (i.e. the generalisability of the economic study to the population of interest), using the format recommended and applied in the CRD NHS Economic Evaluation Database (see details on: http://www.york.ac.uk/inst/crd/index.html).

Methods of analysis/synthesis

- The clinical effectiveness will be synthesised through a narrative review with tabulation of results of included studies.
- Data will be combined statistically if of sufficient quantity, quality and if sufficiently similar by meta-analysis using Review Manager Software.

Methods for estimating qualify of life, costs and cost-effectiveness and/or cost/QALY

- The costs and effects associated with once daily versus more frequent application of topical corticosteroids will be considered as part of this review.
- Published cost-effectiveness studies will be reviewed in detail, comprising a narrative review with a tabulation of results where appropriate. Cost-effectiveness studies will be identified as part of the search strategy documented above. Initial indications are that there are very few cost-effectiveness studies reporting on the comparison of topical corticosteroids (i.e. frequency of application) in atopic eczema.
- A cost-analysis will be undertaken to inform on the resource use and cost-consequences associated with the comparison of once daily versus more frequent

application of products of the same potency. Costs will be obtained from the published literature, NHS sources and industry submissions where applicable. Costs to be considered will include the costs associated with treatment, and those NHS costs related to a difference in patient experience with respect to the comparison of treatment regimes (e.g. treatment of adverse events where a significant difference is identified). The perspective of the economic analysis will be that of the NHS and Personal Social Services Decision-Maker.

- Cost-effectiveness analysis will compare once daily versus more frequent application of topical corticosteroids (same potency), on the basis of the primary outcome measures specified above (e.g. response to treatment, relapse rate, impact on clinical features), and additional quality of life outcomes where documented as part of the literature review. Where clinical effect/outcomes are the same for both treatment regimes, the analysis may be limited to a cost-minimisation analysis.
- Where data are available an economic model will be constructed by SHTAC, using best available evidence, to synthesise the evidence on effectiveness of treatments and their associated costs, to determine cost-effectiveness in a UK setting. Where cost-effectiveness models have been reported in the literature in the area of atopic eczema (i.e. topical corticosteroids versus tacrolimus ointment), summary cost-effectiveness results have been presented as cost per disease-controlled-day (e.g. Ellis et al, 2003). However, where possible cost-utility estimates in terms of cost per QALY will be pursued and presented.
- The robustness of the results to the assumptions made in the cost analysis and the cost-effectiveness model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

A. **Handling the company submission(s)**

- SHTAC methods for reviewing the literature on cost-effectiveness/cost-utility, and for the cost-effectiveness analysis to be undertaken, are stated above.
- Industry submissions will be checked for additional studies that meet the SHTAC inclusion criteria, for data on costs, and for data on the current use of topical corticosteroids for atopic eczema in England and Wales.
- Results of cost-effectiveness analyses from industry will be compared with the SHTAC analysis, but this will not be a line by line critique of sponsors' models.
- Any ‘commercial in confidence’ data taken from the industry submissions will be clearly marked (underlined) in the report submitted to NICE. A separate version with any such data removed will also be submitted.

Appendix 3 Sources of information, search terms and flow chart of study identification

The databases were searched for published studies, and recently completed and ongoing research. All searches were limited to English language only.

Clinical effectiveness searches

The following strategy was used to search Medline 1966 to October 2003, and was adapted as appropriate for the remaining databases listed below.

1 Skin Diseases, Eczematous/
2 exp Eczema/
3 Dermatitis/
4 Dermatitis, Atopic/
5 eczema.ti,ab.
6 excema.ti,ab.
7 1 or 2 or 3 or 4 or 5 or 6
8 dermatitis.ti,ab.
9 7 or 8
10 hydrocortisone.ti,ab,rw.
11 Hydrocortisone, Topical/
12 Hydrocortisone/
13 beclamethasone.ti,ab.
14 beclomethasone.ti,ab,rw.
15 Beclomethasone/
16 exp Betamethasone/
17 betamethasone.ti,ab,rw.
18 Clobetasol/
19 clobetasol.ti,ab,rw.
20 clobetasone.ti,ab,rw.
21 Desoximetasone/
22 desoximetasone.ti,ab,rw.
23 Diflucortolone/
24 diflucortolone.ti,ab,rw.
25 Fluocinolone Acetonide/
26 fluocinolone.ti,ab,rw.
27 Fluocinonide/
28 fluocinonide.ti,ab,rw.
29 Fluocortolone/
30 fluocortolone.ti,ab,rw.
31 fluticasone.ti,ab,rw.
32 Halcinonide/
33 halcinonide.ti,ab,rw.
34 mometasone.ti,ab,rw.
35 Triamcinolone Acetonide/
36 triamcinolone.ti,ab,rw.
37 alclometasone.ti,ab,rw.
38 dioderm.ti,ab.
39 efcortelan.ti,ab.
40 mildison.ti,ab.
41 locoid.ti,ab.
42 modrasone.ti,ab.
43 propaderm.ti,ab.
44 betacap.ti,ab.
45 betnovate$.ti,ab.
46 bettamousse.ti,ab.
47 diprosone.ti,ab.
48 dermovate.ti,ab.
49 eumovate.ti,ab.
50 stiedex.ti,ab.
51 nerisone.ti,ab.
52 haelan.ti,ab.
53 synalar.ti,ab.
54 metosyn.ti,ab.
55 ultralanum.ti,ab.
56 cutivate.ti,ab.
57 halciderm.ti,ab.
58 elocon.ti,ab.
59 hydrocal.ti,ab.
60 calacort.ti,ab.
61 dayleve.ti,ab.
62 notisone.ti,ab.
63 corteze.ti,ab.
64 hydrocortisyl.ti,ab.
65 hydrocortistab.ti,ab.
66 dermacort.ti,ab.
67 hc45.ti,ab.
68 lanacort.ti,ab.
69 zenoxone.ti,ab.
70 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or

49 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 64 or 67
71 steroid$.ti,ab.
72 corticosteroid$.ti,ab,hw,rw.
73 glucocorticosteroid$.ti,ab,hw,rw.
74 glucocorticoid$.ti,ab,hw,rw.
75 Anti-Inflammatory Agents, Steroidal/
76 Adrenal Cortex Hormones/
77 71 or 72 or 73 or 74 or 75 or 76
78 70 or 77
79 7 and 78
80 9 and 78
81 limit 80 to human
82 limit 81 to english language

Cost effectiveness, quality of life and patient compliance searches

The following strategy was used to search Medline 1966 to October 2003, and was adapted as appropriate for the remaining databases listed below.

1 exp "Costs and Cost Analysis"/
2 ECONOMICS/
3 exp Economics, Hospital/
4 exp Economics, Medical/
5 exp Economics, Nursing/
6 exp Economics, Pharmaceutical/
7 exp "Fees and Charges"/
8 exp BUDGETS/
9 budget$.ti,ab.
10 cost$.ti.
11 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
12 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti.
13 (price$ or pricing$).ti,ab.
14 (financial or finance or finances or financed).ti,ab.
15 (fee or fees).ti,ab.
16 DERMATITIS/ec [Economics]
17 Dermatitis, Atopic/ec [Economics]
18 Eczema/ec [Economics]
19 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 letter.pt.
21 editorial.pt.
22 comment.pt.
23 20 or 21 or 22
24 19 not 23
25 Skin Diseases, Eczematous/
26 exp Eczema/
27 Dermatitis/
28 Dermatitis, Atopic/
29 eczema.ti,ab.
30 excema.ti,ab.
31 25 or 26 or 27 or 28 or 29 or 30
32 dermatitis.ti,ab.
33 31 or 32
34 24 and 31
35 limit 34 to human
36 limit 35 to english language

Additional searching
Bibliographies: All references of articles for which full papers were retrieved were checked to ensure that no eligible studies had been missed.

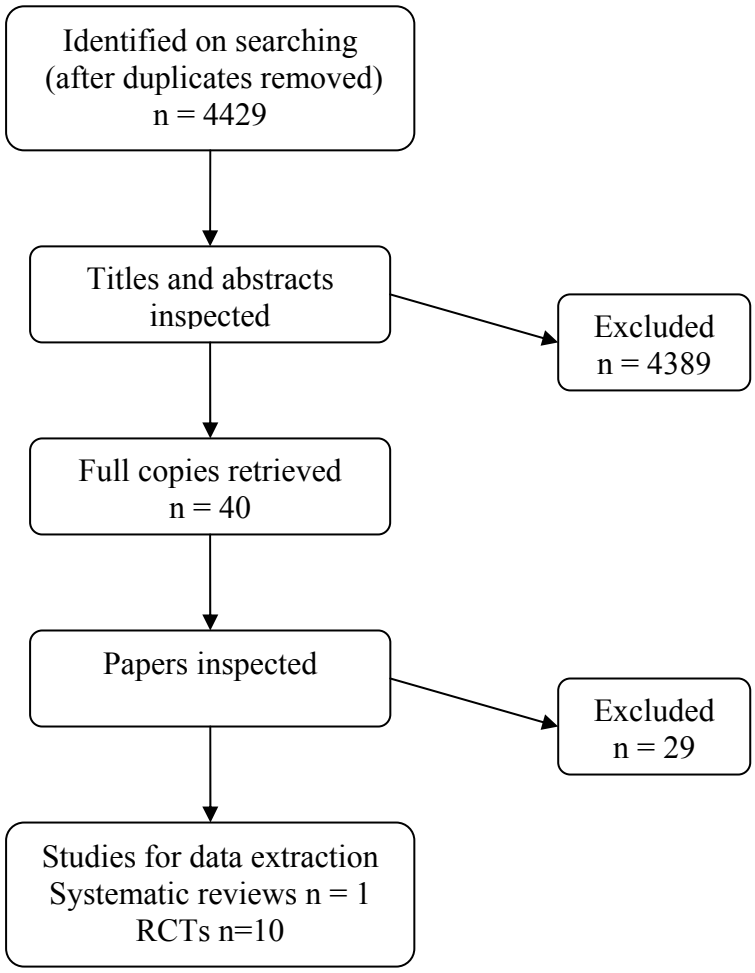
Industry submissions to NICE were examined for any further studies that met the inclusion criteria.

The Cochrane Skin Group's Specialized Skin Register was searched.

Table 1 Additional databases searched

	Date or issue of databases searched	
	Clinical effectiveness	**Cost effectiveness and QoL**
Cochrane Library	Issue 3, 2003	Issue 3, 2003
Embase	1980 – October 2003	1980 – October 2003
Science Citation Index	1981 – October 2003	1981 – October 2003
BIOSIS	1985 – October 2003	1985 – October 2003
DARE	1995 – October 2003	1995 – October 2003
HTA Database	1998 – October 2003	1998 – October 2003
National Research Register	2000 – October 2003	2000 – October 2003
Early Warning System	June 2003	
Current Controlled Trials	October 2003	
Clinical Trials.gov	October 2003	
MRC Trials database	October 2003	
ISI Web of Science Proceedings	1990 – October 2003	1990 – October 2003
CSA Conference Papers Index	1982 – October 2003	
Zetoc	1993 – October 2003	
NHS EED		1995 – October 2003
EconLit		1969 – October 2003

Figure 1 Flowchart of identification of studies for inclusion in the systematic review of clinical effectiveness



Appendix 4 Quality assessment criteria for systematic reviews

Quality Assessment for Systematic Reviews (NHS CRD)	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	
2. Is there evidence of a substantial effort to search for all relevant research?	
3. Is the validity of included studies adequately assessed?	
4. Is sufficient detail of the individual studies presented?	
5. Are the primary studies summarised appropriately?	

1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?
A good review should focus on a well-defined question, which ideally will refer to the inclusion / exclusion criteria by which decisions are made on whether to include or exclude primary studies.

The criteria should relate to the four components of study design, participants, health-care intervention or organisation, and outcomes of interest.
In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?
This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided.

The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?
Authors should have taken account of study design and quality, either by restricting inclusion criteria, or systematic assessment of study quality. For example, if inclusion criteria have been restricted to 'double-blind randomised controlled trials, with at least 200 participants' then the need for quality assessment is not so crucial as when authors have less stringent inclusion criteria and/or include less rigorous study designs.

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomisation, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?
The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), efficacious results and side-effects (adverse events).

5. Are the primary studies summarised appropriately?
The authors should attempt to synthesise the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews which incorporate a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

For some reviews, it may be inappropriate to include a meta-analysis, and therefore a narrative synthesis of studies should be presented. It is not usual to include a formal assessment of heterogeneity or to introduce weighting in such syntheses, so a discussion relating to the main differences between studies, and the better sources of evidence, should be highlighted.

Appendix 5 Quality assessment criteria for randomised controlled trials

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	

Appendix 6 Summary of data from the published systematic review

Reference	Methods
Study Ref: [1] Author: Hoare et al Year: 2000 Country: UK Study design: Systematic review Funding: NHS R&D HTA Programme	Aim/Objective: To produce an up-to-date coverage 'map' of RCTs of treatments of atopic eczema. To assist in making treatment recommendations by summarising the available RCT evidence using qualitative and quantitative methods. Search strategy: electronic searching of Medline, Embase, Cochrane Controlled Clinical Trials Register, Cochrane Skin Group specialised register of trials, handsearching of atopic eczema conference proceedings, follow-up of references in retrieved articles, contact with leading researchers and requests to relevant pharmaceutical companies. Inclusion criteria. *Interventions:* Therapeutic agents used in the prevention and treatment of atopic eczema. For section comparing frequency of application, studies comparing once daily versus more frequent use of the same topical corticosteroids were included (but not different corticosteroids of the same potency), but this is not clearly stated in the methods. *Participants:* People of any age with a physician's diagnosis of atopic eczema. *Outcome measures:* Changes in patient-rated symptoms of atopic eczema, global severity rated by patients or physician, published or modified composite rating scales, adverse events, and changes in individual signs of atopic eczema as assessed by a physician. *Study design:* RCTs. Quality criteria: - a description of method and concealment of allocation of randomisation. - the degree to which assessors and participants were blinded to the study interventions. - whether all those originally randomised were included in the final main analysis. Application of methods: Data extraction was conducted by two observers with discrepancies resolved by discussion. Methods for analysis Results presented in a contingency table and a figure of estimated risk differences (RD). Response rates were compared (defined as a the proportion of patients who obtained at least a good response with treatment), but estimates were not pooled due to disparate study designs.

Results

(Note: data extracted from section comparing once daily versus more frequent use of the same topical corticosteroids only).

Quantity and quality of included studies:
3 studies involving the same active compound were included (Bleehen et al. 1995; Koopmans et al. 1995; Sudilovsky et al. 1981).
A summary table of methods and results of trials comparing once versus twice daily application of different topical corticosteroids (trials involving different active compounds) included in appendices, but no discussion in text.

Method and concealment of randomisation was unclear in all three studies.
Two studies were described as double-blind, one study was probably investigator blinded but unclear.
ITT analysis was carried out in just one study.

Treatment effect
In none of the studies were more frequent applications superior to once daily application. While point estimates suggest that a small difference in favour of more frequent application cannot be excluded, it is doubtful whether this is practically meaningful.
Bleehen – ITT: RD -0.047 (95% CI -0.138 to 0.045)
Bleehen – per protocol analysis: RD -0.015 (95% CI 0.111 to 0.082)
Koopmans: RD -0.040 (95% CI -0.118 to 0.025) (physician assessed)
Koopmans: RD -0.053 (95% CI -0.136 to 0.013) (patient assessed)
Sudilovsky: RD -0.009 (95% CI -0.101 to 0.084)

In the study by Koopmans et al, the proportion of patients who were cleared of eczema was higher in the twice daily group than the once daily group using the doctors' assessment of clearance (rate difference -0.21, 95% CI -0.36 to -0.06) but not the patients' assessment (rate difference 0.13, 95% CI -0.28 to 0.02).

Economic evaluation
Not undertaken.

Conclusions
The review failed to find any evidence to support the use of twice daily as opposed to once daily topical steroids.

Methodological comments

- Search strategy: adequate.
- Participants: atopic eczema.
- Inclusion/exclusion criteria: Not clear for the section on once versus more frequent use: not clear why two of the potentially eligible studies presented in the Appendix were not mentioned in the text.
- Quality assessment of studies: adequate.
- Method of synthesis: Appropriate.

General comments

- Generalisability: Studies comparing once daily versus more frequent application of the same corticosteroid, but not studies comparing different compounds of the same potency.
- Funding: public sector.

Quality Assessment for Systematic Reviews	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Partial
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

Appendix 7 Studies comparing moderate corticosteroids

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [53] Author: Richelli et al. Year: 1990 Country: Italy Study design: RCT Number of centres: one Setting: not reported Funding: not reported	Comparisons of different Interventions: 1. clobetasone 17-butyrate 0.05% lotion once daily at 9pm. 2. clobetasone 17-butyrate 0.05% lotion twice daily at 8am and 3pm. 3. clobetasone 17-butyrate 0.05% lotion twice daily at 3pm and 8pm. Potency: moderate Duration of treatment: 7 days Other interventions used: The steroid lotion was applied in all cases without occlusion.	Number of Participants: 30 randomised. 1. once daily: 9 2. twice daily (8am/3pm): 13 3. twice daily (3pm/8pm): 8 Inclusion criteria for study entry: children with atopic dermatitis who had not used topical steroids during the previous 2 weeks.	Primary outcomes: Dermatitis symptoms (itching, burning, pain) and other clinical manifestations such as erythema, edema, exudation, blisters, bullae, scabs, scaling, and lichenification. Secondary outcomes: Serum cortisol and adrenocorticotropic hormone (ACTH) concentrations evaluated in all 3 patient groups at the beginning and end of the study period at 8am and 4pm. Method of assessing outcomes: Dermatitis and other clinical manifestations were each classified and scored from 0 (none) to 3 (severe). The 3 groups were compared with regard to rapidity of disappearance of symptoms and skin manifestations.

Characteristics of participants:

	Once daily	Twice daily 8am/3pm	Twice daily 3pm/8pm	P Value
Age (mean) yrs	5.56	4.17	5.25	
Sex (no.)	M = 3; F = 6	M = 7; F = 6	M = 5; F = 3	

Results

Outcomes	Once daily	Twice daily 8am/3pm	Twice daily 3pm/8pm	P Value
Mean scores for severity of clinical manifestations (estimated from figure)				
Day 0	1.21	1.26	1.23	
Day 1	1.1	1.09	1.02	
Day 2	0.89	0.71	0.66	
Day 3	0.7	0.52	0.52	
Day 4	0.63	0.48	0.33	
Day 5	0.47	0.30	0.31	
Day 6	0.43	0.22	0.23	

Day 7	0.26	0.28	0.14	

Mean scores for severity of symptoms (estimated from figure)

	Once daily	Twice daily 8am/3pm	Twice daily 3pm/8pm	
Day 0	1.0	1.17	0.95	
Day 1	0.93	0.93	0.78	
Day 2	0.71	0.64	0.81	
Day 3	0.6	0.6	0.64	
Day 4	0.52	0.45	0.45	
Day 5	0.5	0.33	0.36	
Day 6	0.52	0.28	0.36	
Day 7	0.52	0.31	0.36	

There were no differences in the degree or speed of recovery in the three patient groups.

No significant differences in serum cortisol and ACTH levels before and after clobetasone 17-butyrate administration in any of the 3 groups ($p>0.05$), and no significant differences between groups.

Adverse Effects

Not reported

Methodological comments

- Allocation to treatment groups: Each patient was randomly assigned to one of three treatment groups. Method not reported.
- Blinding: Not reported. Assume none due to timing of application and absence of a placebo treatment in the once-daily group.
- Comparability of treatment groups: Baseline characteristics reported for age and sex only.
- Method of data analysis: Cortisol and ACTH levels were analysed using statistically using Student's t test to evaluate differences before and after drug administration for each group and analysis of variance (ANOVA) between groups. Not clear if statistical methods were used to compare severity scores, data presented in figure only.
- Sample size/power calculation: Not reported
- Attrition/drop-out: Not reported

General comments

- Generalisability: Children with atopic dermatitis
- Outcome measures: Severity measures not shown to be valid.
- Inter-centre variability: Not applicable
- Conflict of interests: Not reported

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Inadequate
6. Was the care provider blinded?	n/a
7. Was the patient blinded? (no placebo therefore not blinded)	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9. Did the analyses include an intention to treat analysis?	Inadequate

Appendix 8 Studies comparing potent corticosteroids

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [54] Author: Berth-Jones et al. Year: 2003 Country: UK, Netherlands, Germany, Norway, Belgium, Italy Study design: RCT Number of centres: 39 Setting: Dermatology outpatient clinics Funding: Glaxo Wellcome R&D	Comparisons of different Interventions: 1. Fluticasone propionate cream 0.05% once daily 2. Fluticasone proprionate cream 0.05% twice daily 3. Fluticasone propionate ointment 0.005% once daily 4. Fluticasone proprionate ointment 0.005% twice daily Potency: potent Duration of treatment: 4 wks Other interventions used: None stated. Patients whose disease was brought under control continued into a 16 week maintenance phase – data not extracted.	Number of Participants: Total 376 (295 entered the maintenance phase – data not extracted) 1. Fluticasone propionate cream once daily: 95 2. Fluticasone propionate cream twice daily: 91 3. Fluticasone propionate ointment once daily: 100 4. Fluticasone propionate ointment twice daily: 90 Sample attrition/dropout: 33 discontinued during stabilisation stage. Inclusion: Patients aged 12-65 with recurrent moderate to severe atopic dermatitis. Recruited during a flare of atopic dermatitis, assessed from index lesion. Exclusion: Patients with any medical condition for which topical corticosteroids were contraindicated, those with other dermatological conditions that may have prevented accurate assessment of atopic dermatitis, and those receiving any concomitant medications that might have affected the study's outcome.	Primary outcomes: Time to relapse during maintenance phase (data not extracted). Secondary outcomes: Proportion of patients with controlled atopic dermatitis at the end of the stabilisation stage. Adverse events Methods of assessing outcomes: Three item severity score (sum of three signs: erythema, oedema or papulations, and excoriations): 0 = absent 1 = mild 2 = moderate 3 = severe Remission or control = index lesion score of 1 or lower (absent or mild). Patients assessed every two weeks in stabilisation phase. Questioned at each visit about adverse events, recorded by investigator. Regular examinations for visual evidence of skin atrophy.

Characteristics of participants:

	Fluticasone propionate cream		Fluticasone propionate ointment		P Value
	Once daily (n=95)	**Twice daily (n=91)**	**Once daily (n=100)**	**Twice daily (n=90)**	
Age mean (SD)	28.4 (12.2)	28.1 (11.8)	29.6 (13.3)	28.9 (12.4)	
Sex no (%)	F=51 (54); M=44 (46)	F=49 (54); M=42 (46)	F=54 (54); M=46 (46)	F=51 (57); M=39 (43)	

Race no (%)	White=85 (89) Black=7 (7) Other=3 (3)	White=84 (92) Black=2 (2) Other=5 (5)	White=91 (91) Black=4 (4) Other=5 (5)	White=84 (93) Black= 0 Other=6 (7)	
Duration of atopic dermatitis: No. (%) ≤ 5 years > 5 years	 17 (18) 78 (82)	 10 (11) 81 (89)	 14 (14) 86 (86)	 12 (13) 78 (87)	
Duration of current episode: No. (%) ≤ 3 weeks > 3 weeks	 30 (32) 65 (68)	 26 (29) 65 (71)	 26 (26) 74 (74)	 26 (29) 64 (71)	
Mean (SD) extent of atopic dermatitis (%)*	28.8 (19.0) (data missing for one patient)	17.7 (16.2)	17.5 (14.6)	18.4 (16.1)	
Median three item severity score at index lesion (range)	5.0 (4-6)	5.0 (4-9)	5.0 (4-7)	5.0 (4-7)	

* 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).

Results

Outcomes	**Once daily**	**Twice daily**	**Once daily**	**Twice daily**	**P Value**
Number (%) of patients with controlled atopic dermatitis at end of stabilisation stage (absent or mild)	76 (80)	76 (84)	77 (77)	64 (71)	Cream: p=0.546 Ointment: p=0.249 (once vs. twice daily).

Of the 376 patients who entered the study, 293 had controlled atopic dermatitis at the end of the stabilisation stage. Data from the initial stabilisation phase showed that proportions of patients in remission at the end of the 4 week phase were similar across the four treatment groups. Analysis showed no difference between applications once and twice daily.

Adverse Effects	**Once daily**	**Twice daily**	**Once daily**	**Twice daily**	
Ear, nose and throat infection (most common event)	9 (group not specified)				
Serious adverse event	4 (1 episode of erysipelas, 1 exacerbation of asthma, 2 flares of eczema, groups not specified)				
Visual signs of atrophy related to study treatment*:					
Telangiectasia	0	1	1	0	
Striae	0	0	1	0	

**Note*: Two of these patients had a previous history of skin changes, and therefore only one report was newly observed (group not specified).

Methodological comments

- Allocation to treatment groups: A randomised treatment code determined the treatment that each patient received. Investigators at each centre allocated patients to treatment groups in equal numbers according to a computer generated randomisation code. The block size was eight, and each recruiting centre received 16 treatment allocation numbers.
- Blinding: States double-blind study, but no placebo described for once-daily group.

- Comparability of treatment groups: Groups similar at baseline for age, sex, race, duration of atopic dermatitis, duration of current episode, extent of atopic dermatitis and severity scores.
- Method of data analysis: Adjusting for country, a Cochran-Mantel-Haenszel statistic was used to determine the proportion of patients with controlled atopic dermatitis at the end of the stabilisation phase. ITT analysis.
- Sample size/power calculation: Primary endpoint was the time to relapse during maintenance phase. To detect a treatment difference at the 5% two sided significance level with 90% power (log rank test), estimated that 58 patients were required per treatment group in the stabilisation phase. It was estimated that at least 55% of patients in the stabilisation phase would be eligible for the maintenance phase; therefore at least 110 patients per treatment arm were required.
- Attrition/drop-out: 33 patients dropped out over the course of the stabilisation phase. 10 were lost to follow-up, 5 withdrew consent, 4 were protocol violators, 9 had adverse effects and 5 were categorised as 'other'.

General comments

- Generalisability: Patients between the ages of 12-65 years with recurrent moderate to severe atopic dermatitis.
- Outcome measures: For stabilisation phase, proportion of patients achieving remission (absent or mild).
- Inter-centre variability: Not reported
- Conflict of interests: Funded by Glaxo Wellcome R&D (now GlaxoSmithKine). One author employed full time at GlaxoSmithKine.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	adequate
2. Was the treatment allocation concealed?	adequate
3. Were the groups similar at baseline in terms of prognostic factors?	reported
4. Were the eligibility criteria specified?	adequate
5. Were outcome assessors blinded to the treatment allocation?	partial
6. Was the care provider blinded?	n/a
7. Was the patient blinded?	partial
8. Were the point estimates and measure of variability presented for the primary outcome measure?	adequate
9. Did the analyses include an intention to treat analysis?	adequate

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [43] Author: Bleehen et al Year: 1995 Country: UK Study design: Randomised controlled trial Number of centres:36 Study setting: Hospital. Funding: Glaxo Laboratories Limited.	Comparisons of different Interventions: 1. Fluticasone propionate 0.05% cream once daily and vehicle once daily (propylene glycol, mineral oil, cetostearyl alcohol, polyoxyl 20 cetostearyl ether, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, imidurea) 2. Fluticasone propionate 0.05% cream twice daily Potency: Potent Duration of treatment: 4 weeks or less if eczema target area had cleared. Other interventions used: No dermatological preparations other than the study medication or emollients were allowed during the 4-week study period.	Number of Participants: Randomised : 270 1. Once daily 137 2. Twice daily: 133 After withdrawals: 1. Once daily: 99 2. Twice daily: 98 Inclusion criteria for study entry: Patients aged between 1-65 years, referred to the hospital by their general practitioner and with a diagnosis of atopic eczema confirmed by a dermatologist. Eczema of at least moderate severity (score not less than 6) required. Total severity score for study entry = erythema + pruritus + thickening (see severity scale). Exclusions: frank infection of eczema, severe eczema requiring hospital admission, use of any systemic medications for eczema within 3 weeks prior to study entry (corticosteroid administered by spray or aerosol for asthma or allergic rhinitis allowed), use of antihistamines / antipruritics within 3 days prior to study entry, concomitant unstable or serious disease, history of adverse response to a topical or systemic corticosteroid. Patients using a 'very potent' topical corticosteroid during the previous 3 weeks or a 'potent' category during the previous week only eligible after a washout period of 3 weeks or 1 week respectively. During washout a mild or moderate (Efcortelan® cream or Eumovate® cream) topical steroid could be used.	Primary outcomes: Physician's overall assessment of response at a preselected target area (site of eczema most troublesome to patient). Severity of 6 signs and symptoms scored at each visit (see severity score below): Erythema Pruritus Thickening Lichenification Vesiculation Crusting Adverse events, untoward symptoms (e.g. skin disorders), serious laboratory abnormalities recorded at each visit. Secondary outcomes: Completed patient diary cards Weight of unused tubes Method of assessing outcomes: Clinical response assessed by same investigator at weekly intervals. Physicians overall assessment : Cleared = 100% resolution, except for residual discoloration. Excellent = at least 75% improvement. Good = 50% - 75% improvement Fair = 25% - 50% improvement Little = less than 25% improvement Worse = exacerbation of disease Successful treatment defined as eczema at target area cleared, excellent or good compared with baseline (i.e. > 50% improvement). Severity of signs and symptoms scored on 7-point scale: 0.0 (absent), 0.5, 1.0 (mild), 1.5,

			2.0 (moderate), 2.5, 3.0 (severe). The sum of scores for the different signs and symptoms was calculated for each visit and compared with baseline. A decrease in score compared with baseline indicated successful treatment. Patients completed daily diary cards for severity of itch, rash, sleep disturbance. A finger tip guide was used to indicate how much cream should be applied. Unused medication was returned at each visit and the weight of tubes recorded.

Characteristics of participants:

	Once daily (n=137)	**Twice daily (n=133)**	**P Value**
Mean age (SD, range)	17.3 (14.4, 1-56)	17.0 (13.9, 0-62)	
No further data presented.			

Results

Outcomes	**Once daily (n=137)**	**Twice daily (n=133)**	**P Value**
Investigators overall assessment of target area at last visit attended (patients classified as treatment successes)			
ITT analysis	80% (110/137)	85% (113/133)	p=0.35 95% CI -14.2 to 5.0
Per-protocol population analysis	79% (108/137)	83% (110/133)	p=0.42 95% CI -14.7 to 6.2
(Note: numbers in brackets calculated by reviewer).			
Assessment of clinical signs and symptoms at last visit attended (proportion of patients judged a success, i.e. had a decrease in score compared with baseline)			
ITT analysis	96%	97%	P=0.72
Per-protocol population analysis	95%	96%	P=1.00
Median severity scores of clinical signs and symptoms			
ITT analysis (min, max; 25th, 75th percentile, estimated from figure)	Baseline 10.0 (7,16; 9,12) Last visit attended 2.5 (0,16; 1,5)	Baseline 10.0 (6,16; 9,12) Last visit attended 2.0 (0,14; 0.5,4)	
Per-protocol population analysis (min, max; 25th, 75th percentile, estimated from figure)	Baseline 10.0 (7,16; 9,12) Last visit attended 2.5 (0,16; 1,5)	Baseline 10.5 (6,16; 10,12) Last visit attended 2.0 (0,14; 0.5, 4)	

'Some evidence of a difference' between groups in favour of twice daily treatment for investigators' overall assessment compared with baseline at end of weeks 1, 2, and 3, but not for assessment of signs and symptoms at end of weeks 2 and 3. Data not presented.

Difference in efficacy between morning and evening application of active treatment did not reach statistical significance. Data not presented.

Patient diary cards

Rash improved gradually for 6 days from start of treatment for both groups.
Incremental improvement seen for mean itch score for 5 days from start of treatment for twice-daily group and 6 days for once-daily group. Data not provided.

Sleep 'as good as ever has been' or better	37%	55%	

Amount of active treatment used

Accounting for number of affected areas at baseline where cream applied, little difference between groups in weight of returned morning tubes containing active treatment or weight of returned evening tubes containing active treatment.

Total amount of active treatment used by once-daily group was roughly half that used by twice-daily group.

Adverse Effects (number of reports)	**Once daily (n=137)**	**Twice daily (n=133)**	
Digestive system disorders	2	7	
Diseases and symptoms of the nervous system	2	7	
Diseases of the blood	0	1	
Diseases of the ear	1	4	
Diseases of the eye	0	1	
Diseases of the musculoskeletal system	1	0	
Diseases of the respiratory system* (mainly acute nasopharyngitis, asthma, upper respiratory tract infection, chest infection, coryza, seasonal allergic rhinitis)	21	18	
Infectious and parasitic diseases	2	1	
Injury and poisoning	2	1	
Kidney and urinary system disorders	0	1	

Mental disorders	1	1	
Neoplasms	1	0	
Non-specific symptoms and abnormal findings	1	1	
Skin disorder	34 Exacerbation of eczema: 7 Skin irritation following drug admin: 5 Exacerbation of itching: 4	21 Exacerbation of eczema: 2 Skin irritation following drug admin: 2 Exacerbation of itching: 1	
Total number of reports	68	64	
Total number of patients	46	45	
Events possibly, probably, or almost certainly related to study medication (mostly skin disorders)	26	24	
Deaths, pregnancies, or adverse events of special interest	0	0	
Serious adverse events, due to inpatient hospitalisation, unrelated to study drug	1	1	
*Diseases of respiratory system: 138 patients (69 in each group) had concomitant disease of respiratory system on entering study. Only 1 case (sore throat) was rated as being even possibly related to study medication.			
Reasons for withdrawal	**Once daily (n=137)**	**Twice daily (n=133)**	
Adverse event	3 (1 possibly, probably or almost certainly, related to study medication)	3 (3 possibly, probably or almost certainly, related to study medication)	
Exacerbation of skin disease	7	5	
Patient failed to return	9	10	
Patient withdrew consent	2	1	
Deviation from protocol (22 for concurrent medication violation)	12	14	
Success (early clearance of eczema)	9	5	
Other	3	4	

Total number of reasons	45	42	
Total number of patients	38	35	

Methodological comments

- Allocation to treatment groups: States randomised, no further details. Unit of randomisation: patient. The once daily group also had the active and vehicle treatments randomised.
- Blinding: Double-blind. All tubes of cream were similar size and contents were similar in smell, texture and appearance. A coloured label distinguished morning and evening treatments.
- Comparability of treatment groups: States that groups well matched at baseline for age, sex, ethnic origin, history of eczema and extent, severity and duration of the current exacerbation. However, baseline data reported for age only.
- Method of data analysis: A difference of 15 percentage points was deemed to be the largest reduction in efficacy with once daily treatment that would be tolerable in the light of its expected benefits over twice daily and for which the two could be said to be equivalent. With respect to the investigator's overall assessment, success rates were compared with baseline using the normal approximation to the binomial distribution. Changes in total scores of signs and symptoms from baseline compared using Fisher's exact test. Results from patients in once-daily morning and once-daily evening group pooled for these analyses. Amount of active treatment used from morning tubes compared between once daily morning group and twice daily group by fitting a regression model with the weight on return as the response variable, and group effect and the number of areas affected by eczema at the first assessment visit as exploratory variables. Evening tubes also compared between once-daily evening group and twice daily group. Results presented for ITT population and 'per protocol' population.
- Sample size/power calculation: Not reported.
- Attrition/drop-out: once daily: 38 patients (45 reasons); twice daily: 35 patients (42 reasons). See reasons in results table above.

General comments

- Generalisability: Patients with moderate to severe atopic dermatitis confirmed by a dermatologist.
- Outcome measures: Investigators' overall assessment of response to treatment relies on recall of baseline state, therefore due to recall bias. Data from patients' daily diary records of rash and itch not reported.
- Inter-centre variability: Not reported.
- Conflict of interests: Study sponsored by Glaxo Laboratories Limited.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	Not applicable
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Adequate

Subgroup analysis in children aged 12 years or less (patients also included in Bleehen et al.[43])

Reference and Design	Intervention	Participants	Outcome measures

Subgroup analysis 1999 (unpublished data from GSK) Protocol GL/FLT/001	Comparisons of different Interventions: 1. Fluticasone propionate cream (0.05%) once daily 2. Fluticasone propionate cream (0.05%) twice daily Potency: Potent	Number of Participants: 126 1. Once daily: 63 2. Twice daily: 63	Primary outcomes: Proportion of patients classed as a success for global assessment score at last visit attended. Secondary outcomes: Success rates for overall signs and symptoms. Median itch score, rash score, sleep score. Adverse events and drug related adverse events. Method of assessing outcomes: Success = global assessment score of 'cleared', excellent' or 'good'. Failure = global assessment score of 'fair', 'little', 'worse'. Signs and symptoms: a decrease in overall severity score from visit 1 = success. No change or an increase = failures. Overall severity score = sum of scores for 6 signs and symptoms (min score 0 =all absent, max score 18 = all severe) Itch, scratch and sleep from diary cards, scale: 1 (worse than ever has been) to 7 (better than ever has been).

Characteristics of participants (Data also presented by age category, not extracted)

	Once daily	**Twice daily**	**P Value**
Age at last birthday, mean (SD; min, max)	4.3 years (2.9; 1, 12)	4.7 years (3.5; 0, 12)	
<1 year	0	1	
1-3 years	32	29	
4-7 years	20	19	
8-12 years	11	14	
Female	24 (38%)	18 (29%)	
Male	39 (62%)	45 (71%)	
Asian	5 (8%)	6 (10%)	
Caucasian	53 (84%)	47 (75%)	
Afro-Caribbean	3 (5%)	5 (8%)	
Oriental	1 (2%)	1 (2%)	
Other	1 (2%)	4 (6%)	
Duration eczema history, median (25^{th}, 75^{th} percentile; min, max)	36 months (24, 60; 6, 144)	36 months (24, 84; 3, 150)	

Duration current exacerbation, median (25^{th}, 75^{th} percentile; min, max)	6 months (2, 16; 0.3, 72)	4 months (1.5, 12; 0.5, 120)	
Concurrent illness:			
Digestive system disorders	0	1	
Diseases & symptoms of nervous system	1	0	
Diseases of ear	1	1	
Diseases of the respiratory system	26	29	
Infectious and parasitic diseases	3	2	
Mental disorders	1	1	
Nutritional deficiencies & symptoms	0	1	
Skin disorder	0	2	
Total number disorders	32	37	
Total number patients	26	31	

Results (Some data also presented by age category; extracted for primary outcome (success rates) only)

Outcomes	**Once daily**	**Twice daily**	**P Value**
Global assessment score			
Proportion with success (%) (cleared, excellent, good)	Visit 2: 33/60 (55%) Visit 3: 42/56 (72%) Visit 4: 43/52 (83%) Visit 5: 40/44 (91%) Last visit: 48/56 (86%)	Visit 2: 42/57 (74%) Visit 3: 45/52 (87%) Visit 4: 45/50 (90%) Visit 5: 40/44 (91%) Last visit: 47/53 (89%)	-3% (95% CI -15.5% to 9.6%), p=0.644
Cleared (%)	Visit 2: 0 Visit 3: 3/56 (5%) Visit 4: 7/52 (13%) Visit 5: 7/44 (16%) Last visit: 13/56 (23%)	Visit 2: 0 Visit 3: 3/52 (6%) Visit 4: 3/50 (6%) Visit 5: 10/44 (23%) Last visit: 13/53 (25%)	
Excellent (%)	Visit 2: 19/60 (32%) Visit 3: 22/56 (39%) Visit 4: 16/52 (31%) Visit 5: 18/44 (41%) Last visit: 18/56 (32%)	Visit 2: 20/57 (35%) Visit 3: 27/52 (52%) Visit 4: 35/50 (70%) Visit 5: 24/44 (55%) Last visit: 28/53 (53%)	
Good (%)	Visit 2: 14/60 (23%) Visit 3: 17/56 (30%) Visit 4: 20/52 (38%) Visit 5: 15/44 (34%) Last visit: 17/56 (30%)	Visit 2: 22/57 (39%) Visit 3: 15/52 (29%) Visit 4: 7/50 (14%) Visit 5: 6/44 (14%) Last visit: 6/53 (11%)	
Fair (%)	Visit 2: 13/60 (22%) Visit 3: 10/56 (18%) Visit 4: 8/52 (15%) Visit 5: 3/44 (7%)	Visit 2: 9/57 (16%) Visit 3: 4/52 (8%) Visit 4: 4/50 (8%) Visit 5: 3/44 (7%)	

	Last visit: 6/56 (11%)	Last visit: 4/53 (8%)	
Little (%)	Visit 2: 11/60 (18%) Visit 3: 4/56 (7%) Visit 4: 1/52 (2%) Visit 5: 0 Last visit: 0	Visit 2: 6/57 (11%) Visit 3: 3/52 (6%) Visit 4: 1/50 (2%) Visit 5: 1/44 (2%) Last visit: 1/53 (2%)	
Worse (%)	Visit 2: 3/60 (5%) Visit 3: 0 Visit 4: 0 Visit 5: 1 (2%) Last visit: 2/56 (4%)	Visit 2: 0 Visit 3: 0 Visit 4: 0 Visit 5: 0 Last visit: 1/53 (2%)	
Global assessment scores at the last visit attended on treatment effect adjusting for age: Odds ratio (twice/once daily): 1.91 (95% CI 0.94 to 3.86). Significance of treatment effect: p=0.072. Significance of age effect p= 0.017.			
Global assessment scores by age group (proportion with a success (%))			
<1 year	Visit 2: 0/0 Visit 3: 0/0 Visit 4: 0/0 Visit 5: 0/0 Last visit: 0/0	Visit 2: 1/1 (100%) Visit 3: 0/0 Visit 4: 0/0 Visit 5: 0/0 Last visit: 1/1 (100%)	
1-3 years	Visit 2: 18/30 (60%) Visit 3: 23/29 (79%) Visit 4: 20/24 (83%) Visit 5: 18/20 (90%) Last visit: 25/28 (89%)	Visit 2: 21/27 (78%) Visit 3: 22/25 (88%) Visit 4: 20/23 (87%) Visit 5: 17/19 (89%) Last visit: 20/23 (87%)	
4-7 years	Visit 2: 13/20 (65%) Visit 3: 15/18 (83%) Visit 4: 17/19 (89%) Visit 5: 15/16 (94%) Last visit: 16/18 (89%)	Visit 2: 11/16 (69%) Visit 3: 12/14 (86%) Visit 4: 14/14 (100%) Visit 5: 12/12 (100%) Last visit: 14/15 (93%)	
8-12 years	Visit 2: 2/10 (20%) Visit 3: 4/9 (44%) Visit 4: 6/9 (67%) Visit 5: 7/8 (88%) Last visit: 7/10 (70%)	Visit 2: 9/13 (69%) Visit 3: 11/13 (85%) Visit 4: 11/13 (85%) Visit 5: 11/13 (85%) Last visit: 12/14 (86%)	
≤ 12 years	Visit 2: 33/60 (55%) Visit 3: 42/56 (75%) Visit 4: 43/52 (83%) Visit 5: 40/44 (91%) Last visit: 48/56 (86%)	Visit 2: 42/57 (74%) Visit 3: 45/52 (87%) Visit 4: 45/50 (90%) Visit 5: 40/44 (91%) Last visit: 47/53 (89%)	
Overall signs and symptoms			
Proportion of success (%) (decrease in overall severity from visit 1)	Visit 2: 52/60 (87%) Visit 3: 55/56 (98%) Visit 4: 52/52 (100%) Visit 5: 44/44 (100%) Last visit: 55/56 (98%)	Visit 2: 56/58 (97%) Visit 3: 53/53 (100%) Visit 4: 50/51 (98%) Visit 5: 44/44 (100%) Last visit: 51/53 (96%)	p=0.611
Overall signs and symptoms scores, median (25^{th}, 75^{th} percentile; min, max)	Visit 1: 10.5 (9.0,12.0; 6.5,16.0) Visit 2: 6.25 (4.0,8.75; 0.5,14.5) Visit 3: 4.0 (1.5,6.0; 0,12.5)	Visit 1: 10.5 (9.0,12.0; 7.5,15.0) Visit 2: 6.0 (3.5,7.5; 0.5,11.5) Visit 3: 3.5 (2.0,6.0; 0,10.5) Visit 4: 2.5 (1.0,5.0; 0,12.5)	

	Visit 4: 3.0 (1.5,5.0; 0,8.5) Visit 5: 2.5 (1.0,4.25; 0,8.5) Last visit: 2.5 (1.0,4.5; 0,13)	Visit 5: 1.75 (0.5,3.75; 0,7.0) Last visit:1.5 (0.5,4.0; 0,13.5)	
Median itch score			
1 Worse than ever has been	0	0	
2 As bad as ever has been	3/60 (5%)	3/59 (60%)	
3 Moderately bad	4/60 (7%)	1/59 (2%)	
4 Usual state	6/60 (10%)	6/59 (10%)	
5 Moderately good	25/60 (42%)	18/59 (31%)	
6 As good as ever has been	11/60 (18%)	18/59 (31%)	
7 Better than ever has been	11/60 (18%)	13/59 (22%)	
Median rash score			
1 Worse than ever has been	0	0	
2 As bad as ever has been	1/60 (2%)	1/59 (2%)	
3 Moderately bad	3/60 (5%)	1/59 (2%)	
4 Usual state	8/60 (13%)	6/59 (10%)	
5 Moderately good	25/60 (42%)	17/59 (29%)	
6 As good as ever has been	11/60 (18%)	19/59 (32%)	
7 Better than ever has been	12/60 (20%)	15/59 (25%)	
Median sleep score			
1 Worse than ever has been	0	1/50 (2%)	
2 As bad as ever has been	3/57 (5%)	0	
3 Moderately bad	5/57 (9%)	0	
4 Usual state	9/57 (16%)	5/50 (10%)	
5 Moderately good	15/57 (26%)	11/50 (22%)	
6 As good as ever has been	17/57 (30%)	21/50 (42%)	
7 Better than ever has been	8/57 (14%)	12/50 (24%)	
Adverse events			
Digestive system disorders	0	4	
Diseases & symptoms of nervous system	2	3	
Diseases of the ear	1	3	
Diseases of the eye	0	1	
Diseases of the respiratory system	14	10	
Infectious and parasitic diseases	1	1	
Injury and poisoning	0	1	
Kidney and urinary system disorders	0	1	
Mental disorders	1	1	

Non-specific symptoms / abnormal findings	0	1	
Skin disorder	17	8	
Total reportings	36	34	
Total number of patients	23	22	
Drug related adverse events			
Blister(s)	0	Possible: 1	
Eczema	Possible: 1	0	
Exacerbation of eczema	Possible: 2	0	
Exacerbation of itching	Probable: 1	Probable: 1	
Folliculitis	0	Probable: 1	
Hyperactivity	0	Possible: 1	
Increased temperature	Possible: 1	0	
Infected eczema	0	Possible: 2	
Inflammatory condition	0	Almost certain: 1	
Mild papules with impetiginization	Possible: 1	0	
Pallor/flushing	Possible: 1	0	
Pruritus	0	Almost certain: 1	
Redness	0	Possible: 1	
Skin infection	Possible: 1	0	
Skin irritation	Probable: 1	0	
Skin irritation following drug admin	Possible: 1 Probable: 1 Almost certain: 3	Almost certain: 1	
Sore throat	Possible: 1	0	
Warts on inner thighs	0	Possible: 1	
Total reportings	Possible: 9 Probable: 3 Almost certain: 3	Possible: 6 Probable: 2 Almost certain: 3	

Withdrawals

Adverse event	1	3	
Exacerbation of skin disease	1	2	
Patient failed to return	6	7	
Patient withdrew consent	1	1	
Deviation from protocol	6	9	
Success	7	2	
Other	2	1	
Total number of reasons	24	25	
Total number of patients	19	19	

Methodological comments

- Comparability of treatment groups: Demographic characteristics were balanced. Groups had similar duration of eczema history, but the once daily group had a longer duration of their current exacerbation.
- Method of data analysis: Success for global assessment score: data analysed using the normal approximation to the binomial test, as per the original analysis of the full study population. Data summarised by category (cleared, excellent, good, fair, little, worse), by visit and by age category for last visit attended. Data analysed using a proportional odds model, using age category as an explanatory variable in the model. Interaction between age and treatment also tested. Success rate for overall signs and symptoms at last visit attended compared using Fisher's exact test. Not ITT analysis.

- Sample size/power calculation: Not performed. Power would be less than for the main analysis.
- Attrition/drop-out: 19 patients in each group withdrew from study. See table above for reasons.

General comments

- Generalisability: Children aged 12 years or less.

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [46] GSK Report No. 135L (Protocol No. GL/FLT/002) Year: 1995 Also published as abstract: James 1999[48] Country: UK Study design: RCT Number of centres: 35 Setting: Hospital centres Funding: Glaxo Wellcome R&D.	Comparisons of different Interventions: 1. Fluticasone proprionate 0.005% ointment once daily and placebo ointment base once daily 2. Fluticasone proprionate 0.005% ointment twice daily Potency: potent Duration of treatment: four weeks or until eczema is cleared if sooner. Other interventions used: Patients who had applied a 'very potent' topical corticosteroid during the previous three weeks or a 'potent' topical corticosteroid during the previous week were eligible to enter the study only after entering either a 3 week or 1 week washout period with a 'moderately potent' topical steroid. Patients received either three (3 week washout period) or one (1 week washout period) 50g cartons of ™Eumovate ointment to cover the treatment period. No dermatological	Number of Participants: 248 randomised. (3 patients had unverifiable data excluded from all analyses) Total: 245 (ITT population) 1. Once daily: 123 2. Twice daily: 122 11 patients (not included in the total patients recruited) were withdrawn during washout period. Inclusion criteria: aged from 1 to 65 years inclusive; male or female; atopic eczema score of at least moderate severity at the chosen target area, i.e.: severity score not less than 7; patients, or parents where appropriate, who had written informed consent to participate. Exclusion criteria: frank infection of eczema requiring antibacterial treatment; eczema of severity that required hospital admission; use of a 'very potent' topical corticosteroid within 3 weeks prior to start of study (washout period provided); use of a 'potent' topical corticosteroid in week prior to start of study (washout period provided); systemic anti-inflammatory medications 4 weeks prior; antihistamines 3 days prior; concomitant unstable or serious disease; history of adverse response to topical or systemic corticosteroid; participation in another clinical trial within previous month; considered	Primary outcomes: Physician's global assessment of response to therapy of the target area at the last visit attended compared to baseline. Secondary outcomes: Patient's self-assessment of the target area. Signs and symptoms: erythema, pruritus, thickening/lichenification, scaling. Weight of returned tubes Adverse events. Method of assessing outcomes: Global assessment: seven point scale Cleared: 100% resolution, except for residual discolouration Good: Marked improvement Moderate: Moderate improvement Fair: Slight improvement No change: No apparent change Worse: Some exacerbation of disease Much worse: Marked exacerbation of disease Successful treatment defined as cleared, good or moderate compared to baseline. Each patient was evaluated by the same physician at initial and subsequent visits. Patient self-assessment of target area scale: totally cleared; greatly improved; moderately improved; slightly improved; not changed; worsened; greatly worsened. Successful treatment was defined as being assessed cleared, good or moderate compared to baseline. Signs and symptoms scale: 0.0 (Absent); 0.5; 1.0 (Mild); 1.5; 2.0 (Moderate); 2.5; 3.0 (Severe).

	medication other than study medication and emollients was allowed. If it was taken, it was recorded.	would have difficulty in keeping regular attendance and records; women who were pregnant, lactating and/or of child bearing age and not using adequate contraception.	Scores added together to give total severity score. A serious adverse event was classed as a fatal event; life threatening event; event which was significantly disabling or incapacitating, events which involved or prolonged in-patient hospitalisation; overdose, cancer or congenital anomaly; laboratory abnormality predefined as serious in the protocol or thought by the investigator to be of major clinical concern especially when associated with relevant clinical signs/symptoms. Approximate mean amount of cream used in each week = mean weight of unused tube (based on 4 sample tubes) minus mean amount returned.

Characteristics of participants:

	Once daily (n=123)	**Twice daily (n=122)**	**P Value**
Age (years), median (min, max; 25th, 75th percentile)	11 years (1, 63; 3, 24)	14 years (0, 65; 4, 30)	
Sex: no. (%)	M: 62 (50); F: 61 (50)	M: 67 (55); F: 55 (45)	
Ethnic Origin no. (%) Caucasian: Asian: Negroid: Oriental: Other	 104 (85%) 9 (7%) 7 (6%) 1 (1%) 2 (2%)	 105 (86%) 6 (5%) 6 (5%) 3 (2%) 2 (2%)	
Duration current exacerbation (months) median (min, max; 25th, 75th percentile)	12.0; (0.3, 553.0; 3.0, 24.0)	8.00; (0.3, 525.0; 3.0, 24.0)	
Duration eczema history (months) median (min, max; 25th, 75th percentile)	66.0; (2, 696; 24.0, 192.0)	72.0; (4, 720; 30.0, 228.0)	
Note: Text differs from data in table, states median duration of eczema history 49 months in once daily group and 38 months in twice daily group.			
Concurrent Disease			
Breast, female pelvic organs and genital	4	1	
Congenital abnormalities	1	1	

Digestive system	1	5	
Nervous system	4	1	
Blood	2	2	
Eye	0	1	
Musculoskeletal system	1	0	
Respiratory system	58	64	
Endocrine	1	0	
Hypertensive diseases	3	2	
Infectious and parasitic diseases	1	0	
Injury and poisoning	1	1	
Ischematic heart disease	1	2	
Mental disorders	4	2	
Non-specific symptoms and abnormal findings	1	2	
Nutritional deficiencies and symptoms	0	1	
Rheumatic fever	1	0	
Skin disorders	4	0	
Total number of disorders	88	85	
Total number of patients	67 (54%)	64 (52%)	

Results

Outcomes	**Once daily (n=123)**		**Twice daily (n=122)**	**P Value**
Investigators global assessment scores no. (%)				
Proportion with success (%) (cleared, good, moderate)	Visit 2: 80/116 (69%) Visit 3: 77/98 (79%) Visit 4: 70/94 (74%) Visit 5: 64/82 (78%) Last visit: 86/119 (72%)		Visit 2: 83/117 (71%) Visit 3: 83/106 (78%) Visit 4: 78/91 (86%) Visit 5: 68/80 (85%) Last visit: 99/118 (84%)	Difference (95% CI): 2.0% (-9.8, 13.7) p=0.74 -0.3% (-11.6, 11.0) p=0.96 11.2% (-0.1, 22.6) p=0.056 7.0% (-4.9, 18.8) p=0.25 11.6% (1.2, 22.1) p=0.031
Proportion with success (%) (cleared, good, moderate)	*Morning* Last visit: 40/60 (67%)	*Evening* Last visit: 46/59 (78%)		*Morning vs evening:* 11.3% (-4.6, 27.2) p=0.17 *Evening vs twice daily:* 5.9% (-6.6, 18.4) p=0.33
1 (Cleared)	Visit 2: 4/116 (3%) Visit 3: 3/98 (3%) Visit 4: 9/94 (10%)		Visit 2: 3/117 (3%) Visit 3: 7/106 (7%) Visit 4: 8/91 (9%)	

	Visit 5: 6/82 (7%) Last visit: 20/119 (17%)	Visit 5: 9/80 (11%) Last visit: 27/118 (23%)	
2 (Good)	Visit 2: 37/116 (32%) Visit 3: 44/98 (45%) Visit 4: 37/94 (39%) Visit 5: 38/82 (46%) Last visit: 42/119 (35%)	Visit 2: 46/117 (39%) Visit 3: 53/106 (50%) Visit 4: 47/91 (52%) Visit 5: 38/80 (48%) Last visit: 48/118 (41%)	
3 (Moderate)	Visit 2: 39/116 (34%) Visit 3: 30/98 (31%) Visit 4: 24/94 (26%) Visit 5: 20/82 (24%) Last visit: 24/119 (20%)	Visit 2: 34/117 (29%) Visit 3: 23/106 (22%) Visit 4: 23/91 (25%) Visit 5: 21/80 (26%) Last visit: 24/118 (20%)	
4 (Fair)	Visit 2: 24/116 (21%) Visit 3: 16/98 (16%) Visit 4: 17/94 (18%) Visit 5: 12/82 (15%) Last visit: 19/119 (16%)	Visit 2: 20/117 (17%) Visit 3: 21/106 (20%) Visit 4: 10/91 (11%) Visit 5: 9/80 (11%) Last visit: 13/118 (11%)	
5 (No change)	Visit 2: 9/116 (8%) Visit 3: 3/98 (3%) Visit 4: 5/94 (5%) Visit 5: 5/82 (6%) Last visit: 10/119 (8%)	Visit 2: 11/117 (9%) Visit 3: 1/106 (1%) Visit 4: 3/91 (3%) Visit 5: 2/80 (3%) Last visit: 2/118 (2%)	
6 (Worse)	Visit 2: 3/116 (3%) Visit 3: 2/98 (2%) Visit 4: 2/94 (2%) Visit 5: 1/82 (1%) Last visit: 4/119 (3%)	Visit 2: 3/117 (3%) Visit 3: 1/106 (1%) Visit 4: 0/91 Visit 5: 1/80 (1%) Last visit: 4/118 (3%)	
7 (Much worse)	Visit 2: 0/116 Visit 3: 0/98 Visit 4: 0/94 Visit 5: 0/82 Last visit: 0/119	Visit 2: 0/117 Visit 3: 0/106 Visit 4: 0/91 Visit 5: 0/80 Last visit: 0/118	
Logistic regression model of investigator's unaggregated global assessment scores at last visit attended on treatment effect adjusting for age: Odds ratio for the treatment effect (twice daily/once daily) 1.76; (95% CI 1.10, 2.81); (99% CI 0.95, 3.26); significance of treatment effect: p=0.017; significance of age effect: p=0.0019. Scores increased (worsened) as age increased. Difference in treatment effect was constant between age category.			
Investigators global assessment scores (proportion with success) by age			
0-5 years	Visit 2: 35/43 (81%) Visit 3: 35/39 (90%) Visit 4: 28/35 (80%) Visit 5: 24/28 (86%) Last visit: 35/44 (80%)	Visit 2: 35/40 (88%) Visit 3: 30/36 (83%) Visit 4: 26/27 (96%) Visit 5: 20/21 (95%) Last visit: 37/40 (93%)	
5-15 years	Visit 2: 16/27 (59%) Visit 3: 17/26 (65%) Visit 4: 17/26 (65%) Visit 5: 20/23 (87%) Last visit: 21/28 (75%)	Visit 2: 17/20 (85%) Visit 3: 14/17 (82%) Visit 4: 14/15 (93%) Visit 5: 12/15 (80%) Last visit: 16/20 (80%)	
16+ years	Visit 2: 29/46 (63%) Visit 3: 25/33 (76%) Visit 4: 25/33 (76%) Visit 5: 20/31 (65%) Last visit: 30/47 (64%)	Visit 2: 31/57 (54%) Visit 3: 39/53 (74%) Visit 4: 38/49 (78%) Visit 5: 36/44 (82%) Last visit: 46/58 (79%)	

At last visit attended the percentage of patients who were classed as successes decreased as age increased in both groups.			
Patient's self-assessment scores no.(%)			
Self-assessment success	Visit 2: 79/118 (67%) Visit 3: 81/104 (78%) Visit 4: 73/96 (76%) Visit 5: 61/82 (74%) Last visit: 82/118 (69%)	Visit 2: 81/118 (69%) Visit 3: 88/106 (83%) Visit 4: 74/92 (80%) Visit 5: 63/79 (80%) Last visit: 93/117 (79%)	Difference (95% CI): 1.7% (-10.2, 13.6) p=0.78 5.1% (-5.6, 15.8), p=0.35 4.4% (-7.4, 16.2), p=0.47 5.4% (-7.6, 18.3), p=0.42 10.0% (-1.1, 21.1), p=0.079
1 (totally cleared)	Visit 2: 5/118 (4%) Visit 3: 3/104 (3%) Visit 4: 8/96 (8%) Visit 5: 3/82 (4%) Last visit: 16/118 (14%)	Visit 2: 3/118 (3%) Visit 3: 7/106 (7%) Visit 4: 10/92 (11%) Visit 5: 9/79 (11%) Last visit: 26/117 (22%)	
2 (greatly improved)	Visit 2: 45/118 (38%) Visit 3: 47/104 (45%) Visit 4: 37/96 (39%) Visit 5: 41/82 (50%) Last visit: 49/118 (42%)	Visit 2: 50/118 (42%) Visit 3: 53/106 (50%) Visit 4: 43/92 (47%) Visit 5: 41/79 (52%) Last visit: 52/117 (44%)	
3 (moderately improved)	Visit 2: 29/118 (25%) Visit 3: 31/104 (30%) Visit 4: 28/96 (29%) Visit 5: 17/82 (21%) Last visit: 17/118 (14%)	Visit 2: 28/118 (24%) Visit 3: 28/106 (26%) Visit 4: 21/92 (23%) Visit 5: 13/79 (16%) Last visit: 15/117 (13%)	
4 (slightly improved)	Visit 2: 27/118 (23%) Visit 3: 12/104 (12%) Visit 4: 13/96 (14%) Visit 5: 15/82 (18%) Last visit: 20/118 (17%)	Visit 2: 26/118 (22%) Visit 3: 16/106 (15%) Visit 4: 13/92 (14%) Visit 5: 10/79 (13%) Last visit: 14/117 (12%)	
5 (not changed)	Visit 2: 5/118 (4%) Visit 3: 6/104 (6%) Visit 4: 6/96 (6%) Visit 5: 5/82 (6%) Last visit: 8/118 (7%)	Visit 2: 6/115 (5%) Visit 3: 2/106 (2%) Visit 4: 5/92 (5%) Visit 5: 4/79 (5%) Last visit: 5/117 (4%)	
6 (worsened)	Visit 2: 6/118 (5%) Visit 3: 4/104 (4%) Visit 4: 3/96 (3%) Visit 5: 1/82 (1%) Last visit: 5/118 (4%)	Visit 2: 5/118 (4%) Visit 3: 0/106 Visit 4: 0/92 Visit 5: 1/79 (1%) Last visit: 4/117 (3%)	
7 (greatly worsened)	Visit 2: 1/118 (1%) Visit 3: 1/104 (1%) Visit 4:1/96 (1%) Visit 5: 0/82 Last visit: 3/118 (3%)	Visit 2: 0/118 Visit 3: 0/106 Visit 4: 0/92 Visit 5: 1/79 (1%) Last visit: 1/117 (1%)	
Odds ratio for the treatment effect for self-assessment at last visit attended (unaggregated) twice daily/once daily: 1.26 (95% CI 1.07, 1.45); (99% CI 1.01, 1.51); significance of treatment by score effect: p=0.019; significance of age by score effect: p=0.0021.			

Signs/symptoms scores			
Total severity score median (min, max; 25th, 75th percentile)	Visit 2: 5.3; (0.0, 12.0; 4.0, 7.0) Visit 3: 4.0; (0.0, 10.0; 2.5, 5.5) Visit 4: 3.5; (0.0, 9.5; 2.0, 5.5) Visit 5: 3.0; (0.0, 8.5; 2.0, 5.0) Last visit: 3.0; (0.0, 10.5; 1.5, 6.0)	Visit 2: 5.0; (0.0, 10.0; 3.0, 7.0) Visit 3: 4.0; (0.0, 10.0; 2.0, 5.5) Visit 4: 3.0; (0.0, 9.5; 1.5, 5.0) Visit 5: 2.5; (0.0, 11.0; 1.5, 4.5) Last visit: 2.3; (0.0, 11.0; 1.0; 4.5)	* 1.16 (95% CI 0.71, 1.90) p=0.55 1.20 (95% CI 0.72, 2.02) p=0.48 1.14 (95% CI 0.66, 1.98) p=0.64 1.60 (95% CI 0.89, 2.86) p=0.11 1.72 (95% CI 1.05, 2.82) p=0.033
*Logistic regression model of total severity score on treatment effect adjusting for prognostic factors (age and baseline total severity score) at visits 2 to 5 and last visit attended: odds ratio for treatment effect (twice/once daily), (95% CI), significance of treatment effect.			
Adverse Events (no)			
Digestive system disorder	4	6	
Diseases and symptoms of the nervous system	13	7	
Diseases of the ear	1	1	
Diseases of the eye	0	1	
Diseases of the musculoskeletal system	2	2	
Diseases of the respiratory system (most common: acute nasopharyngitis, viral infection of upper respiratory tract, cough, chest infection, sore throat)	27	25	
Infectious and parasitic diseases	4	2	
Injury and poisoning	3	5	
Kidney and urinary system disorders	0	1	
Metabolic and immunity disorders	0	1	
Skin disorder Including: - exacerbation of eczema - pruritus	32 13 6	24 6 4	
Total number of reportings	86	75	
Total number of patients	54 (44%)	49 (40%)	

Serious adverse events (all unrelated to study medication)	1 (severe eczema attack)		2 (1 exacerbation of eczema; 1 foot and mouth disease)	
One serious adverse event (unrelated to the study medication) occurred in patient in washout period prior to randomisation (not included in adverse events occurrence rates).				
Relationship to study medication (no. of reportings)				
Unrelated	44		47	
Unlikely	21		14	
Possibly	6		8	
Probably	9		3	
Almost certain	6		3	
Total number of reasons	86		75	
Total number of patients	54 (44%)		49 (40%)	
Possibly, probably or almost certainly related to study medication: mainly skin related disorders, including exacerbation of eczema, pruritus and redness of skin.				
Mean amount of cream used each week (g)				
	Morning group	*Evening group*		
Morning tube	Week 1: 15.9 Week 2: 13.0 Week 3: 10.6 Week 4: 11.6	Week 1: 15.4 Week 2: 13.2 Week 3: 13.9 Week 4: 14.2	Week 1: 15.0 Week 2: 14.2 Week 3: 11.1 Week 4: 10.5	
Evening tube	Week 1: 15.8 Week 2: 13.8 Week 3: 12.9 Week 4: 11.3	Week 1: 20.7 Week 2: 18.7 Week 3: 17.9 Week 4: 15.8	Week 1: 16.8 Week 2: 14.8 Week 3: 12.4 Week 4: 10.3	
Reason for Withdrawal				
Target area eczema cleared	15		18	
Adverse event	6		8	
Exacerbation of disease	6		5	
Failed to return	8		8	
Patient withdrew consent	4		1	
Patient violated the protocol	4		6	
Other	2		1	
Total no. of reasons for withdrawal	45		47	
Total no. of patients	39		42	

Methodological comments

- Allocation to treatment groups: A randomisation code was generated by computer by Statistics and Data Management. A block size of four was used. Sealed envelopes containing details of the randomisation codes were held at four locations. Once daily group randomised to receiving active treatment morning or evening.
- Blinding: Double blind trial. All patients were provided with two tubes of treatment, Tube A for morning and Tube B for evening application. For the once daily group, one tube contained a placebo

treatment ointment base. Neither the patients in this group nor the investigator knew which tube contained the non-active treatment. All tubes were identical in size and appearance, other than different coloured labels to distinguish morning and evening treatment.

- Comparability of treatment groups: Baseline characteristics were similar in both treatment groups. Age slightly higher in twice daily group. Duration of current exacerbation longer in once daily group. Duration of eczema history slightly longer in twice daily group.
- Method of data analysis: All analyses were performed using SAS Institute Inc. software. All tests for the analyses were two-sided. All analysis was ITT. Per protocol analysis reported if results different to ITT. Success rates compared using the normal approximation to the binomial distribution. For self-assessment an odds ratio (twice daily/once daily) greater than one favoured the twice daily group and an odds ratio less than one favoured the once daily group.
- Sample size/power calculation: A total of 224 evaluable patients required to show once daily is as effective as twice daily within 15 percentage points, based on 80% power at the two-tailed 5% level of significance. A true four week success rate for the investigator's global assessment at the last visit attended of 80% for both treatment regimens was assumed.
- Attrition/drop-out: States in text that 194 patients completed the study and 54 patients were withdrawn, but lists 81 patients in table as withdrawn.

General comments

- Generalisability: Patients aged between 1 to 65 years with moderate to severe atopic eczema.
- Outcome measures: Investigator's and patient's assessment.
- Inter-centre variability: Not reported
- Conflict of interests: Study carried out by Glaxo Wellcome R&D. Manufacturers of ™Cutivate, ™Eumovate and ™Betnovate.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	n/a
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Adequate

Subgroup analysis in children aged 12 years or less (patients also included in GSK Report 135L [46])

Reference and Design	Intervention	Participants	Outcome measures
Study ref[47] Subgroup analysis from GSK Report 135L (Protocol No. GL/FLT/002) 1999	Comparisons of different Interventions: 1. Fluticasone proprionate 0.005% ointment once daily 2. Fluticasone proprionate 0.005%	Number of participants: 120 1.Once daily: 63 2. Twice daily: 57	Primary outcomes: Proportion of patients classed as a success for global assessment score at last visit attended. Secondary outcomes: Proportion of patient's classed as a success for patients self assessment score at last visit attended.

Also published as abstract: Glazenburg 2000[49]	ointment twice daily Potency: potent		Adverse events. Method of assessing outcomes: Success = global assessment score of 'cleared', 'good' or 'moderate'. Failure = global assessment score of 'fair', 'no change', 'worse', or 'much worse'. Success=patient self-assessment of 'totally cleared', greatly improved', or 'moderately improved'. Failure=patient self-assessment score of 'slightly improved', 'not changed', 'worsened' or 'greatly worsened'.

Characteristics of participants:

	Once daily (n=63)	**Twice daily (n=57)**	**P Value**
Age last birthday, median (min, max; 25th, 75th percentile) <1 year 1-3 years 4-7 years 8-12 years	3.0 years (1, 12; 2.0, 6.0) n=0 n=37 n=16 n=10	3.0 years (0, 12; 2.0, 6.0) n=1 n=29 n=15 n=12	
Sex: no. (%) Female Male	 28 (44%) 35 (56%)	 23 (40%) 34 (60%)	
Ethnic Origin no. (%) Caucasian: Asian: Negroid: Oriental: Other	 49 (78%) 5 (8%) 7 (11%) 1 (2%) 1 (2%)	 48 (84%) 3 (5%) 4 (7%) 1 (2%) 1 (2%)	
Duration current exacerbation (months) median (min, max; 25th, 75th percentile)	8 months (0.3, 72.0; 2.50, 24.00)	6 months (0.3, 120.0; 2.00, 12.00)	
Duration eczema history (months) median (min, max; 25th, 75th percentile)	30 months (5, 144; 21.0, 60.0)	37 months (6, 144; 23.0, 55.0)	
Concurrent Diseases:			
Congenital abnormalities	1	0	
Digestive system disorders	0	1	
Diseases & symptoms of	1	0	

nervous system			
Diseases of the blood	2	2	
Diseases of the eye	0	1	
Diseases of the respiratory system	27	30	
Infectious and parasitic diseases	1	0	
Injury and poisoning	1	0	
Mental disorders	1	1	
Non-specific symptoms/abnormal findings	0	1	
Nutritional deficiencies and symptoms	0	1	
Total no. of disorders	34	37	
Total no. of patients	29 (46%)	28 (49%)	

Results

Outcomes	**Once daily (n=63)**	**Twice daily (n=57)**	**P Value**
Investigators global assessment scores no. (%)			
Proportion with success (%) (cleared, good, moderate)	Visit 2: 45/60 (75%) Visit 3: 46/56 (82%) Visit 4: 39/52 (75%) Visit 5: 36/42 (86%) Last visit: 48/62 (77%)	Visit 2: 49/55 (89%) Visit 3: 42/48 (88%) Visit 4: 37/38 (97%) Visit 5: 29/31 (94%) Last visit: 50/55 (91%)	Difference 13.5% (95% CI 0.6, 26.4) p=0.048
1 (Cleared)	Visit 2: 2/60 (3%) Visit 3: 2/56 (4%) Visit 4: 7/52 (13%) Visit 5: 3/42 (7%) Last visit: 12/62 (19%)	Visit 2: 3/55 (5%) Visit 3: 5/48 (10%) Visit 4: 4/38 (11%) Visit 5: 5/31 (16%) Last visit: 17/55 (31%)	
2 (Good)	Visit 2: 21/60 (35%) Visit 3: 29/56 (52%) Visit 4: 22/52 (42%) Visit 5: 22/42 (52%) Last visit: 24/62 (39%)	Visit 2: 27/55 (49%) Visit 3: 27/48 (56%) Visit 4: 24/38 (63%) Visit 5: 20/31 (65%) Last visit: 27/55 (49%)	
3 (Moderate)	Visit 2: 22/60 (37%) Visit 3: 15/56 (27%) Visit 4: 10/52 (19%) Visit 5: 11/42 (26%) Last visit: 12/62 (19%)	Visit 2: 19/55 (35%) Visit 3: 10/48 (21%) Visit 4: 9/38 (24%) Visit 5: 4/31 (13%) Last visit: 6/55 (11%)	
4 (Fair)	Visit 2: 12/60 (20%) Visit 3: 8/56 (14%) Visit 4: 9/52 (17%) Visit 5: 4/42 (10%) Last visit: 8/62 (13%)	Visit 2: 3/55 (5%) Visit 3: 5/48 (10%) Visit 4: 1/38 (3%) Visit 5: 2/31 (6%) Last visit: 4/55 (7%)	

5 (No change)	Visit 2: 3/60 (5%) Visit 3: 0/56 Visit 4: 3/52 (6%) Visit 5: 1/42 (2%) Last visit: 2/62 (3%)	Visit 2: 2/55 (4%) Visit 3: 1/48 (2%) Visit 4: 0/38 Visit 5: 0/31 Last visit: 0/55	
6 (Worse)	Visit 2: 0/60 Visit 3: 2/56 (4%) Visit 4: 1/52 (2%) Visit 5: 1/42 (2%) Last visit: 4/62 (6%)	Visit 2: 1/55 (2%) Visit 3: 0/48 Visit 4: 0/38 Visit 5: 0/31 Last visit: 1/55 (2%)	
7 (Much worse)	Visit 2: 0/60 Visit 3: 0/56 Visit 4: 0/52 Visit 5: 0/42 Last visit: 0/62	Visit 2: 0/55 Visit 3: 0/48 Visit 4: 0/38 Visit 5: 0/31 Last visit: 0/55	
Logistic regression model of investigator's global assessment scores at last visit attended on treatment effect adjusting for age: Odds ratio for the treatment effect (twice daily/once daily) 2.45; (95% CI 1.23, 4.88); (99% CI 0.99, 6.06); significance of treatment effect: p=0.011; significance of age effect: p=0.409; significance of baseline total severity score effect: p<0.001			
Investigators global assessment scores by age group (proportion with success (%))			
< 1 year	Visit 2: 0/0 Visit 3: 0/0 Visit 4: 0/0 Visit 5: 0/0 Last Visit: 0/0	Visit 2: 1/1 (100%) Visit 3: 0/0 Visit 4: 0/0 Visit 5: 0/0 Last Visit: 1/1 (100%)	
1-3 years	Visit 2: 27/35 (77%) Visit 3: 27/31 (87%) Visit 4: 21/28 (75%) Visit 5: 17/21 (81%) Last Visit: 27/36 (75%)	Visit 2: 24/28 (86%) Visit 3: 21/25 (84%) Visit 4: 17/18 (94%) Visit 5: 15/16 (94%) Last Visit: 25/28 (89%)	
4-7 years	Visit 2: 12/15 (80%) Visit 3: 12/16 (75%) Visit 4: 13/15 (87%) Visit 5: 13/14 (93%) Last Visit: 14/16 (88%)	Visit 2: 13/14 (93%) Visit 3: 11/13 (85%) Visit 4: 11/11 (100%) Visit 5: 6/7 (86%) Last Visit: 13/14 (93%)	
8-12 years	Visit 2: 6/10 (60%) Visit 3: 7/9 (78%) Visit 4: 5/9 (56%) Visit 5: 6/7 (86%) Last Visit: 7/10 (70%)	Visit 2: 11/12 (92%) Visit 3: 10/10 (100%) Visit 4: 9/9 (100%) Visit 5: 8/8 (100%) Last Visit: 11/12 (92%)	
≤ 12 years	Visit 2: 45/60 (75%) Visit 3: 46/56 (82%) Visit 4: 39/52 (75%) Visit 5: 36/42 (86%) Last Visit: 48/62 (77%)	Visit 2: 49/55 (89%) Visit 3: 42/48 (88%) Visit 4: 37/38 (97%) Visit 5: 29/31 (94%) Last Visit: 50/55 (91%)	
Patient's self-assessment scores at last visit no. (%)			
Self-assessment success	Visit 2: 45/62 (73%) Visit 3: 48/58 (83%) Visit 4: 40/53 (75%) Visit 5: 33/42 (79%) Last visit: 44/61 (72%)	Visit 2: 46/55 (84%) Visit 3: 46/48 (96%) Visit 4: 35/38 (92%) Visit 5: 28/30 (93%) Last visit: 49/54 (91%)	18.6% (95% CI, 5.0, 32.3) p=0.011

1 (totally cleared)	Visit 2: 2/62 (3%) Visit 3: 3/58 (5%) Visit 4: 6/53 (11%) Visit 5: 2/42 (5%) Last visit: 11/61 (18%)	Visit 2: 3/55 (5%) Visit 3: 5/48 (10%) Visit 4: 4/38 (11%) Visit 5: 5/30 (17%) Last visit: 17/54 (31%)	
2 (greatly improved)	Visit 2: 27/62 (44%) Visit 3: 28/58 (48%) Visit 4: 23/53 (43%) Visit 5: 24/42 (57%) Last visit: 26/61 (43%)	Visit 2: 31/55 (56%) Visit 3: 29/48 (60%) Visit 4: 26/38 (68%) Visit 5: 21/30 (70%) Last visit: 28/54 (52%)	
3 (moderately improved)	Visit 2: 16/62 (26%) Visit 3: 17/58 (29%) Visit 4: 11/53 (21%) Visit 5: 7/42 (17%) Last visit: 7/61 (11%)	Visit 2: 12/55 (22%) Visit 3: 12/48 (25%) Visit 4: 5/38 (13%) Visit 5: 2/30 (7%) Last visit: 4/54 (7%)	
4 (slightly improved)	Visit 2: 13/62 (21%) Visit 3: 7/58 (12%) Visit 4: 7/53 (13%) Visit 5: 7/42 (17%) Last visit: 11/61 (18%)	Visit 2: 8/55 (15%) Visit 3: 2/48 (4%) Visit 4: 2/38 (5%) Visit 5: 1/30 (3%) Last visit: 3/54 (6%)	
5 (not changed)	Visit 2: 2/62 (3%) Visit 3: 1/58 (2%) Visit 4: 4/53 (8%) Visit 5: 1/42 (2%) Last visit: 1/61 (2%)	Visit 2: 0/55 Visit 3: 0/48 Visit 4: 1/38 (3%) Visit 5: 1/30 (3%) Last visit: 1/54 (2%)	
6 (worsened)	Visit 2: 2/62 (3%) Visit 3: 1/58 (2%) Visit 4: 2/53 (4%) Visit 5: 1/42 (2%) Last visit: 3/61 (5%)	Visit 2: 1/55 (2%) Visit 3: 0/48 Visit 4: 0/38 Visit 5: 0/30 Last visit: 1/54 (2%)	
7 (greatly worsened)	Visit 2: 0/62 Visit 3: 1/58 (2%) Visit 4: 0/53 Visit 5: 0/42 Last visit: 2/61 (3%)	Visit 2: 0/55 Visit 3: 0/48 Visit 4: 0/38 Visit 5: 0/30 Last visit: 0/54	
Total severity score			
Total severity score median (min, max; 25th, 75th percentile)	Visit 2: 5.25 (0.0, 9.5; 4.00, 6.50) Visit 3: 4.00 (0.0, 10.0; 2.00, 5.50) Visit 4: 3.00 (0.0, 9.5; 1.50, 5.00) Visit 5: 3.00 (0.0, 8.0; 2.00, 4.50) Last visit: 3.00 (0.0, 10.5; 1.00, 5.00)	Visit 2: 4.50 (0.0, 9.0; 3.00, 6.00) Visit 3: 3.00 (0.0, 8.5; 1.50, 5.00) Visit 4: 3.00 (0.0, 8.5; 1.50, 4.00) Visit 5: 2.00 (0.0, 7.0; 1.00, 3.50) Last visit: 2.00 (0.0, 9.0; 1.00, 4.00)	
Comments: Logistic regression model of total severity score on treatment effect adjusting for age and baseline severity: Odds ratio for the treatment effect (twice daily/once daily) 1.85; (95% CI 0.88, 3.89); (99% CI 0.70, 4.91); significance of treatment effect: p=0.103; significance of age effect: p=0.667; significance of baseline total severity score effect: p<0.001.			

Adverse Events (no)			
Digestive system disorder	4	2	
Diseases and symptoms of the nervous system	5	1	
Diseases of the ear	0	1	
Diseases of the musculoskeletal system	1	0	
Diseases of the respiratory system	19	14	
Infectious and parasitic diseases	3	2	
Injury and poisoning	2	5	
Metabolic and immunity disorders	0	1	
Skin disorder	15	10	
Total number of reportings	49	36	
Total number of patients	31 (49%)	23 (40%)	
Relationship to study medication (no. of reportings)			
Unrelated	28	22	
Unlikely	17	8	
Possibly	2	4	
Probably	1	1	
Almost certain	1	1	
Total number of reasons	49	36	
Total number of patients	31 (49%)	23 (40%)	
Reason for Withdrawal			
Target area eczema cleared	10	12	
Adverse event	2	6	
Exacerbation of skin disease	4	3	
Failed to return	3	4	
Patient withdrew consent	2	0	
Deviation from protocol	1	4	
Other	0	1	
Total no. of reasons for withdrawal	22	30	
Total no. of patients	19	26	

Methodological comments

- Comparability of treatment groups: The two groups were balanced in terms of duration of eczema history. Some evidence that once daily group had a longer duration of their current exacerbation

(median of 8 months) than those in the twice daily group (median of 6 months).

- Method of data analysis: Global assessment scores were analysed using a proportional odds model, using age category as an explanatory variable in the model. Similarly, the total severity scores at last visit were compared using a proportional odds model, also including the baseline severity score in the model.
- Sample size/power calculation: It was felt that there were sufficient numbers of subjects to allow a meaningful comparison to be made. However, it was recognised that the power to detect any treatment effects would be less than the original study had planned.
- Attrition/drop-out: 45 subjects withdrew from the study prematurely.

General comments

- Generalisability: Patients aged 12 years or under with moderate to severe atopic eczema.

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [55] Author: Hoybye et al Year: 1991 Country: Denmark Study design: RCT Number of centres: 3 Setting: Not reported. Funding: Assistance from Schering-Plough A/S Denmark	Comparisons of different Interventions: 1. Mometasone furoate in fatty cream base (Elocon ®) once daily. 2. Hydrocortisone 17-butyrate in fatty cream base (Locoid ®) twice daily. Potency: Potent Duration of treatment: Three weeks. Note: paper also reports on a further 3 weeks of intermittent treatment, data not extracted. Other interventions used: Patients instructed to use only lubricant cream (Essex ®) in addition to topical steroid.	Number of Participants: 96 randomised. Total: 94 1. once-daily: 49 2. Twice daily: 45 Inclusion criteria for study entry: Age 18 to 70 years with a clinical diagnosis of typical atopic dermatitis. Scores of 0 to 3 were assigned to severity of erythema, infiltration and pruritus. Only total scores of 4.5 or more and stable or slowly progressive disease included. Exclusions: skin atrophy or use of topical corticosteroids within one week or systemic corticosteroids within one month.	Primary outcomes: Severity of disease Global evaluation Atrophy Patients' evaluation of severity at baseline, and change in disease activity after 3 weeks. Side effects Morning cortisol levels Method of assessing outcomes: Evaluations made after 3 weeks by dermatologists. Scores of 0 to 3 assigned by dermatologist for severity of erythema, infiltration and pruritus (3 greatest severity). Global evaluation scores for effect of treatment: 1 to 6 (cleared to exacerbation). Atrophy scores: 0 to 4 (none to severe). Patients' evaluation of severity at baseline rated on visual analogue scale (VAS) from no eczema to severe eczema. Change in disease activity at 3 weeks rated by patients: free of symptoms, improvement, no change, or deterioration. Patients also noted whether any change in degree of eczema during previous week. Morning cortisol levels determined at baseline and 3 weeks. Normal range 190-600nmol/L).

Characteristics of participants:

Median age	26 years
Disease duration more than 1 year	92/96 (or possibly 92/94, denominator not clear)
Percent of body surface area with dermatitis	2% to 50% of body surface area
No further details reported.	

Results

Outcomes	Once daily (Mometasone furoate)	Twice daily (Hydrocortisone 17-butyrate)	P Value
Improvement in symptoms at 3 weeks			
Pruritus	Significantly more improvement with momestasone furoate. Data not reported.		p=0.0069
Erythema	No difference in improvement between groups. Data not reported.		p=ns
Infiltration	No difference in improvement between groups. Data not reported.		p=ns
Both groups experienced statistically significant improvement of erythema, infiltration and pruritus after 3 weeks.			

	Once daily (Mometasone furoate)	Twice daily (Hydrocortisone 17-butyrate)	P Value
Global evaluation at 3 weeks			
Cleared or improved markedly	43/49 (88%)	35/45 (78%)	p=0.28
1 (cleared)	10/49	7/45	
2 (marked improvement)	33/49	28/45	
3 (moderate improvement)	6/49	7/45	
4 (slight improvement)	0	0	
5 (no change)	0	3/45	
6 (exacerbation)	0	0	
Patient evaluation of severity on VAS at 3 weeks	No difference in efficacy between treatments. Data not reported.		p=0.30
Plasma cortisol levels, nmol/L (median, range)	Baseline (n=9): 430 (330-920) 3 weeks (n=9): 450 (273-710)	Baseline (n=10): 470 (183-720) 3 weeks (n=9): 420 (183-910)	p=ns
Adverse Effects	States that treatment-related side effects were few, and these were similar in both groups. Reported side-effects were stinging, burning, itching, dryness, acne, folliculitis and hair growth. None showed evidence of skin atrophy.		

Methodological comments

- Allocation to treatment groups: States randomised, no further details reported.
- Blinding: Single blind. States that evaluations made by dermatologists who had no knowledge of which preparation was being used by the individual patient.
- Comparability of treatment groups: Baseline characteristics not reported, therefore unclear.
- Method of data analysis: Statistical evaluation of demographic variables and of differences in treatment results and side effects carried out using chi-square test, Fisher's exact test, or Mann Whitney U-test.
- Sample size/power calculation: Not reported.
- Attrition/drop-out: 96 randomised, but number in each group at randomisation not reported. Data reported for 94 patients. Not clear which group patients missing from, or reasons for withdrawal.

General comments

- Generalisability: Adults with atopic eczema.

- Outcome measures: Not shown to be valid.
- Inter-centre variability: Not reported.
- Conflict of interests: Assistance in carrying out the trial and materials used in study provided by Schering-Plough A/S Denmark (manufacturers of Elocon ®).
- Other: Although both products are classified by the BNF as 'potent', the paper describes hydrocortisone 17-butyrate as less potent.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Unknown
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	n/a
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9. Did the analyses include an intention to treat analysis?	Inadequate

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [44] Author: Koopmans et al Year: 1995 Country: Denmark, Norway, Finland, The Netherlands Study design: randomised controlled trial Number of centres: four Study setting: Not reported. Funding: Yamanouchi Europe BV, Leiderdorp, The Netherlands	Comparisons of different Interventions: 1. Locoid Lipocream fatty cream (0.1% hydrocortisone17-butyrate in an oil-in-water emulsion vehicle comprising 70% fatty substances and 30% water) once daily and Locobase once daily. 2. Locoid Lipocream fatty cream twice daily. Potency: potent Duration of treatment: until lesions had resolved or for a maximum of 4 weeks. Other interventions used: No occlusive dressings were used.	Number of Participants: 150 1. 75 2. 75 Sample attrition/dropout: Up to 3 missing. Inclusion criteria for study entry: over 12 years of age with atopic eczema. Exclusions: clear secondary infection of lesions and patients requiring concomitant use of systemic steroids.	Primary outcomes: Clinical features: erythema induration pruritus excoriation overall severity Investigators' and patients' opinions of overall improvement in skin disease at end of treatment. Method of assessing outcomes: Assessed before inclusion in trial and after 2 and 4 weeks of treatment. Features graded on 5-point scale: 0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe Overall improvement: +4 = clearance of lesions +3 = considerable improvement +2 = definite improvement +1 = minimal improvement 0 = no change -1 = worse

Characteristics of participants:

	Once daily	Twice daily	P Value
Mean age (SD, range)	28.7 (16.3, 12-78)	28.2 (14.6, 12-81)	
Sex (male/female)	27 / 48	27 / 47 no record 1	
Mean duration of illness, years (SD, range)	17.6 (13.6, 0.1-70)	19.0 (13.0, 0.5-60)	
Treatment during previous 6 months (yes / no)	66 / 9	64 / 9 no record 2	
Concomitant medication (yes / no)	26 / 40 no record 9	27 / 38 no record 10	
Symptom severity ratings (mean)			
Erythema	2.8	2.7	
Induration	2.3	2.1	

Scaling	1.7	1.6	
Pruritus	2.9	2.7	
Excoriation	1.9	1.8	
Overall	2.2	2.3	
Calculated total score	11.5	11.0	
Results			
Outcomes	**Once daily**	**Twice daily**	**P Value**
Ratings of clinical features			
Erythema (estimated from figure)	Week 2: 1.5 Week 4: 0.9	Week 2: 1.25 Week 4: 0.6	
Induration (estimated from figure)	Week 2: 1.4 Week 4: 0.8	Week 2: 1.0 Week 4: 0.5	
Scaling (estimated from figure)	Week 2: 0.7 Week 4: 0.4	Week 2: 0.6 Week 4: 0.25	
Pruritus (estimated from figure)	Week 2: 1.0 Week 4: 0.6	Week 2: 0.9 Week 4: 0.25	
Excoriation (estimated from figure)	Week 2: 1.0 Week 4: 0.4	Week 2: 0.9 Week 4: 0.3	
Overall severity (estimated from figure)	Week 2: 1.4 Week 4: 0.9	Week 2: 1.25 Week 4: 0.7	
Total score (estimated from figure)	Week 2: 5.3 Week 4: 3.0	Week 2: 4.3 Week 4: 1.8	
Clinically and statistically significant improvement in all ratings in both groups ($p<0.001$). Twice daily group showed greater reduction in ratings than once daily group ($p=0.04$ at two weeks). At 4 weeks $p= 0.08$. At 4 weeks, twice daily group showed more pronounced reduction in ratings for erythema ($p=0.03$).			
Total clearance of lesions at 2 weeks	9/73 (12%)	14/74 (19%)	P=0.29
Total clearance of lesions at 4 weeks	20/73 (27%)	35/75 (47%)	P=0.02
Overall improvement (%)	Investigators' opinion (n=74) Patients' opinion (n=73)	Investigators' opinion (n=74) Patients' opinion (n=75)	
Clearance of lesions	Investigators' opinion 36 (49) Patients' opinion 41 (55)	Investigators' opinion 52 (70) Patients' opinion 51 (68)	
Considerable improvement	Investigators' opinion 26 (35) Patients' opinion 17 (23)	Investigators' opinion 15 (20) Patients' opinion 19 (25)	
Definite improvement	Investigators' opinion 9 (12) Patients' opinion 12 (16)	Investigators' opinion 7 (9) Patients' opinion 4 (5)	
Minimal improvement	Investigators' opinion 3 (4) Patients' opinion 2 (3)	Investigators' opinion 0 (0) Patients' opinion 0 (0)	
No change	Investigators' opinion 0 (0) Patients' opinion 1(1)	Investigators' opinion 0 (0) Patients' opinion 1 (1)	
Worse	Investigators' opinion 0 (0) Patients' opinion 0 (0)	Investigators' opinion 0 (0) Patients' opinion 0 (0)	
Analysis of above showed an overall preference for twice daily treatment for the investigators ($p=0.01$) and patients ($p=0.006$).			
Adverse Effects	**Once daily**	**Twice daily**	

Total adverse events	4	4	
Folliculitis in all skin areas after 1 week of treatment; treatment stopped	1	0	
Folliculitis but treatment continued	0	4	
Burning, itching and stinging sensations; treatment continued	3	0	

Methodological comments

- Allocation to treatment groups: States randomised but no further details. Unit of randomisation: patient.
- Blinding: Double blind. Patients received two tubes, one to be used in the morning containing either Locobase or Locoid Lipocream, and the other to be used in the evening, containing Locoid Lipocream. Does not state whether Locoid Lipocream and Locobase were identical in appearance and texture.
- Comparability of treatment groups: Similar sex ratio, ages, duration of illness, concomitant medication and pre-treatment symptoms.
- Method of data analysis: Pretreatment characteristics compared using Student's t-test for parametric data, Mann Whitney test for non-parametric data, and Chi-squared tests for contingency tables for all other categorical data. Treatment data analysed using Chi-squared tests for contingency tables and Mantel-Haenszel procedures.
- Sample size/power calculation: Sample of 75 patients in each group gave an 80% power to detect differences in the overall score at $p<0.05$ allowing for dropouts and withdrawals. However, this outcome was reported in a figure only and the statistical significance not reported individually.
- Attrition/drop-out: 3 patients missed one of their clinic visits. States they were from the Locoid Lipocream group, this could mean the twice daily group but unclear. Numbers given for patient and investigator assessment of overall improvement, but not for clinical features at 2 and 4 weeks. Not clear where the 3 reported patients are missing.

General comments

- Generalisability: Patients over the age of 12 with atopic eczema.
- Outcome measures: Outcome measures subjective, potential recall bias for measures of overall improvement.
- Inter-centre variability: Not reported.
- Conflict of interests: Study is sponsored by Yamanouchi Europe BV, Leiderdorp, The Netherlands. Correspondence is not to one of the listed authors but to a Dr GA Rodgers at Yamanouchi Europe BV.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	Not applicable
7. Was the patient blinded?	Partial
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9. Did the analyses include an intention to treat analysis?	Inadequate

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [56] Author: Marchesi et al. Year: 1994 Country: Italy Study design: RCT Number of centres: One Setting: Not reported Funding: not reported; although contact address given as Schering Plough	Comparisons of different Interventions: 1. Mometasone furoate ointment 0.1% once daily 2. Betamethasone dipropionate ointment 0.05% twice daily Potency: potent Duration of treatment: Up to 3 weeks Other interventions used: Any other medication interfering with drug was not allowed; all other medications given during the study were recorded.	Number of Participants: Randomised : 60 1. Once daily : 30 2. Twice daily : 30 Inclusion criteria for study entry: The disease condition was stable or worsening for more than a week; patients showed all three symptoms (erythema, induration and pruritus) in target area; total severity score at entry at least 6 or more (score 0 to 3); patients had not received corticosteroids either topically in the week before or systemically in the 4 weeks before; no signs of skin atrophy in target area; not hypersensitive to the drug or the components of its formulation.	Primary outcomes: Individual signs and symptoms of illness (erythema, induration, pruritus) and skin atrophy A global evaluation of changes from baseline of disease status by physician. Safety Method of assessing outcomes: Evaluations of response to treatment were carried out at day 2, 3, 4, 7, 14 and 21. Evaluation of individual signs and symptoms of disease and of signs of skin atrophy scored at baseline and evaluation visits according to scale: 0 = none 1 = mild 2 = moderate 3 = severe Physician's global evaluation of changes from baseline of disease status according to scale: 1 = symptoms cleared: 100% improvement 2 = marked improvement: 75% to less than 100% clearance of symptoms 3 = moderate improvement: 50% to less than 75% clearance of symptoms 4 = slight improvement: less than 50% clearance of symptoms 5 = no change: no improvement 6 = exacerbation: worsening Safety was evaluated at each visit by examination and questioning of the patients. Lab tests checked at beginning and end of the treatment (no further information).

Characteristics of participants:

	Once daily (mometasone furoate) (n = 30)	Twice daily (betamethasone diproprionate) (n = 30)	P Value
Mean age (SD, range)	37.7 (17.1, 18-65)	41.9 (17.1, 18-65)	
Sex	M = 18; F = 12	M = 20; F = 10	
Total duration of	28.3 (34.2)	37.1 (48.1)	

disease (months), mean (SD)			
Disease status at entry (%)	Stable: 6.7 Worsening: 93.3	Stable: 3.4 Worsening: 96.6	
Percent of body involved	Up to 25%: 96.7 26-50%: 3.3	Up to 25%: 86.7 26-50%: 13.3	
Target area (no of patients)			
Shoulders	1	1	
Chest	1	2	
Abdomen	0	1	
Buttocks	0	1	
Neck	2	0	
Arms	17	14	
Forearms	9	11	
Other treated area (no of patients)			
Shoulders	0	1	
Arms	6	3	
Hands	7	6	
Legs	2	2	
Neck	2	0	
Ears	1	0	
Buttocks	0	1	
None	12	17	
No baseline difference was seen between drugs for the three symptoms (p>0.05)			
Results			
Outcomes	**Once daily (mometasone furoate) (n = 30)**	**Twice daily (betamethasone diproprionate) (n = 30)**	**P Value**
Percent reduction of signs and symptoms severity score (estimated from figure)			
Erythema	Day 2: 12 Day 3: 27 Day 4: 44 Day 7: 66 Day 14: 83 Day 21: 91	Day 2: 9 Day 3: 21 Day 4: 35 Day 7: 54 Day 14: 80 Day 21: 90	p=ns
Induration	Day 2: 5 Day 3: 19 Day 4: 34 Day 7: 61 Day 14: 84 Day 21: 92	Day 2: 5 Day 3: 15 Day 4: 25 Day 7: 54 Day 14: 80 Day 21: 95	p=ns
Pruritus	Day 2: 20 Day 3: 45 Day 4: 67 Day 7: 88 Day 14: 97 Day 21: 100	Day 2: 32 Day 3: 48 Day 4: 64 Day 7: 83 Day 14: 97 Day 21: 99	p=ns
Mean score values were significantly reduced at all visits compared to baseline as of the second day of treatment (p<0.01). Mometasone once daily induced a slightly greater reduction of erythema and induration mean score at an earlier stage, although at the end of treatment there was no difference between the two drugs.			
Physician's global evaluation of response to treatment, number of patients / response			

Cleared	day 2: 0 day 3: 0 day 4: 0 week 1: 5 (16.7%) week 2: 12 (40%) week 3: 16	day 2: 0 day 3: 0 day 4: 0 week 1: 3 (10%) week 2: 9 (30%) week 3: 15	
Good improvement	day 2: 2 day 3: 5 day 4: 8 week 1: 11 (36.7%) week 2: 15 week 3: 14	day 2: 2 day 3: 3 day 4: 6 week 1: 9 (30%) week 2: 20 week 3: 15	
Moderate improvement	day 2: 2 day 3: 7 day 4: 8 week 1: 9 week 2: 3 week 3: 0	day 2: 0 day 3: 5 day 4: 6 week 1: 15 week 2: 1 week 3: 0	
Slight improvement	day 2: 11 day 3: 10 day 4: 14 week 1: 5 week 2: 0 week 3: 0	day 2: 13 day 3: 18 day 4: 16 week 1: 3 week 2: 0 week 3: 0	
Unchanged	day 2: 15 day 3: 8 day 4: 0 week 1: 0 week 2: 0 week 3: 0	day 2: 15 day 3: 4 day 4: 2 week 1: 0 week 2: 0 week 3: 0	
Exacerbation	day 2: 0 day 3: 0 day 4: 0 week 1: 0 week 2: 0 week 3: 0	day 2: 0 day 3: 0 day 4: 0 week 1: 0 week 2: 0 week 3: 0	
More than one third of patients start to show slight improvement as from the second day of treatment. After 1 week, 5 (16.7%) of the mometasone group and 3 (10%) of the betamethasone diproprionate group were completely cleared.			
Adverse Effects (number of reports)			
Telangiectasias of mild severity in last 2 weeks of treatment	4	5	
Loss of skin marks and reduced elasticity	0	1	
Neither systemic nor local reactions occurred. In all patients checked for blood tests, values varied within a very narrow range.			
Methodological comments • Allocation to treatment groups: Randomised, but no further details. • Blinding: States third-party blind evaluator. No further information provided. Patients appear not to have been blinded, no mention of a placebo in the once-daily group. • Comparability of treatment groups: The two groups were evenly distributed for all demographic and			

epidemiological characteristics considered.

- Method of data analysis: Analysis of variance used to determine the statistical significance of the score differences between the two groups of patients at each visit. The Fisher's exact test was used in the evaluation of the score differences of both the physician's global evaluation and the patient's self evaluation.
- Sample size/power calculation: Not reported.
- Attrition/drop-out: States that all patients completed the study.

General comments

- Generalisability: Adults with atopic dermatitis of at least moderate severity.
- Outcome measures: Not shown to be valid.
- Inter-centre variability: Not applicable.
- Conflict of interests: Not stated. Address for reprints is to named author based at Schering-Plough.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	n/a
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9. Did the analyses include an intention to treat analysis?	Inadequate

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [57] Author: Rajka et al Year: 1993 Country: Norway, Denmark, Sweden Study design: RCT Number of centres: 4 Study setting: Dermatologic centres Funding: Schering Plough A/S, Norway.	Comparisons of different Interventions: 1. Mometasone furoate fatty cream 0.1% (Elocon ®) once daily 2. Betamethasone valerate cream (Betnovate ®) 0.1% twice daily Potency: Potent Duration of treatment: 3 weeks Other interventions used: Antihistamines were not permitted during study period. Concomitant medication during study was monitored.	Number of Participants: Total 117 1. once-daily: 57 2. twice-daily: 60 Inclusion/exclusion criteria for study entry: Aged over 16 years of age with an established diagnosis of atopic dermatitis in a stable phase of mild to moderate intensity. Area of involvement, mostly on chest, back, neck and forearms was 25% to 50% of body surface. Exclusions: Pregnant women, subjects with drug or alcohol abuse, subjects who had received systemic steroids within 4 weeks or topical corticosteroids one week before study. Patients will allergic contact dermatitis also included, data not extracted.	Primary outcomes: Percent improvement in total atopic dermatitis scores. The following outcomes are listed in the methods, but data not presented for atopic dermatitis separately. Severity of erythema, induration and pruritus. Global evaluation of involve areas compared with baseline. Changes in concomitant therapy Signs of skin thinning or adverse reactions. Patient description of severity. Patient evaluation of overall response at end of study. Cosmetic acceptability. Method of assessing outcomes: Comparable lesions on both sides of the body were selected as target sites, except facial and hand lesions. Patients evaluated weekly. Severity rated on 4-point scale: 0 = none 1 = mild 2 = moderate 3 = severe Global evaluation compared with baseline: 1 = cleared (100% disappearance of signs and symptoms) 2 = marked improvement (75% to 100%) 3 = moderate improvement (50% to 75%) 4 = slight improvement (<50%) 5 = no change 6 = exacerbation Global evaluation score on day 22 was based on changes in severity and total symptoms and signs. Patients described severity of skin lesions on a diary card.

Characteristics of participants:
Not reported for atopic dermatitis separately.

Results

Outcomes	Once daily mometasone	Twice daily betamethasone	P Value
Percent improvement in total atopic dermatitis scores	8 days: 80% 15 days: 93% 22 days: 96% End study: 98%	8 days: 58% 15 days: 75% 22 days: 86% End study: 86%	p<0.01 p<0.01 p<0.01 p<0.01

The difference for atopic dermatitis patients was statistically significant ($p<0.01$) in favour of once-daily mometasone for all visits according to the analysis of variance.
The diary cards of patients showed the same tendency, showing significant improvement after 3 to 4 days. The effect of twice-daily betamethasone was slower.

Adverse Effects

Not reported for atopic dermatitis separately.
No suppression of plasma cortisol levels was observed, nor were there significant changes in laboratory values.

Methodological comments

- Allocation to treatment groups: States randomised, method not stated.
- Blinding: Single blind, no further details. No placebo treatment in once-daily group, therefore assume patients not blinded.
- Comparability of treatment groups: Total group (atopic dermatitis and allergic contact dermatitis) similar in age, sex, distribution and duration of disease, but data for atopic dermatitis not presented separately.
- Method of data analysis: Not reported.
- Sample size/power calculation: Not reported.
- Attrition/drop-out: 7 of 160 (atopic dermatitis and allergic contact dermatitis) were dropouts or noncompliant with the protocol, but data for atopic dermatitis not reported separately.

General comments

- Generalisability: Patients over 16 years with mild to moderate atopic dermatitis.
- Outcome measures: Data reported for improvement in total atopic dermatitis scores only, despite list of other outcomes described in methods. Not clear how this outcome was assessed or by whom (patient or physician).
- Inter-centre variability: Not reported.
- Conflict of interests: Study funded by Schering-Plough, manufacturer of Elocon ®

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Unknown
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Partial
6. Was the care provider blinded?	n/a
7. Was the patient blinded?	Inadequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9. Did the analyses include an intention to treat analysis?	Inadequate

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [58] Author: Tharp Year: 1996 Country: USA Study design: RCT Number of centres: 9 Study setting: Not reported. Funding: Not stated, but data referenced to Glaxo Wellcome Inc.	Comparisons of different Interventions: 1. Fluticasone propionate cream 0.05% once daily and vehicle once daily. 2. Fluticasone propionate cream 0.05% twice daily. 3. Vehicle twice daily. Potency: Potent Duration of treatment: 4 weeks or until complete remission. Mean duration: Once daily: 26.8 days. Twice daily: 26.1 days. Vehicle: 24.5 days. Other interventions used: Occlusive dressings were not used. No other treatments or medications were used.	Number of Participants: 238 enrolled 1. once daily: 79 2. twice daily: 79 3. vehicle 80 232 evaluated and included in analysis: 1. once daily: 77 2. twice daily: 77 3. vehicle 78 Sample attrition/dropout: 55 (23.1%) Inclusion criteria for study entry: 12 years and older with an established diagnosis of eczema. Exclusion criteria: prescribed medications with associated washout periods, interfering disease states, sensitivity to ingredients of study medication or to other topical or systemic steroid therapy, circumstances affecting ability of patient to comply with protocol or give valid informed consent. Patients with acute, self-limited eczema (e.g. allergic contact eczema) and patients whose eczema would be likely to improve spontaneously without treatment.	Primary outcomes: Physician's gross assessment of clinical response of target lesion. Severity of signs and symptoms of eczema (erythema, pruritus, skin thickening, lichenification, vesiculation, crusting). Total severity score (erythema, pruritus, thickening). Patient's subjective assessment of treatment effects. Occurrence of adverse events. Method of assessing outcomes: Investigator identified one target lesion for efficacy evaluation; lesions of the scalp, face, axillae and groin were not chosen as the target lesion. Clinical evaluations made weekly for four weeks (day 8, 15, 22, 29). The same investigator evaluated the same patients throughout study. If complete remission or target lesion was obtained prior to day 29, patient was instructed to continue to apply study medication and a final visit scheduled as soon as possible. All efficacy and safety evaluations were conducted then (end-of treatment evaluations). Physician's gross assessment of response to therapy compared with baseline was made at each visit using scale: 1 = cleared (100% resolution of signs and symptoms except for residual discoloration) 2 = excellent (75% to 99% improvement) 3 = good (50% to 74% improvement) 4 = fair (25% to 49% improvement) 5 = poor (<25% improvement) 6 = worse (exacerbation) Severity of each sign and symptom rated by physician at each visit using 7-point ordinal scale in 0.5 point increments: 0 = absent 0.5 to 1 = mild 1.5 to 2.5 = moderate 3 = severe Total sign and severity score derived by summing scores for erythema, pruritus and thickening on a scale of 0 to 3.

			Patient's subjective assessment of treatment effects obtained at each visit, rated on scale: 1 = excellent 2 = good 3 = fair 4 = poor Occurrence of adverse events monitored throughout study (method not stated). Relationship of adverse events to use of study medication judged by investigator. Adverse events judged to be possibly, probably or almost certainly related to study medication were categorised as drug-related events.

Characteristics of participants:

	Once daily (n=79)	**Twice daily (n=79)**	**Vehicle (n=80)**	**P Value**
Age, mean (SE, range)	38 (1.9, 14-77)	38 (1.8, 14-82)	36 (1.8, 12-87)	0.584
Sex (%) male, Female	54 (68) 25 (32)	50 (63) 29 (37)	56 (70) 24 (30)	0.656
Ethnic origin (%) White Black Asian Other	 55 (70) 15 (19) 4 (5) 5 (6)	 50 (63) 11 (14) 6 (8) 12 (15)	 57 (71) 11 (14) 5 (6) 7 (9)	0.543
Disease status (%) worsening stable	 51 (65) 28 (35)	 50 (64) 28 (36)	 51 (64) 29 (36)	0.994
History of eczema (yrs), median (range)	13 (0.4-70)	10.5 (0-60)	10.5 (0-71)	0.701
Duration of current episode (wks), median (range)	8 (1-1300)	6 (1-1820)	9 (1-1404)	0.337
Mean sign and symptom severity scores:				
Erythema	2.3	2.3	2.4	
Pruritus	2.5	2.5	2.5	
Skin thickening	2.1	2.1	2.2	
Lichenification	1.6	1.6	1.7	
Vesiculation	0.6	0.6	0.6	
Crusting	0.8	0.9	1.0	
Sites evaluated: arms (%)	22%	38%	23%	0.04

Each enrolled patient has a combined target lesion severity score for erythema, skin thickening and pruritus of at least 6.

Results

Outcomes	**Once daily**	**Twice daily**	**Vehicle**	**P Value**

Physician's gross assessment (% of patients with target lesion response rated cleared or excellent)	Day 8 (n=76): 29 Day 15 (n=73): 42 Day 22 (n=69): 57 Day 29 (n=65): 69	Day 8 (n=76): 39 Day 15 (n=73): 62 Day 22 (n=68): 70 Day 29 (n=60): 78	Day 8 (n=78): 6 Day 15 (n=65): 14 Day 22 (n=60): 23 Day 29 (n=58): 33	Treatments vs vehicle p<0.001 at each visit. Day 22 only: once vs twice p<0.014 (other visits p=ns).
Patients whose arms were evaluated constituted a subset separate from patients with other evaluation sites. Analysis indicated that the results of the physician's gross assessment were not altered by the imbalance in evaluation sites among treatment groups.				
Severity of symptoms and signs (day 29)				
Erythema (p value vs baseline)	0.6 (p<0.001)	0.5 (p<0.001)	1.3 (p=ns)	
Pruritus (p value versus baseline)	0.4 (p<0.001)	0.3 (p<0.001)	1.2 (p=ns)	
Skin thickening (p value vs baseline)	0.5 (p<0.001)	0.5 (p<0.001)	1.3 (p=ns)	
Lichenification (p value vs baseline)	0.4 (p<0.001)	0.4 (p<0.001)	1.0 (p=ns)	
Vesiculation (p value vs baseline)	0.1 (p=ns)	0 (p=ns)	0.2 (p=ns)	P=ns
Crusting (p value vs baseline)	0.2 (p=ns)	0.1 (p=ns)	0.4 (p=ns)	P=ns
At end of treatment, both treatments had significantly greater improvements compared with vehicle for all signs and symptoms (p≤ 0.005). No significant differences were found between mean sign and symptom scores for once daily versus twice daily groups at day 29 and at end of treatment (p≥ 0.07).				
Total severity scores (mean percentage change)	Day 8 (n=76): 3.4 (-51.7%) Day 15 (n=73): 2.6 (-63.9%) Day 22 (n=69): 2.1 (-70.7%) Day 29 (n=65): 1.5 (-79.5%) End of treatment: 1.7	Day 8 (n=76): 3.2 (-55.1%) Day 15 (n=73): 1.9 (-73.0%) Day 22 (n=68): 1.5 (-77.9%) Day 29 (n=60): 1.3 (-81.8%) End of treatment: 1.4	Day 8 (n=78): 5.4 (-23.4%) Day 15 (n=65): 4.7 (-34.6%) Day 22 (n=60): 4.1 (-42.2%) Day 29 (n=58): 3.8 (-46.0%) End of treatment: 4.5	Both treatments superior to vehicle at each visit (p<0.0001) End of treatment p=0.9
Patients' subjective assessment (percent rating treatment excellent or good)	Day 8 (n=76): 74 Day 15 (n=73): 73 Day 22 (n=69): 72 Day 29 (n=65): 74	Day 8 (n=76): 76 Day 15 (n=73): 84 Day 22 (n=68): 81 Day 29 (n=60): 71	Day 8 (n=78): 37 Day 15 (n=65): 40 Day 22 (n=60): 44 Day 29 (n=58): 43	Both treatments superior to vehicle at each visit (p<0.0001). Once vs twice: Day 15 p=0.01 Day 22 p=0.02 (other visits p=ns)
A differential trend (p=0.093) favoured twice daily over once daily at the end of treatment.				

Adverse Effects No. of patients (%)	**(n=77)**	**(n=77)**	**(n=78)**	
Burning	2 (3)	0	4 (5)	
Dryness	2 (3)	0	0	
Pruritus	0	1 (1)	5 (6)	
Erythema	0	0	1 (1)	
Stinging	0	1 (1)	2 (3)	
Irritation	0	1 (1)	0	
Total	4 (5)	3 (4)	8 (10)	
None of the adverse events was judged to be serious or unexpected.				
Withdrawals	**(n=79)**	**(n=79)**	**(n=80)**	
Patients withdrawn (% of patients treated)	14 (17.7)	19 (24.1)	22 (27.5)	
Treatment failure	2 (2.5)	4 (5.1)	14 (17.5)	
Early cure	5 (6.3)	12 (15.2)	0	
Adverse events	1 (1.3)	1 (1.3)	4 (5.0)	
Protocol violation	2 (2.5)	1 (1.3)	1 (1.3)	
Noncompliant / personal	4 (5.1)	1 (1.3)	3 (3.8)	

Methodological comments

- Allocation to treatment groups: States random, but method not described.
- Blinding: States double-blind. Study medications packaged in identical 30g tubes, each patient received four tubes. Twice daily group and vehicle group received two tubes for morning and two tubes for evening containing either fluticasone or vehicle, respectively. Once daily group received two morning tubes (vehicle) and two evening tubes (fluticasone). No description of contents.
- Comparability of treatment groups: No statistically significant differences between treatment groups with respect to gender, ethnic origin, age or baseline disease characteristics. Severity of signs and symptoms were comparable. No statistically significant difference between groups in percentage of patients missing at least one study medication, sites affected, or sites treated. However, greater proportion of patients in twice daily group had their arms evaluated.
- Method of data analysis: All statistical tests were two sided and at 5% significance level. Comparison of the three treatments were made at baseline and at each postbaseline evaluation. With the exception of the mean change (decrease) in the total severity score, the p values for the group comparisons (once daily or twice daily vs vehicle and once daily vs twice daily) were based on the Van Elteren Rank Sum Test, adjusted for investigator differences. For the mean change in total severity score, pairwise tests were made using a t test.
- Sample size/power calculation: based on an expected difference between active and vehicle treatment groups of at least 25%. Given this assumption, sixty patients per treatment group were found to be sufficient to detect this difference with power of 80%.
- Attrition/drop-out: of 238 enrolled patients, 2 from each group did not return for any follow-up visits. 55/232 (24%) withdrew from study prior to completion of day 29 evaluation (see table above).

General comments

- Generalisability: Patients with an established diagnosis of eczema (moderate to severe).
- Outcome measures: Not shown to be valid or reproducible. Subjective, and rely on memory of condition at baseline, therefore possibility of recall bias.
- Inter-centre variability: Not reported.
- Conflict of interests: None stated, but all data referenced to Glaxo Dermatology, Division of Glaxo Wellcome Inc.
- Other: Diagnosis of patients described as ‘eczema’ rather than ‘atopic eczema’. Therefore the reviewers

sought clinical advice, which suggested that in view of exclusion criteria (see above), these patients would likely have atopic eczema.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	n/a
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9. Did the analyses include an intention to treat analysis?	Inadequate

Appendix 9 Studies comparing very potent corticosteroids

Reference and Design	Intervention	Participants	Outcome measures
Study Ref: [42] Author: Sudilovsky et al Year: 1981 Country: USA Study design: Randomised controlled trial (side of body randomised) Number of centres: multicentre (number not clear) Study setting: Not reported. Funding: Not reported.	Comparisons of different Interventions: 1. halcinonide cream 0.1% once daily plus placebo (cream base vehicle, castor oil formula) twice daily 2. halcinonide cream 0.1% three times daily Potency: very potent Duration of treatment: Maximum 3 weeks, or when complete remission obtained if sooner. Other interventions used: No concomitant local or systemic therapy that could have affected condition. No occlusive dressings used. (Note: study also compared halcinonide cream 0.1% once daily versus placebo, data not extracted)	Number of Participants: 149 (Note: the study also included 343 psoriasis patients, data not extracted). Sample attrition/dropout: 138 patients at week 2 assessment, 116 patients at week 3 assessment. Inclusion criteria for study entry: atopic dermatitis with bilateral lesions of similar severity and chronicity. None had received corticosteroid medication for at least one week prior to entry. Exclusions: previous history of poor response to topical corticosteroids.	Primary outcomes: Comparative clinical response Absolute therapeutic response Overall response Method of assessing outcomes: 3 weekly follow-up visits: 1. Comparative response of similar lesions on each side determined, including erythema, edema, changes in size and thickness of lesions: Markedly superior – easily discernible difference in response. Slightly superior – a barely discernible difference. Equal response – no observable difference. 2. Absolute response of lesions on each side according to estimated percentage improvement over pre-treatment condition: Excellent (75-100% improvement) cleared or essentially cleared, including cases with residual pinkness of skin, but no edema and little or no thickening. Good (50-74% improvement) – substantial, easily perceived improvement. Fair (25-49% improvement) – some discernible improvement (in at least one parameter). Poor (<25% improvement) – no significant improvement or worsening. End of treatment: Overall evaluation of both the comparative and absolute responses made by investigator

Characteristics of participants:
Not reported for atopic dermatitis patients separately.

Results

Outcomes	Once daily	Twice daily	P Value
Comparative			

clinical response			
Week 1 (n=149) (number with equal response: 85)	Markedly superior 5 Slightly superior 21	Markedly superior 11 Slightly superior 27	p=ns
Week 2 (n=138) (number with equal response: 87)	Markedly superior 3 Slightly superior 18	Markedly superior 15 Slightly superior 15	p<0.05
Week 3 (n=116) (number with equal response: 81)	Markedly superior 2 Slightly superior 9	Markedly superior 12 Slightly superior 12	p<0.01
Overall (n=149) (number with equal response: 70 (47.0%))	Markedly superior 2 (1.3%) Slightly superior 30 (20.1%) Total with better response: 32 (21.5%)	Markedly superior 12 (8.1%) Slightly superior 35 (23.5%) Total with better response: 47 (31.5%)	p<0.05
Absolute therapeutic response (Excellent + Good)			
Week 1 (n=149)	80 (53.7%)	87 (58.4%)	p=ns
Week 2 (n=138)	104 (75.4%)	108 (78.3%)	p=ns
Week 3 (n=116)	99 (85.3%)	100 (86.2%)	p=ns
Overall (n=149)	122 (81.9%)	125 (83.9%)	p=ns

Comparison of the rate of increase in numbers of responses judged satisfactory over the three-week treatment period revealed no statistically significant difference between regimens (ie no evidence of tachyphylaxis)

No significant relationships were observed to severity of episode of prior chronicity.

Adverse Effects

States that side-effects were generally of a mild nature, the most common being burning, puritus and erythema, with no differences in incidence between once daily and three times daily regimens. However, not reported for eczema and psoriasis separately. No systemic effects were observed.

Methodological comments

- Allocation to treatment groups: Side of body allocated by table of random numbers.
- Blinding: States double-blind. States that part of the study patient assigned to (once daily versus placebo, once daily versus three times daily) and the side of the body chosen for a specific treatment was unknown to investigators. Halcinonide cream and placebo packaged in identical tubes, but contents not mention (base cream used as placebo).
- Comparability of treatment groups: Patients were required to have 'bilateral lesions of similar severity and chronicity'.
- Method of data analysis: Comparative and absolute response categories were assigned numerical values. Paired t-test used to compare once daily and three times daily regimens. Regression analysis performed on results to determine whether in observed results were related to pre-treatment severity of chronicity of condition. Paired t-test was used to analyse the week to week change in number of 'excellent', 'good', 'fair', and 'poor' responses and the overall response curves to determine if there was any difference with respect to changes in response rate over time, ie to determine if one regimen was subject to tachyphylaxis with respect to the other. With regard to response curves, only patients with observations at all three weekly time points were analysed. Orthogonal contrasts were used to fit linear and quadratic curves to the once daily and three times daily responses of each patient.

- Sample size/power calculation: Not reported.
- Attrition/drop-out: Not reported. Only 138/149 patients at week 2 and 116/149 at week 3 were assessed, but it is not clear whether these are drop-outs or whether complete remission was achieved (in which case treatment was stopped).

General comments

- Generalisability: Not clear as characteristics of the included atopic eczema patients were not reported.
- Outcome measures: Measures not objective. Assessed by investigator, comparing sides of body and improvement over pre-treatment condition. Potentially subject to recall bias.
- Inter-centre variability: Not reported.
- Conflict of interests: Not reported.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Unknown
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	Not applicable
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
9. Did the analyses include an intention to treat analysis?	Inadequate

Appendix 10 List of excluded studies

Aalto-Korte K, Turpeinen M. Pharmacokinetics of topical hydrocortisone at plasma level after applications once or twice daily in patients with widespread dermatitis. *British Journal of Dermatology* 1995;133(2):259-63. [Not RCT]

Belknap BS, Dobson RL. Efficacy of halcinonide cream, 0.1 percent, in the treatment of moderate and severe dermatoses. *Cutis* 1981;27(4):433-5. [Not RCT]

Bigby M. A thorough systematic review of treatments for atopic eczema. *Archives of Dermatology* 2001;137(12):1635-6. [Editorial, not a systematic review]

Chu AC, Munn S. Fluticasone propionate in the treatment of inflammatory dermatoses. *British Journal of Clinical Practice* 1995;49(3):131-3. [Non-systematic review]

Dominguez L, Hojyo T, Vega E, Jones ML, Peets E. Comparison of the safety and efficacy of mometasone furoate cream 0.1% and clobetasone butyrate cream 0.05% in the treatment of children with a variety of dermatoses. *Current Therapeutic Research, Clinical & Experimental* 1990;48(1):128-39. [Different potencies]

Eaglstein WH, Farzad A, Capland L. Editorial: Topical corticosteroid therapy: efficacy of frequent application. *Archives of Dermatology* 1974;110(6):955-6. [Not RCT]

English JS, Bunker CB, Ruthven K, Dowd PM, Greaves MW. A double-blind comparison of the efficacy of betamethasone dipropionate cream twice daily versus once daily in the treatment of steroid responsive dermatoses. *Clinical & Experimental Dermatology* 1989;14(1):32-4. [Patients not limited to atopic eczema]

Fredriksson T, Lassus A, Bleeker J. Treatment of psoriasis and atopic dermatitis with halcinonide cream applied once and three times daily. *British Journal of Dermatology* 1980;102(5):575-7. [Patients not limited to atopic eczema]

Garretts M. Controlled double-blind comparative trial with fluprednylidene acetate cream and its base. *Archiv fur Dermatologische Forschung* 1975;251(3):165-8. [Patients not limited to atopic eczema]

Gartner L, Tarras-Wahlberg C. A double-blind controlled evaluation of Diproderm cream 0.05%, twice a day treatment in comparison with once a day treatment in eczema. *Journal of International Medical Research* 1984;12(1):59-61. [Patients not limited to atopic eczema]

Goh CL, Lim JT, Leow YH, Ang CB, Kohar YM. The therapeutic efficacy of mometasone furoate cream 0.1% applied once daily vs clobetasol propionate cream 0.05% applied twice daily in chronic eczema. *Singapore Medical Journal* 1999;40(5):341-4. [Different potencies]

Haneke E. The treatment of atopic dermatitis with methylprednisolone aceponate (MPA), a new topical corticosteroid. *Journal of Dermatological Treatment* 1992;3(SUPPL. 2):13-5. [Product not listed in BNF, potency unclear]

Harder F, Rufli T. [Therapy of eczema. Once daily use of diflorasone diacetate in comparison to thrice daily use of betamethasone-17-valerate]. [German]. *Schweizerische Rundschau fur Medizin Praxis* 1983;72(39):1240-2. [Non-English language, potency of product unclear]

Hersle K, Mobacken H. Once daily application of diflorasone diacetate ointment compared with betamethasone valerate ointment twice daily in patients with eczematous dermatoses. *Journal of International Medical Research* 1982;10(6):423-5. [Patients not limited to atopic eczema, potency unclear]

Johansson EA, Stiger TR. Comparative efficacy of once a day diflorasone diacetate and twice a day betamethasone valerate ointment applications in eczematous dermatitis. *Current Medical Research & Opinion* 1984;9(4):259-64. [Patients not limited to atopic eczema, potency unclear]

Lawless, and S, S.-S. Comparative efficacy of once-a-day diflorasone diacetate and t.i.d. hydrocortisone in treating eczematous dermatitis. *Current Therapeutic Research Clinical and Experimental* 1978;23(2):159. [Patients not limited to atopic eczema, potency unclear]

Lebwohl M. A comparison of once-daily application of mometasone furoate 0.1% cream compared with twice-daily hydrocortisone valerate 0.2% cream in pediatric atopic dermatitis patients who failed to respond to hydrocortisone: mometasone furoate study group. *International Journal of Dermatology* 1999;38(8):604-6. [Hydrocortisone valerate 0.2% not in BNF, potency unclear]

Levy A. Comparison of 0.1% halcinonide with 0.05% betamethasone dipropionate in the treatment of acute and chronic dermatoses. *Current Medical Research & Opinion* 1977;5(4):328-32. [Different potencies]

Lucky AW, Leach AD, Laskarzewski P, Wenck H. Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. *Pediatric Dermatology* 1997;14(4):321-4. [CCT, groups not comparable]

Meenan FO. The treatment of atopic dermatitis with clobestasol propionate. *Irish Medical Journal* 1977;70(10):316. [Not RCT]

Muzaffar F, Hussain I, Rani Z, Aziz A, Sultan B. Emollients as an adjunct therapy to topical corticosteroids in children with mild to moderate atopic dermatitis. *Journal of Pakistan Association of Dermatologists* 2002;12(APR./JUNE):64-8. [Not RCT]

Rafanelli A, Rafanelli S, Stanganelli I, Marchesi E. Mometasone furoate in the treatment of atopic dermatitis in children. *Journal of the European Academy of Dermatology and Venereology* 1993;2(3):225-30. [Different potencies]

Reidhav I, Svensson A. Betamethasone valerate versus mometasone furoate cream once daily in atopic dermatitis. *Journal of Dermatological Treatment* 1996;7(2):87-8. [Both products once-daily]

Ronn HH. Fluocinonide compared with betamethasone in the treatment of eczema and psoriasis. *Practitioner* 1976;216(1296):704-6. [Patients not limited to atopic eczema]

Squires DJ, Masson EL. An evaluation of once-daily applications of diflorasone diacetate in eczematous dermatoses. *Journal of International Medical Research* 1981;9(1):79-81. [Not RCT]

Vernon HJ, Lane AT, Weston W. Comparison of mometasone furoate 0.1% cream and hydrocortisone 1.0% cream in the treatment of childhood atopic dermatitis. *Journal of the American Academy of Dermatology* 1991;24(4):603-7. [Different potencies]

Viglioglia P, Jones ML, Peets EA. Once-daily 0.1% mometasone furoate cream versus twice-daily 0.1% betamethasone valerate cream in the treatment of a variety of dermatoses. *Journal of International Medical Research* 1990;18(6):460-7. [Patients not limited to atopic eczema]

Wishart JM, Lee I-S. Mometasone versus betamethasone creams: a trial in dermatoses. *New Zealand Medical Journal* 1993;106:203-5. [Patients not limited to atopic eczema]

Wolkerstorfer A, Strobos MA, Glazenburg EJ, Mulder PG, Oranje AP. Fluticasone propionate 0.05% cream once daily versus clobetasone butyrate 0.05% cream twice daily in children with atopic dermatitis. *Journal of the American Academy of Dermatology* 1998;39(2:Pt 1):226-31. [Different potencies]