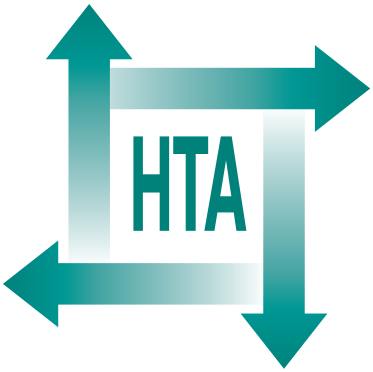
Health Technology Assessment 2004; Vol. 8: No. 47

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

C Green, JL Colquitt, J Kirby, P Davidson and E Payne

November 2004

Health Technology Assessment
NHS R&D HTA Programme



How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

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

C Green,* JL Colquitt, J Kirby, P Davidson and E Payne

Southampton Health Technology Assessments Centre, Southampton, UK

* Corresponding author

Declared competing interests of authors: None. Peter Davidson is a member of the editorial board for *Health Technology Assessment*, although he was not involved in the editorial process for this report.

Published November 2004

This report should be referenced as follows:

Green C, Colquitt JL, Kirby J, Davidson P, Payne E. 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. *Health Technol Assess* 2004;**8**(47).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/19/01. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

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

C Green,* JL Colquitt, J Kirby, P Davidson and E Payne

Southampton Health Technology Assessments Centre, Southampton, UK

* Corresponding author

Objectives: 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.

Data sources: Electronic databases. Bibliographies of included studies and related papers. Experts in the field. Manufacturer submissions to the National Institute for Clinical Excellence.

Review methods: Studies were assessed for inclusion according to predefined criteria by two reviewers. Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Clinical effectiveness data were synthesised through a narrative review with full tabulation of results.

Results: One RCT comparing moderately potent corticosteroids, eight RCTs comparing potent corticosteroids and one RCT comparing very potent corticosteroids were included. No RCTs or CCTs of mild corticosteroids were eligible. Most RCTs were of poor methodological quality, although two were judged to be of good quality. The only study that compared moderately potent corticosteroids found no significant difference between once- and twice-daily application. For potent corticosteroids, some statistically significant differences in numbers of patients responding to treatment were identified favouring twice-daily treatment, but these were inconsistent between physician and patient assessment and outcomes selected for analysis. Two studies found a significant improvement in some symptoms with once-daily mometasone furoate compared with twice-daily application of a different active compound, while a third study found no significant differences. One good-quality study favoured twice-daily application of fluticasone propionate ointment, while other studies found no significant difference or an improvement in one symptom but not others. The only study comparing very potent corticosteroids found a statistically significant difference in comparative clinical response in favour of three-times daily treatment, but no difference in number of patients with at least a good response. There appears to be little difference in the frequency or severity of short-term events, however data are limited. No published economic evaluations were identified. Given findings on clinical effectiveness, where outcomes from the comparators are similar, the relative cost-effectiveness of once-daily 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. Topical corticosteroid products included in this review have a wide variation in price; the cost per 30 g/30 ml varies between £0.60 and £4.88. 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. 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. However, 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 should there be a general recommendation in favour of once-daily use of topical corticosteroids, compared to more frequent use.

Conclusions: The literature is very limited; that available indicates 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 will depend on the generalisability of the findings to the specific treatment decision and the relative product prices. The trials included in this review generally refer to moderate to severe atopic eczema, whereas most patients have mild disease, and furthermore most of the included trials report on potent topical corticosteroids (eight of 10 RCTs); therefore the generalisability of the findings is limited. Further research is required on the clinical and cost-effectiveness of once-daily versus more frequent use of same potency corticosteroids, specifically on mild potency products for mild to moderate atopic eczema. Outcomes should include quality of life and compliance.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Erythema Redness

Lichenification Thickening of the skin as a result of chronic scratching

Pruritus Itching

Telangiectasia A permanent dilation of pre-existing blood vessels, creating small focal red lesions

List of abbreviations

ACTH	adrenocorticotropic hormone
ANOVA	analysis of variance
BNF	British National Formulary
CCT	controlled clinical trial
CI	confidence interval
CRD	Centre for Reviews and Dissemination
GSK	GlaxoSmithKline
IgE	immunoglobulin E
ITT	intention-to-treat
NIC	net ingredient cost
NICE	National Institute for Clinical Excellence
ns	not significant
OR	odds ratio
OTC	over-the-counter
PCA	Department of Health Prescription Cost Analysis
pp	per protocol
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RD	risk difference
RR	risk ratio/relative risk
SASSAD	six-area six-sign atopic dermatitis severity score
SCORAD	Severity Scoring of Atopic Dermatitis
SD	standard deviation
SF-36	Medical Outcomes Study Short-form 36, generic health
SPCs	summaries of product characteristics
VAS	visual analogue scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive 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 diminish their psychological well-being 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). 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 languages and studies published only 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 through 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 10 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 furoate (Elocon®) compared with twice-daily application of a different active compound was found to result in a greater percentage improvement in total atopic dermatitis scores in one study and an improvement in pruritus only in another study, whereas a third study found no statistically significant differences. Again, these studies were of poor quality. One good-quality study favoured twice-daily application of fluticasone propionate ointment (Cutivate®) whereas 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 were not reported in 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 that 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 revealed a wide range of products and a wide variation in the price of these products; the cost per 30 g/30 ml 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 10 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 with 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, whereas most patients have mild disease, and furthermore most of the included trials report on potent topical corticosteroids (eight of 10 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).

Chapter 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.

Chapter 2
Background

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 and 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 immunoglobulin E (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,[4] building on earlier work on the clinical features of atopic dermatitis,[5] developed criteria (*Table 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]

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]

TABLE 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 2 years[a] (ii) History of flexural involvement (iii) History of a generally dry skin (iv) Personal history of other atopic disease[b] (v) Visible flexural dermatitis as per photographic protocol
[a] Not used in children under 4 years of age. [b] In children under 4 years old, history of atopic disease in a first-degree relative may be included.

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. Severity Scoring of Atopic Dermatitis (SCORAD),[10] six-area six-sign atopic dermatitis severity score (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 0–3, at six defined body sites, giving a maximum score of 108, or the ADSI (Atopic Dermatitis Severity Index),[11] which assesses five clinical features on a scale of 0–3, 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, owing to the small number of community studies, the dominance of cross-sectional rather than 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 (approximately 1.4–1.9 million children, for England and Wales)[15] and 2–10% of adults (approximately 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, 25–40 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. Friedmann[2] reports that 65% of cases present before the age of 6 months and 80% in the first year of life, and a review by Hoare and colleagues[1] reports that approximately 80% of cases start before the age of 5 years. Kay and colleagues[14] report that atopic eczema developed in the first 12 months of life in 60% of children who had the condition in their study, and that it had developed in the first 6 months of life in three-quarters of these children. Williams[6] suggests that epidemiological studies undertaken in a secondary care setting may overestimate 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 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 socio-economic groups. Williams and colleagues report an inverse socio-economic relation, whereby reported and examined eczema was almost twice as common in children of higher socio-economic groups, among the 8279 children followed up in the UK 1958 National Child Development Study.[18,19]

Table 2 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 by Hoare and colleagues[1] concluded that "no reliable incidence estimates are available" (p. 2). However, findings from the National Child Development Study

TABLE 2 *Estimates of prevalence of atopic eczema in England and Wales*

	England	Wales	England and Wales	Former Health Region of North and Mid Hampshire
Population	49,138,831	2,903,085	52,049,916	554,529
Prevalence estimate:				
Williams[4] 5–20% 0–11 years	367,802–1,471,208	21,570–86,282	389,373–1,557,491	3,987–15,949
Friedmann[2] 12–26% under 12 years	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

developed from the birth cohort of 1958 suggest around 50 cases per 1000 in the first year of life, falling to five 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 1760 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.

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 (HRQoL) because it can have an impact on work, sleep and social relations. Patients with atopic eczema may experience distress and anxiety that diminish their psychological well-being 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 cycle, 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.

Current service provision

Treatment of atopic eczema involves a combination of preventive 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, and their use should therefore 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 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 vasoconstriction 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] For the purposes of this report, and in accordance with the position taken by the National Institute for Clinical Excellence (NICE), we assume all included 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 1* and *2* show the distribution of total prescriptions and total cost by product potency. However, over 43% of the topical corticosteroids dispensed (~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 this 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

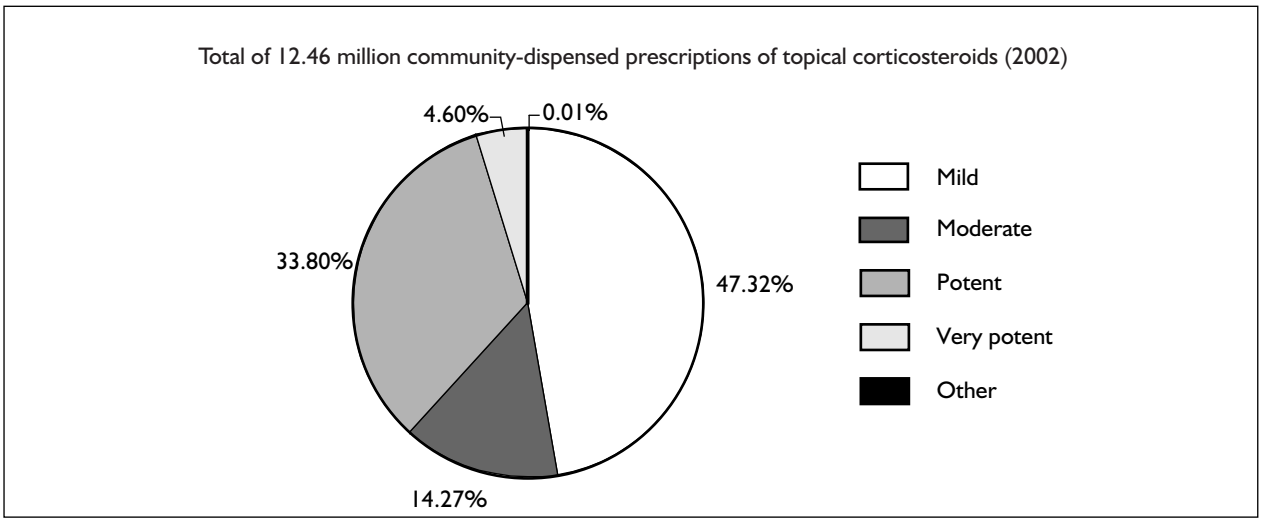


FIGURE 1 *Proportion of total prescriptions (community dispensed) of topical corticosteroids, by potency groupings*

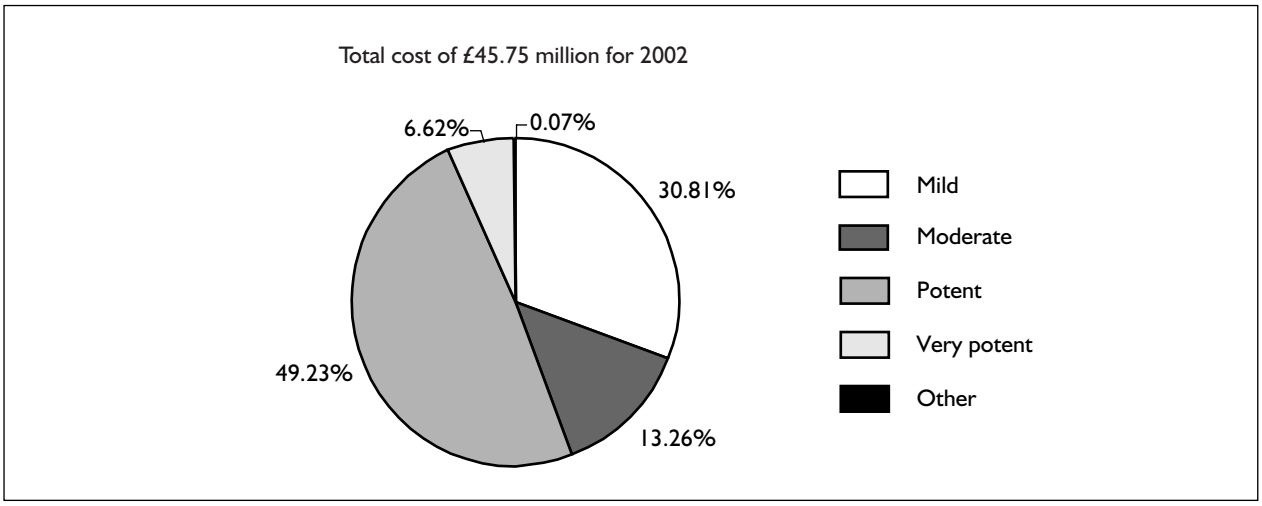


FIGURE 2 *Total cost for all community-dispensed prescriptions (2002) of topical corticosteroids by potency groupings. These data cover net ingredient costs (NIC) only, excluding those products prescribed generically but only available as a proprietary product (PCA refer to these costs as 'owc2 costs'). 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 prepayment certificate.*

corticosteroids are for atopic eczema,[37] giving an estimate of prescribing cost of over £11.6 million for atopic eczema (community-dispensed prescriptions, 2002).

Atopic eczema is predominantly treated in the community, with patient care being delivered through a primary healthcare 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 4–6 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]

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 that 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 subgroups are (1) those patients treated in the community versus those treated in a hospital setting and (2) 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 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 or 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 that all topical corticosteroid products listed in the BNF can be prescribed for once-daily use.[32]

TABLE 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 (No. 45) recommended frequency	Licence frequency from SPC,[34] where available
Mild potency			
Hydrocortisone	Generic[a] 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
Betametasone valerate	Betnovate RD cream/ointment 0.025%	1–2 times daily	2–3 times daily
Clobetasone butyrate	Eumovate cream/ointment 0.05%	1–2 times daily	Up to 4 times daily
Desoximethasone	Stiedex LP oily cream 0.05%	1–2 times daily	2–3 times daily
Fluocinolone acetonide	Synalar cream/ointment 1/4, 0.00625%	1–2 times daily	N/A
Fluocortolone	Ultralanum cream/ointment Plain	1–2 times daily	N/A
Flurandrenolone	Haelan cream/ointment 0.0125%	1–2 times daily	2–3 times daily
Potent			
Beclometasone dipropionate	Propaderm cream/ointment 0.025%	1–2 times daily	N/A
Betametasone dipropionate	Diprosone cream/ointment/lotion 0.05%	1–2 times daily	1–2 times daily
Betametasone valerate	Betnovate cream/ointment/lotion/scalp application 0.1%	1–2 times daily	2–3 times daily
Betametasone valerate	Bettamousse foam 0.12%	1–2 times daily	Twice daily
Betametasone valerate	Betacap scalp application 0.1%	1–2 times daily	–
Betametasone valerate	Generic betametasone valerate cream/ointment 0.1%	1–2 times daily	N/A
Diflucortolone valerate	Nerisone cream/ointment/oily cream 0.1%	1–2 times daily up to 4 weeks	N/A
Fluocinolone acetonide	Synalar cream/ointment/gel 0.025%	1–2 times daily	N/A
Fluocinonide	Metosyn FAPG cream/ointment 0.05%	1–2 times daily	N/A
Fluticasone propionate	Cutivate cream 0.05%	1–2 times daily	Once daily
Fluticasone propionate	Cutivate ointment 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/ointment/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/ointment/scalp lotion 0.1%	Once daily	Once daily
Very potent			
Clobetasol propionate	Dermovate cream/ointment/scalp application 0.05%	1–2 times daily up to 4 weeks	1–2 times daily
Diflucortolone valerate	Nerisone Forte ointment/oily cream 0.3%	1–2 times daily up to 4 weeks	N/A
Halcinonide	Halciderm cream 0.1%	1–2 times daily	2–3 times daily

[a] Include generic hydrocortisone products from scope.
N/A, not available/identified.

Figure 3 shows the general pattern/distribution of community-dispensed prescriptions for these products in 2002 (the specific product cost per 30 mg/30 ml is reported later in the report; see *Table 10*). Although there is a wide range of products available, *Figure 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 betametasone valerate (Betnovate®) are the dominant products in the moderate potency products, mometasone furoate (Elocon®), betametasone valerate (Betnovate®) and generic betametasone valerate are the three most common products in the potent grouping, with clobetasol propionate (Dermovate®) dominating amongst the very potent products.

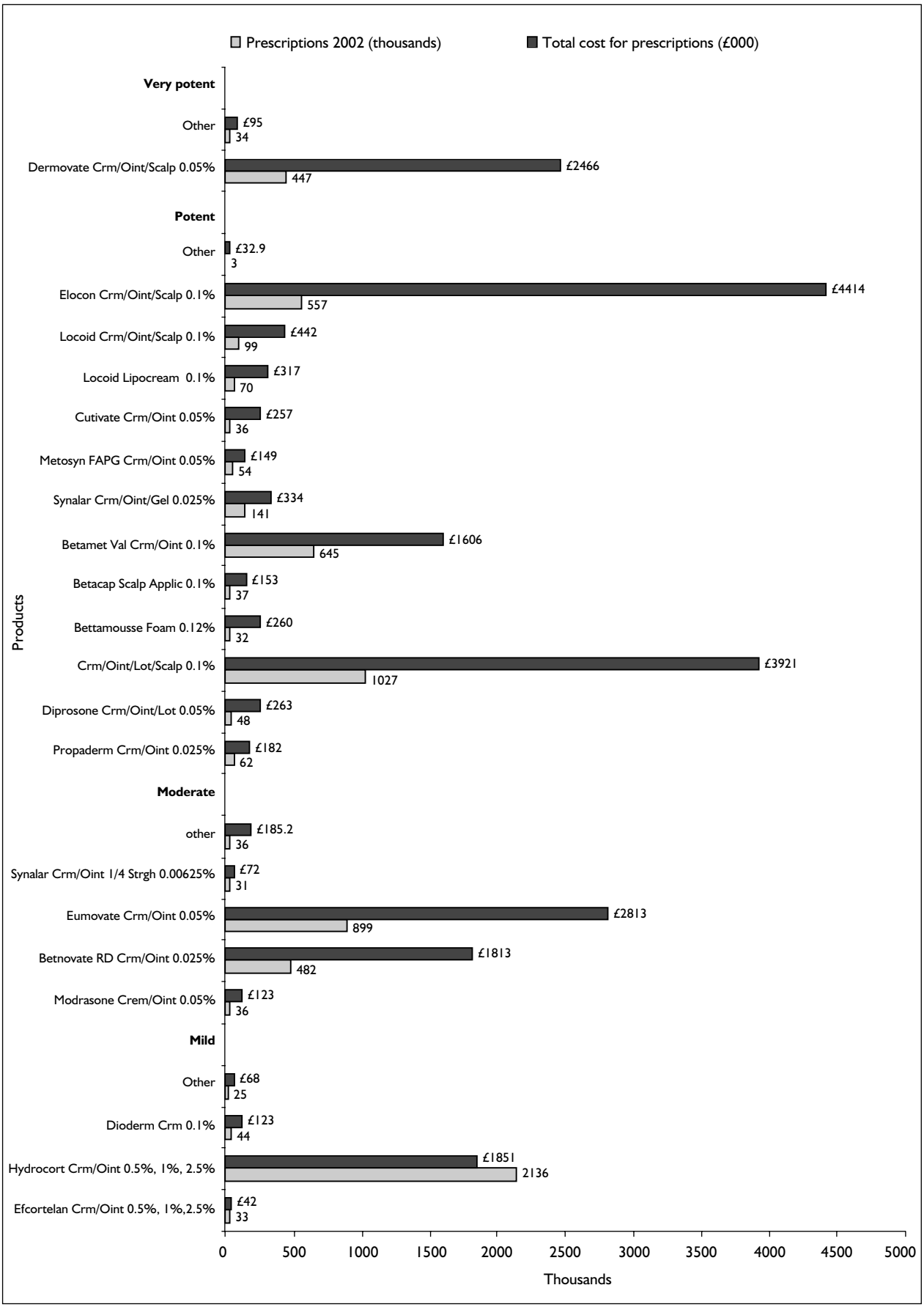


FIGURE 3 *Prescribing patterns for eligible topical corticosteroids (community-dispensed prescriptions, 2002). Source: PCA.*

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 ['Estimation of net costs' (p. 32)] the variations in product costs; the cost per 30 g/30 ml 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 expected 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 (currently £6.30 per item), and this will impact on the overall NHS costs associated with prescription of topical corticosteroids for atopic eczema.

Chapter 3
Clinical effectiveness

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', p. 53). 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 randomised controlled trials (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 given in Appendix 3. The most recent search was performed in October 2003.

Industry 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 Chapter 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 and also 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 (QoL).

Data synthesis

Data were synthesised through a narrative review with tabulation of results of all included studies. Full data extraction forms are presented in

Appendices 6–9. It was considered inappropriate to combine the studies in a meta-analysis owing 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 (RRs) 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.

Results

Quantity and quality of research available

A total of 4429 references were identified and, of these, one systematic review[1] (Appendix 6) and 10 RCTs 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 10 RCTs, seven compared frequency of application of the same active compound and three RCTs compared once-daily application of mometasone furoate with twice-daily application of a different active compound (hydrocortisone butyrate,[55] betametasone valerate[57] or betametasone dipropionate[56]). A summary of products compared in the studies is given in *Table 4*. No RCTs or CCTs of mild corticosteroids were eligible for inclusion in this review.

A list of selected excluded studies is given in Appendix 10. No studies available as abstracts only were identified.

The systematic review[1] was judged to be of good methodological quality (*Table 5*), 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 were generally poor (*Table 6*). 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, and 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[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 (ITT) 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 7 days in the study by Richelli and colleagues,[53] and up to either 3 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,[57] 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]

TABLE 4 *Summary of comparisons*

Study	Once-daily application	More frequent application	UK brand name and manufacturer[a]
Moderate			
Richelli *et al*., 1990[53]	Clobetasone 17-butyrate 0.05% lotion at 9 p.m.	Clobetasone 17-butyrate 0.05% lotion 1. at 8 a.m and 3 p.m. 2. at 3 p.m and 8 p.m.	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	Betametasone valerate cream 0.1% twice daily	Elocon® Schering-Plough vs Betnovate® GSK
Marchesi *et al*., 1994[56]	Mometasone furoate ointment 0.1% once daily	Betametasone dipropionate ointment 0.05% twice daily	Elocon® Schering-Plough vs Diprosone® Schering Plough
Very potent			
Sudilovsky *et al*., 1981[42]	Halcinonide cream 0.1% once daily Placebo twice daily	Halcinonide cream 0.1% three times daily	Halciderm Topical® Squibb

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

TABLE 5 *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 6 *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.

Richelli and colleagues included only children in their study,[53] whereas 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[47,50] for the GSK Report and the study by Bleehen and colleagues. Power to detect any differences within the subgroups would be less than in the main analyses.

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 although point estimates suggest that a small difference in favour of more frequent application cannot be excluded, it is doubtful whether this is practically meaningful.

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 10 trials did not have adequate blinding of either the outcome assessors or the patients (*Table 6*).

Response rates

All studies apart from those of Richelli and colleagues[53] and Rajka and colleagues[57] reported the number of patients responding to treatment, and these results are displayed in *Table 7*. 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] whereas 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 4*, which displays the RRs. Owing 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-daily 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 (CI) 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 5 displays the RRs 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), or when the data is analysed as illustrated in *Figure 4*. When considering patients in the GSK report whose eczema is assessed by physicians as 'cleared' as in *Figure 5*, rather than success ('cleared', 'good' or 'moderate') as in *Figure 5*, 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 4 weeks with once- or twice-daily fluticasone propionate cream or ointment.[54]

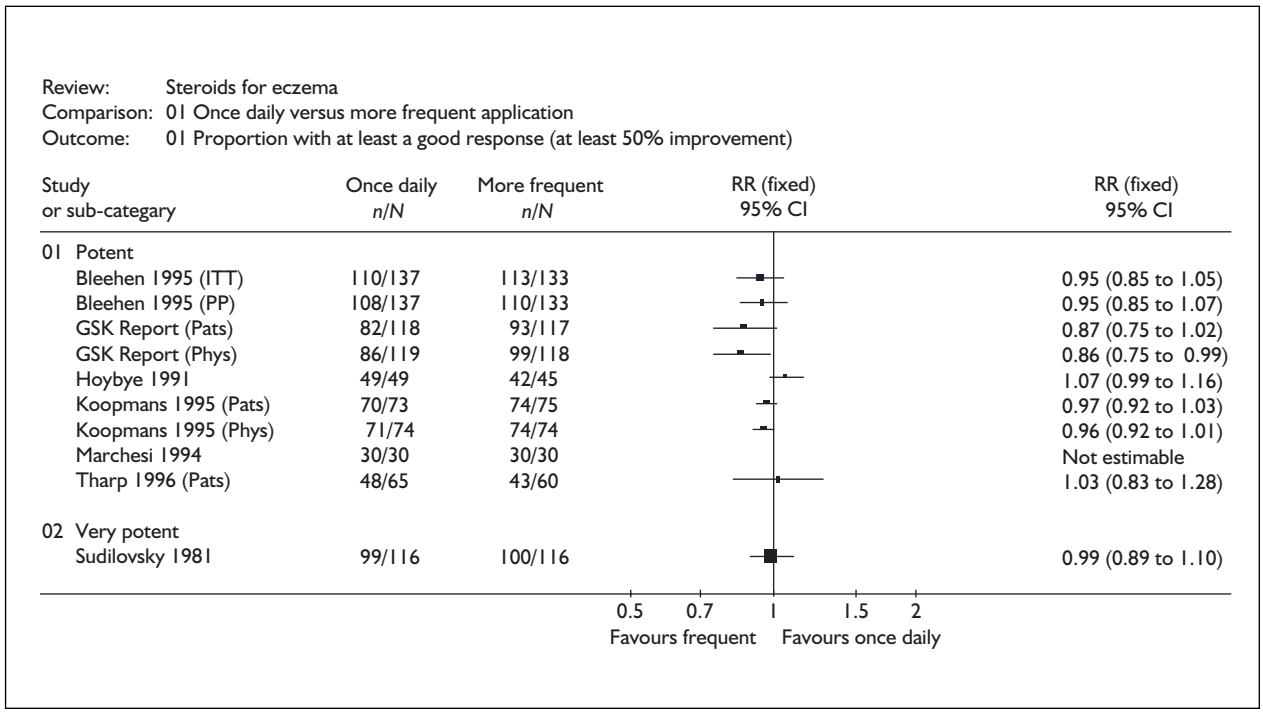


FIGURE 4 *Patients with at least a good response at end of treatment: risk ratios. Note: the patients in the studies by Bleehen and colleagues[43], GSK Report[46] and Koopmans and colleagues[44] are included twice in the figure for illustration of different assessments. ITT, intention-to-treat analysis; Pats, patients' assessment; Phys, physicians' assessment; PP, per-protocol analysis.*

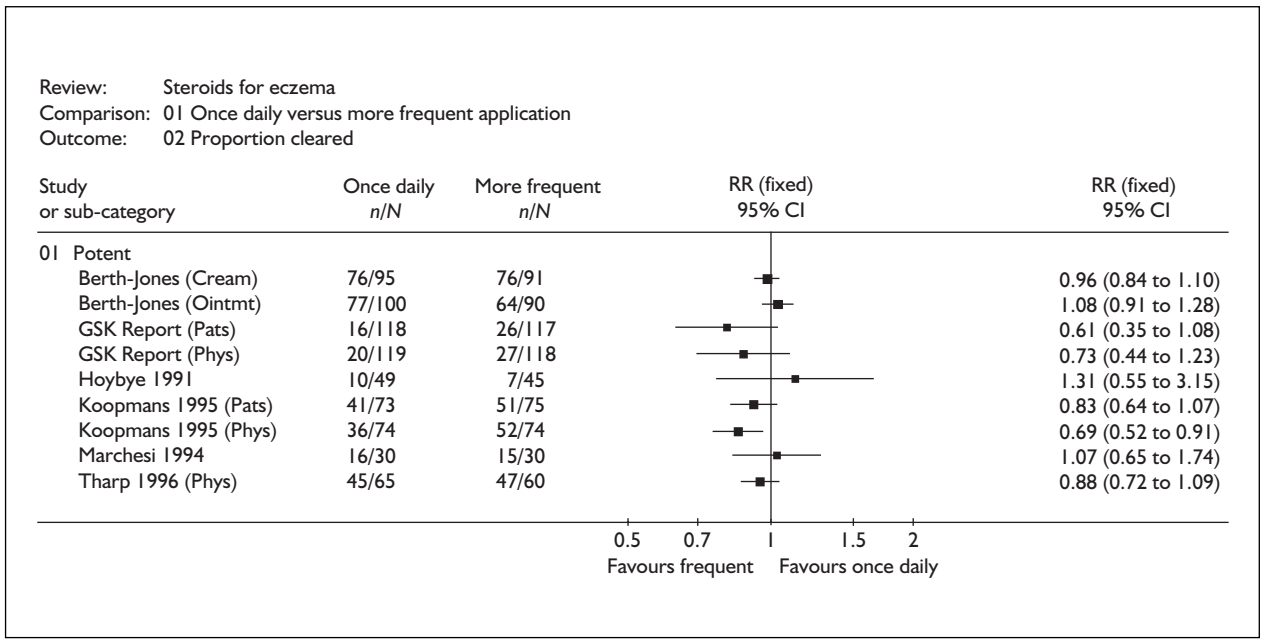


FIGURE 5 *Patients with controlled or cleared atopic eczema: risk ratios. Note: the patients in the studies by Koopmans and colleagues[44] and GSK Report[46] are included twice in the figure for illustration of the different assessments. Pats, patients' assessment; Phys, physicians' assessment.*

TABLE 7 *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 propionate cream 0.05% twice daily (n = 91). 3. Fluticasone propionate ointment 0.005% once daily (n = 100). 4. Fluticasone propionate ointment 0.005% twice daily (n = 90). *Duration of treatment*: 4 weeks. *Patients*: age 12–65 years, moderate to severe	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
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) (For subgroup analysis of patients aged 12 years or less, see Appendix 8)	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
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	Number with success (%) (cleared, good, moderate) *Investigators' assessment* Visit 2: Visit 3: Visit 4: Visit 5: Last visit: *Patients' assessment* Visit 2: Visit 3: Visit 4: Visit 5: Last visit: (For data displayed by category and for subgroup analysis of patients aged 12 years or less, see Appendix 8)	 69% (80/116) 79% (77/98) 74% (70/94) 78% (64/82) 72% (86/119) 67% (79/118) 78% (81/104) 76% (73/96) 74% (61/82) 69% (82/118)	 71% (83/117) 78% (83/106) 86% (78/91) 85% (68/80) 84% (99/118) 69% (81/118) 83% (88/106) 80% (74/92) 80% (63/79) 79% (93/117)	Difference (95% CI): 2.0%, (–9.8 to 13.7), p = 0.74 –0.3% (–11.6 to 11.0), p = 0.96 11.2% (–0.1 to 22.6), p = 0.056 7.0% (–4.9 to 18.8), p = 0.25 11.6% (1.2 to 22.1), p = 0.031 1.7% (–10.2 to 13.6), p = 0.78 5.1% (–5.6 to 15.8), p = 0.35 4.4% (–7.4 to 16.2), p = 0.47 5.4% (–7.6 to 18.3), p = 0.42 10.0% (–1.1 to 21.1), p = 0.079
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* 1 (cleared) 2 (marked improvement) 3 (moderate improvement) 4 (slight improvement) 5 (no change) 6 (exacerbation)	*88% (43/49)* 10/49 33/49 6/49 0 0 0	*78% (35/45)* 7/45 28/45 7/45 0 3/45 0	*p = 0.28*

continued

TABLE 7 *Number of patients responding to treatment*

Study details	Outcome	Once daily	More frequent	Significance
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	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			
	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	Physician's 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 (1.3%)	Markedly 12 (8.1%)	$p < 0.05$
	(equal response: 70 (47.0%))	Slightly 30 (20.1%)	Slightly 35 (23.5%)	
	Total with better response:	32 (21.5%)	47 (31.5%)	

PP, per protocol.

They found no significant difference between once- and twice-daily application of cream (80% versus 84%, $p = 0.546$) or ointment (77% versus 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 4 weeks of once- or twice-daily fluticasone propionate cream [69% versus 78%, p = ns (not significant)].[58] Although this study found a statistically significant difference at 3 weeks (once-daily 57% versus twice-daily 70%, $p < 0.014$), the difference was not statistically significant at 1 (29% versus 39%) or 2 weeks (42% versus 62%).

Other assessments of response rates

In addition to the outcomes included in *Figures 4* and *5* 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 with twice-daily (47%) Locoid Lipocream (0.1% hydrocortisone 17-butyrate) than with once-daily treatment (27%) showed total clearance after 4 weeks ($p = 0.02$), but not after 2 weeks (19% versus 12%, $p = 0.29$).[44] However, it is not clear from the study how this outcome was assessed, or 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* 7), 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 treatment, 0–5 years 80%, 5–15 years 75%, 16+ years 64%; twice-daily treatment, 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.

Severity of signs and symptoms

Studies reporting data on severity scores or percentage improvement in severity are summarised in *Table 8*. 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 pruritus ($p = 0.007$) with once-daily mometasone furoate than with twice-daily hydrocortisone 17-butyrate, but not in erythema or infiltration. Rajka and colleagues, whose study comprised patients with mild to moderate eczema, found that once-daily application of mometasone furoate resulted in a greater percentage

improvement in total atopic dermatitis scores than twice-daily betametasone 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 (betametasone dipropionate) found no statistically significant differences in percentage reduction of signs and symptoms severity.[56]

A greater reduction in scores demonstrated at 2 weeks ($p = 0.04$) for twice-daily Locoid Lipocream was not maintained at 4 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 4 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 (OR) 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 furoate was found to result in a greater percentage improvement in total atopic dermatitis scores compared with twice-daily betametasone 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 percentage 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, whereas 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 were not reported by any of the studies and the clinical significance of a change in these severity scores is not clear.

Quality of life and patient preference

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

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 32–36 g in week one to about 21–30 g in week four[46] (Appendix 8).

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]

Adverse effects

Studies reporting data on adverse effects are summarised in *Table 9*.

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

TABLE 8 *Severity of signs and symptoms*

Study details	Outcome	Once daily		More frequent		Significance
Moderate						
Richelli *et al.*, 1990[53]				8 a.m./ 3 p.m.	3 p.m./ 8 p.m.	
1. Clobetasone 17-butyrate 0.05% lotion once daily at 9 p.m. (n = 9)	Mean scores for severity of clinical manifestations (e.g. erythema, oedema, exudation, blisters, bullae, scabs, scaling, lichenification), score 0–3 (none to severe) (estimated from figure)	Day 0:	1.21	1.26	1.23	
2. Clobetasone 17-butyrate 0.05% lotion twice daily at 8 a.m. and 3 p.m. (n = 13)		Day 1:	1.1	1.09	1.02	
3. Clobetasone 17-butyrate 0.05% lotion twice daily at 3 p.m. and 8 p.m. (n = 8)		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	
Duration of treatment: 1 week	Mean scores for severity of symptoms (itching, burning, pain), score 0–3 (estimated from figure)	Day 0:	1.0	1.17	0.95	
Patients: children		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	
	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]	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)		Baseline 10.0 (6,16; 9,12) Last visit attended 2.0 (0,14; 0.5,4)		
1. Fluticasone propionate 0.05% cream once daily and vehicle once daily (n = 137)		PP analysis: 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)		
2. Fluticasone propionate 0.05% cream twice daily (n = 133).						
Duration of treatment: 4 weeks						
Patients: children and adults. At least moderate severity	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%		97%		p = 0.72
		PP analysis: 95%		96%		p = 1.00
	(For subgroup analysis of patients aged 12 years or less, see Appendix 8)					

continued

TABLE 8 *Severity of signs and symptoms (cont'd)*

Study details	Outcome	Once daily	More frequent	Significance
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)[a]
	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 to 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 to 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 to 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 to 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 to 2.82), p = 0.033
	(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	Improvement in symptoms at 3 weeks:	(Data not reported)		
	Pruritus:	States significantly more improvement with once-daily mometasone furoate		p = 0.0069
	Erythema	States no difference in improvement between groups		p = ns
	Infiltration:	States no difference in improvement between groups		p = ns
	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 2 weeks). At 4 weeks, p = 0.08. At 4 weeks, twice-daily group showed more pronounced reduction in ratings for erythema (p = 0.03)			

continued

TABLE 8 *Severity of signs and symptoms (cont'd)*

Study details	Outcome	Once daily	More frequent		Significance
Marchesi *et al.*, 1994[56]	Percentage reduction of signs and symptoms severity score (estimated from figure)				
1. Mometasone furoate ointment 0.1% once daily (n = 30) 2. Betametasone dipropionate ointment 0.05% twice daily (*n* = 30) *Duration of treatment*: 3 weeks *Patients*: adults. At least moderate severity	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]	Percentage improvement in total atopic dermatitis scores				
1. Mometasone furoate fatty cream 0.1% (Elocon®) once daily (*n* = 57) 2. Betametasone valerate cream (Betnovate®) 0.1% twice daily (*n* = 60) *Duration of treatment*: 3 weeks *Patients*: aged over 16 years. Mild to moderate severity		8 days:	80%	58%	$p < 0.01$
		15 days:	93%	75%	$p < 0.01$
		22 days:	96%	86%	$p < 0.01$
		End of study:	98%	86%	$p < 0.01$
Tharp, 1996[58]	Severity of symptoms and signs at day 29, score 0–3 (absent to severe) (p value vs baseline)				
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	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.*, 1981[42]	Not reported				

[a] Logistic regression model of total severity score on treatment effect adjusting for prognostic factors (age and baseline total severity score): OR for treatment effect (twice/once daily), (95% CI), significance of treatment effect.

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 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 in which treatment group these occurred. 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, and 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 2 weeks of treatment with four (13.3%) cases in the once-daily mometasone furoate group and five (16.7%) cases in the twice-daily betametasone 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 12 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, pruritus 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 were variable between studies. Actual numbers for each group were reported in only six of the 10 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 9 *Adverse effects*

Study details	Adverse effects		Once daily	Twice daily
Moderate				
Richelli *et al.*, 1990[53]			**(*n* = 9)**	**(*n* = 13)/(*n* = 8)**
1. Clobetasone 17-butyrate 0.05% lotion once daily at 9 p.m. 2. Clobetasone 17-butyrate 0.05% lotion twice daily at 8 a.m. and 3 p.m. 3. Clobetasone 17-butyrate 0.05% lotion twice daily at 3 p.m. and 8 p.m. *Patients*: children	Adverse effects not reported No significant differences in serum cortisol and ACTH levels before and after clobetasone 17-butyrate administration in any of the three groups ($p > 0.05$), and no significant differences between groups			
Potent				
Berth-Jones *et al.*, 2003[54]	**No. of patients**	**Cream**	**(*n* = 95)**	**(*n* = 91)**
		Ointment	**(*n* = 100)**	**(*n* = 90)**
1. Fluticasone propionate cream 0.05% once daily 2. Fluticasone propionate cream 0.05% twice daily 3. Fluticasone propionate ointment 0.005% once daily 4. Fluticasone propionate ointment 0.005% twice daily *Patients*: Age 12–65 years, moderate to severe	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[a]:			
	Telangiectasia:	Cream	0	1
		Ointment	1	0
	Striae:	Cream	0	0
		Ointment	1	0
Bleehen *et al.*, 1995[43]	**No. of reports**		**(*n* = 137)**	**(*n* = 133)**
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	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[b] (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 administration		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
	Serious adverse events, due to inpatient hospitalisation, unrelated to study drug		1	1

continued

TABLE 9 *Adverse effects (cont'd)*

Study details	Adverse effects	Once daily	Twice daily
GSK Report, 1995[46]	**No. of reports**	**(*n* = 123)**	**(*n* = 122)**
1. Fluticasone 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	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
	• Exacerbation of eczema	13	6
	• Eruritus	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]		**(*n* = 49)**	**(*n* = 45)**
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	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]	**No. of patients (%)**	**(*n* = 75)**	**(*n* = 75)**
1. Locoid Lipocream (0.1% hydrocortisone 17-butyrate) once daily and Locobase once daily 2. Locoid Lipocream twice daily *Patients*: aged over 12 years	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

continued

TABLE 9 *Adverse effects (cont'd)*

Study details	Adverse effects	Once daily	Twice daily
Marchesi *et al.*, 1994[56]	**No. of patients (%)**	**(*n* = 30)**	**(*n* = 30)**
1. Mometasone furoate ointment 0.1% once daily	Telangiectasias of mild severity in last 2 weeks of treatment	4 (13.3)	5 (16.7)
2. Betamethasone dipropionate ointment 0.05% twice daily	Loss of skin marks and reduced elasticity	0	1 (3.3)
Patients: adults. At least moderate severity	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]		**(*n* = 57)**	**(*n* = 60)**
1. Mometasone furoate fatty cream 0.1% (Elocon®) once daily	Not reported for atopic dermatitis separately		
2. Betamethasone valerate cream (Betnovate®) 0.1% twice daily	No suppression of plasma cortisol levels was observed, nor were there significant changes in laboratory values		
Patients: aged over 16 years. Mild to moderate severity			
Tharp, 1996,[58]		**Vehicle**	
	No. of patients (%)	**(*n* = 78)**	**(*n* = 77)**	**(*n* = 77)**
1. Fluticasone propionate cream 0.05% once daily and vehicle once daily	Burning	4 (5)	2 (3)	0
	Dryness	0	2 (3)	0
	Pruritus	5 (6)	0	1 (1)
2. Fluticasone propionate cream 0.05% twice daily	Erythema	1 (1)	0	0
	Stinging	2 (3)	0	1 (1)
Patients: aged over 12 years. Moderate to severe	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]				**3× daily**
			(*n* = 149)	**(*n* = 149)**
1. Halcinonide cream 0.1% once daily plus placebo twice daily	Side-effects generally of a mild nature, the most common being burning, pruritus 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			
2. Halcinonide cream 0.1% three times daily				
Patients: unclear				

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

[b] Diseases of respiratory system: 138 patients (69 in each group) had concomitant disease of respiratory system on entering study. Only one case (sore throat) was rated as being even possibly related to study medication.

Chapter 4
Economic analysis

Methods for economic analysis

The aim of this chapter 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 QoL 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.

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 (1995–96 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 healthcare cost of £16.20 over a 2-month follow-up period, with health service costs in a hospital cohort (n = 10) at £415 per patient, in the same 2-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 dollars, with Dutch costs converted to US dollars using the Consumer Price Index and the Purchasing Power Parity for The Netherlands.

Estimation of net benefits

In the included trials, the clinical effectiveness of comparisons has been reported using response rates, severity of symptoms and an assessment of adverse effects. None of the included studies reported on other QoL 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 (Chapter 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- and twice-daily application of fluticasone propionate ointment (Cutivate®), favouring the twice-daily use of the product [see the section 'Results' (p. 14)]. 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 the section 'Results' (p. 14)]. Furthermore, we have warned above about the subjective nature of outcome measures used in the reported trials and the difficulties in translating differences in severity scores into clinically meaningful outcomes.

There seems to be no basis upon which to draw firm conclusions about 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 principle is an efficiency comparison based on the cost per patient treated.

It may be that owing 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.

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 and therefore it is difficult to assess the typical intervention cost for once-daily and more frequent use of topical corticosteroids.

Product costs

Table 10 reports the estimated cost per 30 mg/30 ml for topical corticosteroids eligible for inclusion in this review, using prices listed in the BNF, March 2003 (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 30 g/30 ml, with comparator potent products such as betametasone valerate (Betnovate®) or hydrocortisone butyrate (Locoid®) costing £1.31 and £2.07, respectively, per 30 g/30 ml.

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 (Chapter 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, but data were not reported. The GSK study[46] presents data on the estimated amount of topical corticosteroid used per week,

TABLE 10 *Product costs, topical corticosteroids (eligible for inclusion in the review), by BNF potency, with BNF list price for 30 mg/30 ml (BNF 45, March 2003)*

Potency	BNF chemical name	Product name	Cost per 30 g/30 ml (£)[b]
Mild	Hydrocortisone (generic[a])	Hydrocortisone cream/ointment 0.5%	0.60
	Hydrocortisone (generic[a])	Hydrocortisone cream/ointment 1%	0.72
	Hydrocortisone (generic[a])	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%	2.41
	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
	Betametasone valerate	Betnovate RD cream/ointment 0.025%	1.08
	Clobetasone butyrate	Eumovate cream/ointment 0.05%	1.70
	Desoxymetasone	Stiedex LP oily cream 0.05%	2.46
	Fluocinolone acetonide	Synalar cream/ointment 1/4, 0.00625%	0.94
	Fluocortolone	Ultralanum cream/ointment Plain	1.77
	Flurandrenolone	Haelan cream/ointment 0.0125%	1.63
Potent	Beclometasone dipropionate	Propaderm cream/ointment 0.025%	1.74
	Betametasone dipropionate	Diprosone cream/ointment/lotion 0.05%	2.05
	Betametasone valerate	Betnovate cream/ointment/lotion/scalp application 0.1%	1.31
	Betametasone valerate	Bettamousse foam 0.12%	2.25
	Betametasone valerate	Betacap scalp application 0.1%	1.27
	Betametasone valerate (generic)	Betametasone valerate cream/ointment 0.1%	1.40
	Diflucortolone valerate	Nerisone cream/ointment/oily cream 0.1%	2.09
	Fluocinolone acetonide	Synalar cream/ointment 0.025%	1.34
	Fluocinonide	Metosyn FAPG cream/ointment 0.05%	1.19
	Fluticasone propionate	Cutivate cream/ointment 0.05%	4.59
	Hydrocortisone butyrate	Locoid Lipocream 0.1%	2.17
	Hydrocortisone butyrate	Locoid cream/ointment 0.1%	2.07
	Hydrocortisone butyrate	Locoid Crelo 0.1%	2.48
	Mometasone furoate	Elocon cream/ointment/scalp lotion 0.1%	4.88
Very Potent	Clobetasol propionate	Dermovate cream/ointment 0.05%	2.48
	Diflucortolone valerate	Nerisone Forte ointment/oily cream 0.3%	2.09
	Halcinonide	Halciderm cream 0.1%	3.40

[a] Includes generic hydrocortisone products.
[b] Using largest pack sizes available (e.g. where 100 mg is the largest pack size the cost is calculated using the 100-mg price multiplied by 0.30).

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 28.3 g (ranging from 32–36 g in week one to about 21–30 g 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 and Svensson[62] report findings from an RCT comparing betametasone with mometasone furoate cream once daily, comprising 30 patients with atopic dermatitis, aged 15–66 years, (median 26.4 years). 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 34.1 g of betametasone and 31.4 g of mometasone furoate had been used per patient, a total of 65.5 g 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 25 g (42.8–89.5 g), in children to be 45 g (80–135 g) and in adolescents and adults to be 95 g (180–304 g). Findings are not presented by frequency of application (i.e. once-daily, twice-daily treatment).

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-week period the authors report an average of 68 g of hydrocortisone used.

Ellis and colleagues,[30] comparing the cost-effectiveness of topical corticosteroids (high potency) with tacrolimus ointment (topical immodulator), using a Markov modelling approach, assumed patients used 17.5 g 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 owing 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 (grams/millilitres) 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 betametasone valerate, betametasone 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. Mildison® 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. First, not all prescription costs fall on the NHS, as 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 reports that 85% of community-dispensed prescriptions were dispensed free of charge in 2002.[35] Second, 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 once or twice daily (see *Table 3*), and we would expect the BNF to be the dominant guiding instrument for the GP. At present, there are only a small number of products specifically licensed for use once daily (see *Table 3*). However, in this report we assume that in practice all listed products can be prescribed for once-daily use.

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 with more frequent use, the once-daily regimen will represent 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. However, 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 11 illustrates the cost-minimisation approach using the studies included in the review of clinical effectiveness [see the section 'Results' (p. 14)], based on findings on response rates for 'at least a good response or 50% improvement' [the section 'Estimation of net benefits' (p. 32)] 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 10 comparisons in the clinical review. However, in three of the 10 comparisons,[55–57] the twice-daily treatment regimen dominates as costs are expected to be less for the products in these regimens (i.e. cost per gram/millilitre 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 of 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 with 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.

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. In Chapter 3 we 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 1000 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 6* 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 QoL 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-daily 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

TABLE 11 *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 9 p.m.	Clobetasone 17-butyrate 0.05% lotion 1. at 8 a.m. and 3 p.m. 2. at 3 p.m. and 8 p.m.	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[a]
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	Betametasone 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[b]

[a] Note that fluticasone propionate ointment is not licensed for once-daily use.
[b] Note that although no difference is reported in overall therapeutic response, a difference in clinical response was noted.

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- versus twice-daily treatment, and although a significant difference in favour of twice daily treatment is reported by the authors, the trial concludes that once-daily treatment should be the preferred 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]

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

Group A: Twice-daily treatment group (fluticasone propionate ointment)
- Assume for each flare-up treatment comprises 30 g of 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 30 ml (net ingredient cost only)
- Cost per 1000 patients = £73,440 per year
- Total number of flare-ups per 1000 patients = 4000 per year
- Number of flare-ups classed as treatment success (84%) = 3360 per 1000 patients

Group B: Once-daily treatment group (fluticasone propionate ointment)
- Assume for each flare-up treatment comprises 15 g of 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 30 ml (net ingredient cost only)
- Cost per 1000 patients = £36,720 per year
- Total number of flare-ups per 1000 patients = 4000 per year
- Number of patients classed as treatment success (72%) = 2880 per 1000 patients
- Assume no further cost associated with treatment failure

Difference =

£36,720 in extra costs, per 1000 patients
480 additional flare-ups classed as treatment success, per 1000 patients

Cost per treatment success is: £76.50 per additional successful flare-up

Note: These simple cost calculations are presented to reflect what we feel is an upper estimate of the cost per treatment success. For example, in practice (1) the mean flare-up rate is expected to be lower than the estimate used and (2) treatment is not likely to comprise 30 g for 4 weeks for a routine flare-up. Therefore, we would expect the cost per additional treatment success to be much lower than the above estimate. However, a lack of reliable data does not allow more precise estimates. Where we assume two flare-ups per year, and treatment over a 2-week period per flare-up, the cost per additional treatment success (as above) is estimated at £19.12

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

FIGURE 6 *A simple analysis of costs and benefits in relation to the findings in the GSK study*[46]

corticosteroids, compared with 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. These data highlight 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 *Figure 7*.

Figures 8 and *9* 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.

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. After 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

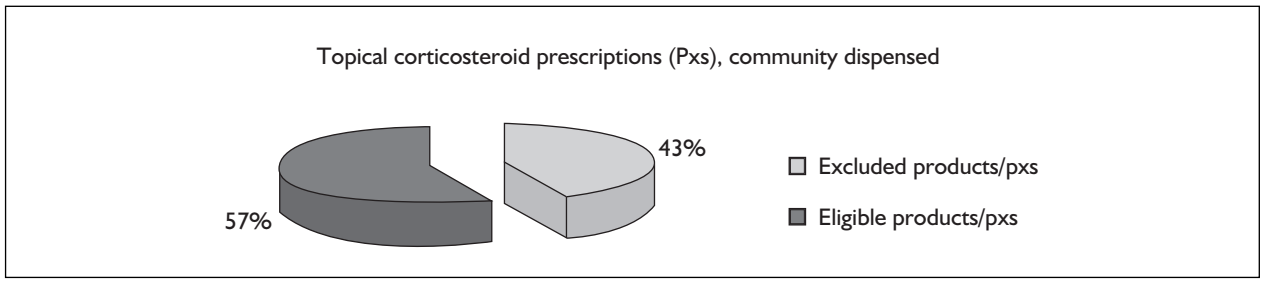


FIGURE 7 *Topical corticosteroids (BNF Chapter 13.4) prescribed in the community in 2002, according to eligibility for inclusion in the present review of clinical and cost-effectiveness*

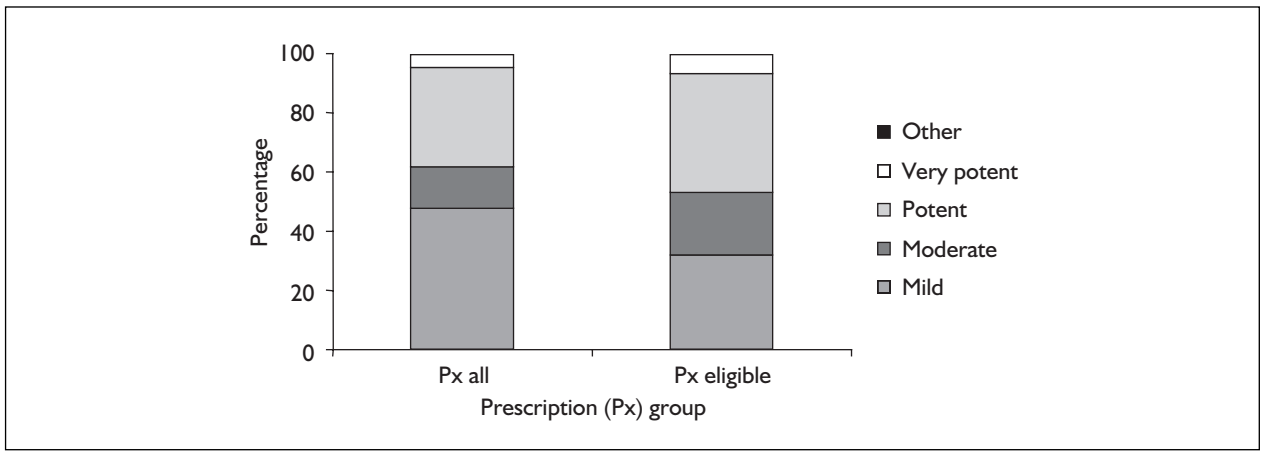


FIGURE 8 *Proportions of prescriptions by potency for 'all' 2002 community-dispensed topical corticosteroid prescriptions and for those products eligible for inclusion in the present review*

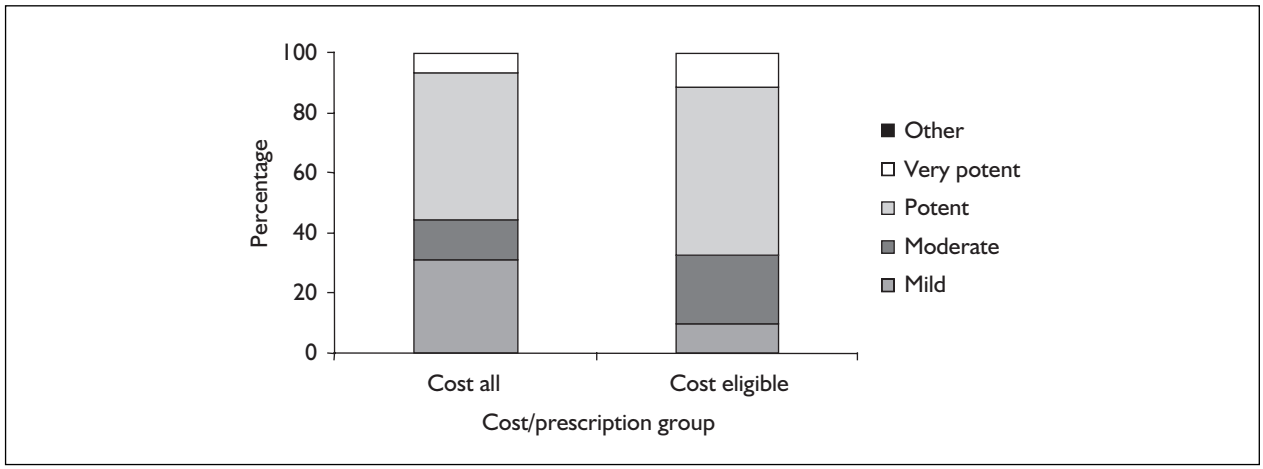


FIGURE 9 *Cost proportions of prescriptions by potency for 'all' 2002 community-dispensed topical corticosteroid prescriptions and for those products eligible for inclusion in the present review*

the cost associated with these 6.43 million prescriptions, offering an 'extreme case' scenario of NHS cost savings at about £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 about £2.24 million assuming a 50% reduction in the quantity of products used (£1.12 million 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 PCA 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 about the differences in product use by treatment frequency. Furthermore, the packaging of products (usually either in 30 mg/30 ml, 50 mg/50 ml or 100 mg/100 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 with 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 are insufficient data for an informed estimate of 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 12* presents some scenario analyses for potential NHS cost savings using this crude 'bottom-up' approach. *Table 12* 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 issue. We assume for a twice-daily treatment regimen that where patients experience a flare-up they apply an average of 30 g of topical corticosteroid per week, over a 4-week period (120 g 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 and Svensson[62] also supports the assumption, as the authors report that once-daily treatment for each flare-up involved 65 g of topical corticosteroid over a 4-week period.

In *Table 12* we use scenarios of two and four flare-ups per year, with a once-daily treatment regimen assumed to result in (1) a 50% reduction in the amount of topical corticosteroid used and (2) 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 about £300,000 to over £3.5 million; however, the reader is reminded of the crude basis on which these estimates are made.

Other issues

It has been suggested that once-daily use of topical corticosteroids, compared with more frequent use of same-potency products, would offer advantages in terms of improved compliance, reduced fear of using topical corticosteroids, QoL 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, and 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 QoL for patients according to the frequency of use of same-potency products.

Generally, the literature to inform on the QoL issues associated with atopic eczema is not extensive. Schiffner and colleagues, in a recent review of the literature related to atopic eczema and QoL, report that QoL studies in this area are scarce.[59] However, a number of studies have shown that patients with atopic eczema have inferior QoL

TABLE 12 *Estimates of potential cost savings to the NHS associated with a move to once-daily application of topical corticosteroids*

		Twice-daily application, quantity of product per year (g or ml) assuming		Once-daily application, quantity of product per year (g or ml) assuming							
				Option 1	Option 2	Option 3	Option 4				
		2 flare-ups per year	4 flare-ups per year	2 flare-ups per year, and o.d. at 50% quantity of b.d.	2 flare-ups per year, and o.d. at 75% quantity of b.d.	4 flare-ups per year, and o.d. at 50% the quantity of b.d.	4 flare-ups per year, and o.d. at 0.75% the quantity of b.d.	Potential saving per patient per year			
Selected products[a]	**Product/cost per 30 mg/ 30 ml (*Table 10*)**	**240**	**480**	**120**	**180**	**240**	**360**	**Option 1**	**Option 2**	**Option 3**	**Option 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: betametasone 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: Betametasone 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%	£2.177	£17.36	£34.72	£8.68	£13.02	£17.36	£26.04	£8.68	£4.34	£17.36	£8.68
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								£6.21	£3.10	£12.41	£6.21
Potential patient numbers		= 100,000 patients		Crude cost-savings (estimate):				£620,571	£310,286	£1,241,143	£620,571
		= 200,000 patients		Crude cost-savings (estimate):				£1,241,143	£620,571	£2,482,286	£1,241,143
		= 300,000 patients		Crude cost-savings (estimate):				£1,861,714	£930,857	£3,723,429	£1,861,714

[a] Most commonly prescribed, see *Figure 7*.

TABLE 13 *Health state utilities for atopic eczema reported by Lundberg and colleagues*[67]

		Health state utilities[a] (mean, SEM)		
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)

[a] 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.

[as shown by generic health status measures, e.g. short form with 36 items (SF-36)] compared with individuals in the general population.[22,66]

A survey in Uppsala, Sweden, 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, 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 13* 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 [standard deviation (SD) 12/year]; 29% were male.

In general, the limited literature reports that atopic eczema can have a considerable impact on QoL.[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 QoL are concerns that patients may have over the use of topical corticosteroids. The literature review by Schiffner and colleagues[59] 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] However, 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 the use of topical corticosteroids in atopic eczema are an important cause of poor patient adherence and an important issue to consider in the management of the condition. In the review of clinical effectiveness of once-daily versus more frequent application of topical corticosteroids (Chapter 3), we 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 than the risk of side-effects from treatment.[31] Therefore, patient education over treatment and its consequences, both under- 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 4 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 review of clinical effectiveness of once-daily versus more frequent application of topical corticosteroids (Chapter 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 on 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. In addition to 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]

Chapter 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 QoL, 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. In addition to any potentially direct impacts on patients, indirect impacts on parents may also be important (e.g. the impact at a family level on QoL).

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 QoL 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 the 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.

Chapter 6

Factors relevant to the 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.

Chapter 7
Discussion

Clinical effectiveness

One published systematic review and 10 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 of poor quality, and 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: (1) the number of patients with at least a good response or 50% improvement and (2) 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 furoate 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- with twice-daily application of mometasone furoate were identified, although it is of note that this product (Elocon®) is marketed as a once-daily product. Twice-daily application of fluticasone propionate ointment was found to improve symptoms significantly 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.

QoL 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.

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, that is, where products are known and specified. We have provided a cost-minimisation judgement against nine of the 10 clinical trials included in this review, with once-daily treatment being favoured on six occasions and twice-daily use on three occasions. Where there is an extra benefit associated with twice-daily compared with once-daily use of a product, 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 present 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 savings 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 £3.5 million, 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.

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 and 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 owing 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 owing 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 were 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 is 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 10 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.
- Owing to the short duration of the studies (up to 4 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.

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, betametasone 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 is 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 QoL, 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.

Chapter 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 the findings is limited.

From the available evidence, the clinical effectiveness of once- 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, in addition to the frequency of treatment, hence there is no basis upon which to favour either once- 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 in the NHS prescribing budget, but any difference at a patient level would be very small (about £2–10 for most patients), and there are a number of factors that could erode any such savings, so 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 issue 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 4 weeks).

Acknowledgements

We are very grateful to the advisory panel which provided expert advice and comments on the protocol and/or draft of this report. The members included: Ms Sue Ward, National Eczema Society, London; Ms Neroli Wilson, Consumer; Professor Hywel C Williams, Professor of Dermato-Epidemiology, University of Nottingham; Dr Rosemary Lever, Consultant Paediatric Dermatologist, Royal Hospital for Sick Children, Glasgow; Dr T Mitchell, Montpelier Health Centre, Bristol; Dr David Paige, Consultant in Dermatology, Royal London Hospital, London; Anne Pitkeathley, Royal Victoria Infirmary, Newcastle upon Tyne; Dr Lucy Ostlere, Consultant in Dermatology, St George's Hospital, London. We would also like to thank Dr Finola Delamere, Trials Search Coordinator Cochrane Skin Group, Ms Liz Hodson at the Information Service, Wessex Institute for Health Research and Development, and Dr Andy Clegg, Southampton Health Technology Assessments Centre.

Contributions of authors

The protocol was devised by C Green (Senior Research Fellow), JL Colquitt (Senior Researcher), P Davidson (Consultant in Public Health Medicine) and J Kirby (Researcher). Literature searching by E Payne (Information Scientist). Inclusion criteria were devised by JL Colquitt, J Kirby, C Green and P Davidson. Data extraction by JL Colquitt and J Kirby. The report was prepared by C Green, JL Colquitt and J Kirby.

This report was commissioned by the NHS R&D HTA Programme on behalf of NICE. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. 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.

References

1. Hoare C, Li Wan PA, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000;**4**(37).
2. Friedmann PS. Allergy and the skin. II – Contact and atopic eczema. *BMJ* 1998;**316**:1226–9.
3. Archer CB. The pathophysiology and clinical features of atopic dermatitis. In: Williams HC, editor. *Atopic dermatitis. The epidemiology, causes and prevention of atopic eczema*. Cambridge: Cambridge University Press, 2000; pp. 25–40.
4. Williams HC. On the definition and epidemiology of atopic dermatitis. *Dermatol Clin* 1995;**13**:649–57.
5. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venereol Suppl* 1980; **92**:44–7.
6. Williams HC. Epidemiology of atopic dermatitis. *Clin Exp Dermatol* 2000;**25**:522–9.
7. Verboom P, Hakkaart-Van L, Sturkenboom M, De Zeeuw R, Menke H, Rutten F. The cost of atopic dermatitis in The Netherlands: an international comparison. *Br J Dermatol* 2002;**147**:716–24.
8. Williams HC. *Atopic dermatitis. The epidemiology, causes and prevention of atopic eczema*. Cambridge: Cambridge University Press; 2000.
9. Charman C, Williams H. Outcome measures of disease severity in atopic eczema. *Arch Dermatol* 2000;**136**:763–9.
10. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. *Dermatology* 1993;**186**:23–31.
11. Berth-Jones J. Six-area, six-sign atopic dermatitis (SASSAD) severity score: a simple system for monitoring disease activity in atopic dermatitis. *Br J Dermatol* 1996;**135** (Suppl 48):25–30.
12. Charman C, Chambers C, Williams H. Measuring atopic dermatitis severity in randomized controlled clinical trials: what exactly are we measuring? *J Investig Dermatol* 2003;**120**:932–41.
13. Fennessy M, Coupland S, Popay J, Naysmith K. The epidemiology and experience of atopic eczema during childhood: a discussion paper on the implications of current knowledge for health care, public health policy and research. *J Epidemiol Commun Health* 2000;**54**:581–9.
14. Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994; **30**:35–9.
15. Topical steroids for atopic dermatitis in primary care. *Drug Ther Bull* 2003;**41**:5–8.
16. Herd RM, Tidman DJ, Prescott RJ, Hunter JAA. Prevalence of atopic eczema in the community: the Lothian atopic dermatitis study. *Br J Dermatol* 1996;**135**:18–19.
17. Neame RL, Berth-Jones J, Kurinczuk JJ, *et al.* Prevalence of atopic dermatitis in Leicester: a study of methodology and examination of possible ethnic variation. *Br J Dermatol* 1995;**132**:772–7.
18. Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? *BMJ* 1994; **308**:1132–5.
19. Williams HC, Pembroke AC, Forsdyke H, Boodoo G, Hay RJ, Burney PG. London-born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol* 1995;**32**:212–17.
20. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *Br J Dermatol* 1998;**139**:73–6.
21. Barnetson RS, Rogers M. Childhood atopic eczema. *BMJ* 2002;**324**:1376–9.
22. Kiebert G, Sorensen SV, Revicki D, Fagan SC, Doyle JJ, Cohen J, *et al.* Atopic dermatitis is associated with a decrement in health-related quality of life. *Int J Dermatol* 2002;**41**:151–8.
23. Absolon C, Cottrell D, Eldridge S, Glover M. Psychological disturbance in atopic eczema: the extent of the problem in school-aged children. *Br J Dermatol* 1997;**137**:241–5.
24. Elliott B, Luker K. The experiences of mothers caring for a child with severe atopic eczema. *J Clin Nurs* 1997;**6**:241–7.
25. Barankin B, DeKoven J. Psychosocial effect of common skin diseases. *Can Fam Physician* 2002; **48**:712–16.
26. Wahlgren CF. Itch and atopic dermatitis: an overview. *J Dermatol* 1999;**26**:770–9.
27. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child* 1997;**76**:159–62.
28. Gil K, Keefe F, Sampson H, McCaskill C, Rodin J, Crisson J. The relation of stress and family environment to atopic dermatitis symptoms in children. *J Psychosom Res* 1987;**31**:673–84.
29. Rudikoff D, Lebwohl M. Atopic dermatitis. *Lancet* 1998;**351**:1715–21.

30. Ellis CN, Drake LA, Prendergast MM, Abramovits W, Boguniewicz M, Daniel CR, *et al*. Cost-effectiveness analysis of tacrolimus ointment versus high-potency topical corticosteroids in adults with moderate to severe atopic dermatitis. *J Am Acad Dermatol* 2003;**48**:553–63.

31. Charman C, Williams H. The use of corticosteroids and corticosteroid phobia in atopic dermatitis. *Clin Dermatol* 2003;**21**:193–200.

32. *British National Formulary*. No. 45. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; 2003.

33. Using topical corticosteroids in general practice. *Merec Bull* 1999;**10**:1–5.

34. The Electronic Medicines Compendium. URL: www.medicines.org.uk. Accessed 7 3 October 2003.

35. Department of Health. Prescription cost analysis. URL: http://www.doh.gov.uk/stats/pca2002.htm

36. National Institute for Clinical Excellence. *Scope for the health technology appraisal: topical corticosteroids for atopic eczema*. London: National Institute for Clinical Excellence; 2003.

37. National Eczema Society. *Health technology appraisal submission to NICE on topical corticosteroids for atopic eczema*. London: National Eczema Society; 2003.

38. Emerson RM, Williams HC, Allen BR. What is the cost of atopic dermatitis in preschool children? *Br J Dermatol* 2001;**144**:514–22.

39. Lamb SR, Rademaker M. Pharmacoeconomics of drug therapy for atopic dermatitis. *Expert Opin Pharmacother* 2002;**3**:249–55.

40. British Association of Dermatology. Guidelines for the management of atopic eczema. URL: www.bad.org.uk/doctors/service%-provision/primary/eczema.htm. Accessed August 2003.

41. Lagos BR, Maibach HI. Frequency of application of topical corticosteroids: An overview. *Br J Dermatol* 1998;**139**:763–6.

42. Sudilovsky A, Muir JG, Bocobo FC. A comparison of single and multiple applications of halcinonide cream. *Int J Dermatol* 1981;**20**:609–13.

43. Bleehen SS, Chu AC, Hamann I, Holden C, Hunter JA, Marks R. Fluticasone propionate 0.05% cream in the treatment of atopic eczema: a multicentre study comparing once-daily treatment and once-daily vehicle cream application versus twice-daily treatment. *Br J Dermatol* 1995; **133**:592–7.

44. Koopmans B, Lasthein AB, Mork NJ, Austad J, Suhonen RE. Multicentre randomized double-blind study of Locoid Lipocream fatty cream twice daily versus Locoid Lipocream once daily and Locobase once daily. *J Dermatol Treat* 1995;**6**:103–6.

45. Williams H. New treatments for atopic dermatitis. *BMJ* 2002;**324**:1533–4.

46. GSK. A four week multicentre, double blind study to compare safety and efficacy with an OD and BD administration of fluticasone propionate 0.005% ointment in the treatment of atopic eczema. Report 135L, Protocol No. GL/FLT/002. 1995.

47. Statistical report of a subgroup analysis of a clinical study comparing the safety and efficacy of fluticasone propionate ointment (0.005%) when applied once or twice daily in the treatment of atopic eczema. Protocol GL/FLT/002. 1999.

48. James M. A 4-week multi-center, double-blind study to compare safety and efficacy of QD and BID administration of fluticasone propionate ointment, 0.005% in the treatment of atopic eczema. *Am Acad Dermatol* (AAD) 1999; abstract 088.

49. Glazenburg E, Herdman M, Daly S, Duncan J. Efficacy and safety of once or twice daily fluticasone propionate (FP) ointment in paediatric eczema. *J Eur Acad Dermatol Venereol* 2000;**14** (Suppl 1:125): P06–21.

50. Statistical report of a subgroup analysis of a clinical study comparing the safety and efficacy of fluticasone propionate cream (0.05%) when applied once or twice daily in the treatment of atopic eczema. Protocol No. GL/FLT/001. 1999.

51. Chu A, Graham-Brown R, Lewis Jones S. Efficacy and safety of fluticasone propionate in paediatric atopic eczema used once or twice daily. *J Eur Acad Dermatol Venereol* 1998;**11** (Suppl 2):S200 (abstract P59).

52. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness*. CRD Report 4 (2nd edition). 2001. York: Centre for Reviews and Dissemination, University of York.

53. Richelli C, Piacentini GL, Sette L, Bonizzato MC, Andreoli A, Boner AL. Clinical efficacy and tolerability of clobetasone 17-butyrate 0.5% lotion in children with atopic dermatitis. *Cur Ther Res Clin Exp* 1990;**47**:413–17.

54. Berth-Jones J, Damstra RJ, Golsch S, Livden JK, Van Hooteghem O, Allegra F, *et al.* Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ* 2003;**32**:1367.

55. Hoybye S, Balk MS, De Cunha BF, Ottevanger V, Veien NK. Continuous and intermittent treatment of atopic dermatitis in adults with mometasone furoate versus hydrocortisone 17-butyrate. *Cur Ther Res Clin Exp* 1991;**50**:67–72.

56. Marchesi E, Rozzoni M, Pini P, Cainelli T. Comparative study of mometasone furoate and betamethasone dipropionate in the treatment of atopic dermatitis. *G Ital Dermatol Venereol* 1994; **129**(1–2):IX–XII.

57. Rajka G, Avrach W, Gartner L, Overgaard-Petersen H. Mometasone furoate 0.1% fatty cream once daily versus betamethasone valerate 0.1% cream twice daily in the treatment of patients with atopic and allergic contact dermatitis. *Cur Ther Res Clin Exp* 1993;**54**:23–9.

58. Tharp MD. A comparison of twice-daily and once-daily administration of fluticasone propionate cream, 0.05%, in the treatment of eczema. *Cutis* 1996;**57**(2: Suppl):19–26.

59. Schiffner R, Schiffner-Rohe J, Landthaler M, Stolz W. Treatment of atopic dermatitis and impact on quality of life: a review with emphasis on topical non-corticosteroids. *Pharmacoeconomics* 2003; **21**:159–79.

60. Herd RM, Tidman MJ, Prescott RJ, Hunter JAA. The cost of atopic eczema. *Br J Dermatol* 1996; **135**:20–3.

61. Prescription Pricing Authority. *Drug tariff*. March. London: The Stationery Office; 2003.

62. Reidhav I, Svensson A. Betamethasone valerate versus mometasone furoate cream once daily in atopic dermatitis. *J Dermatol Treat* 1996;**7**:87–8.

63. Furue M, Terao H, Rikihisa W, Urabe K, Kinukawa N, Nose Y, *et al*. Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. *Br J Dermatol* 2003;**148**:128–33.

64. Thomas KS, Armstrong S, Avery A, Po AL, O'Neill C, Young S, *et al*. Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. *BMJ* 2002;**324**:768.

65. GlaxoSmithKline UK. *Topical steroids for the treatment of atopic eczema*. Submission to NICE Health Technology Appraisal. London: GlaxoSmithKline; 2003.

66. Terreehorst I, Duivenvoorden HJ, Tempels-Pavlica Z, Oosting AJ, de Monchy JG, Bruijnzeel-Koomen CA, *et al*. The unfavorable effects of concomitant asthma and sleeplessness due to the atopic eczema/dermatitis syndrome (AEDS) on quality of life in subjects allergic to house-dust mites. *Allergy* 2002;**57**:919–25.

67. Lundberg L, Johannesson M, Silverdahl M, Hermansson C, Lindberg M. Health-related quality of life in patients with psoriasis and atopic dermatitis measured with SF-36, DLQI and a subjective measure of disease activity. *Acta Derm Venereologica* 2000;**80**:430–4.

68. Herd RM, Tidman MJ, Ruta DA, Hunter JA. Measurement of quality of life in atopic dermatitis: correlation and validation of two different methods. *Br J Dermatol* 1997;**136**:502–7.

69. Howlett S. Emotional dysfunction, child-family relationships and childhood atopic dermatitis. *Br J Dermatol* 1999;**140**:381–4.

70. Lawson V, Lewis-Jones MS, Finlay AY, Reid P, Owens RG. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *Br J Dermatol* 1998;**138**:107–13.

71. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *Br J Dermatol* 2000;**142**:931–6.

72. Fischer G. Compliance problems in paediatric atopic eczema. *Aust J Dermatol* 1996;**37** (Suppl 3).

73. Beattie PE, Lewis-Jones MS. Parental knowledge of topical therapies in the treatment of childhood atopic dermatitis. *Clin Exp Dermatol* 2003; **28**:549–53.

74. Ohya Y, Williams H, Steptoe A, Saito H, Iikura Y, Anderson R, *et al*. Psychosocial factors and adherence to treatment advice in childhood atopic dermatitis. *J Invest Dermatol* 2001;**117**:852–7.

75. 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. *Pediatr Dermatol* 1997;**14**:321–4.

76. Taylor B, Wadsworth J, Wadsworth M, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939–45 war. *Lancet* 1984; **i**:465–71.

77. Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. *BMJ* 1992;**304**:873–5.

78. Butland BK, Strachan DP, Lewis S, Bynner J, Butler N, Britton J. Investigation into the increase in hay fever and eczema at age 16 observed between 1958 and 1970 British birth cohorts. *BMJ* 1997;**315**:717–21.

79. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, *et al*. The UK Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;**131**: 383–96.

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), 14,498 children aged 7, (1958 cohort), 12,982 children aged 5 (1970 cohort)		Cumulative incidence rates 5.1% (1946 cohort) 7.3% (1958 cohort) 12.2% (1970 cohort)
Ninan and Russell, 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 3–11 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 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 to 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 to 9.4) (II) 6.8% (95% CI 5.5 to 8.4) (IIINM) 5.8% (95% CI 4.3 to 7.6) (IIIM) 5.3% (95% CI 4.6 to 6.1) (IV) 3.7% (95% CI 2.8 to 4.8) (V) 5.4% (95% CI 3.5 to 7.9) ($p<0.001$)	Cumulative incidence (by age 16) according to social class: (I) 13.1% (95% CI 10.0 to 16.2) (II) 12.4% (95% CI 10.5 to 14.2) (IIINM) 12.5% (95% CI 10.4 to 14.8) (IIIM) 11.1% (95% CI 10.1 to 12.1) (IV) 8.6% (95% CI 7.2 to 10.2) (V) 8.8% (95% CI 6.4 to 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) dermatologist's 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)	

continued

Authors	Setting	Design	Subjects	Prevalence	Cumulative incidence/prevalence
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 to 18) (point prevalence)	(1) Parental recall 27% (95% CI 22 to 32) (cumulative incidence – 'ever had') (2) GP records 32% (95% CI 28 to 36) (cumulative incidence – 'ever had')
Herd *et al.*, 1996[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. Plus cluster sample of registered patients	General practice of 9786 patients. Sampled 2365 (24%) of patients	One-year period prevalence (SE), by age (years): <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) >40 0.2% (0.15) Overall 1-year 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 to 9 March inclusive. British Cohort Study (1970 cohort). All children born from 5 to 11 April inclusive	Prospective birth cohort studies. Structured interviews	11,195 (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 to 2.32)	
Emerson *et al.*, 1998[20]	Four urban and semiurban general practices in Nottingham	Cross-sectional survey of all children aged 1–5 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 to 18.2%) 22% in children aged 1–2 19% in children aged 3–4 15% in children aged 4–5	

SE, standard error.
Source: sections of this table are taken from Fennessy and colleagues.[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 and colleagues[79] 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 is 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 once or twice daily (BNF); however, the frequency of application seems to have developed empirically[41] 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,[1] whereas 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 and colleagues.[79] 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 and 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 CCTs (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 QoL.

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 at 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 quality 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 QoL 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 the Southampton Health Technology Assessments Centre (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. by Ellis and colleagues[30]). However, where possible cost–utility estimates in terms of cost per quality-adjusted life year (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.

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. A flow chart of identification of studies for inclusion is shown in *Figure 10*.

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 beclomethasone.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.

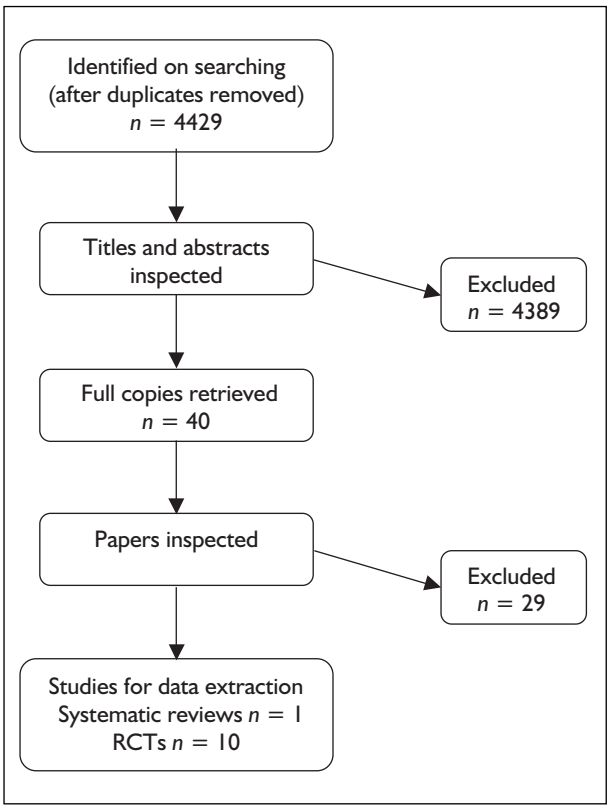


FIGURE 10 *Flow chart of identification of studies for inclusion in the systematic review of clinical effectiveness*

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.

TABLE 14 *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

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.

Additional databases searched are listed in *Table 14*.

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, healthcare intervention or organisation and outcomes of interest. In addition, details should be reported relating to the process of decision-making, that is, 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 handsearching, 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 ITT 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, Authors: 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 of analysis Results presented in a contingency table and a figure of estimated risk differences (RDs). Response rates were compared (defined as 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

Three studies involving the same active compound were included (Bleehen *et al.*, 1995;[43] Koopmans *et al.*, 1995;[44] Sudilovsky *et al.*, 1981[42]).

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. Although point estimates suggest that a small difference in favour of more frequent application cannot be excluded, it is doubtful whether this is practically meaningful.

continued

Reference	Methods

Bleehen: ITT: RD –0.047 (95% CI –0.138 to 0.045)
Bleehen: PP 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-daily 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 potency corticosteroids

Reference and design	Intervention	Participants	Outcome measures
Study Ref.: 53. Authors: Richelli *et al.* Year: 1990. Country: Italy. Study design: RCT. Number of centres: 1. Setting: not reported. Funding: not reported.	Comparisons of different interventions: 1. Clobetasone 17-butyrate 0.05% lotion once daily at 9 p.m. 2. Clobetasone 17-butyrate 0.05% lotion twice daily at 8 a.m. and 3 p.m. 3. Clobetasone 17-butyrate 0.05% lotion twice daily at 3 p.m. and 8 p.m. 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 (8 a.m./3 p.m.): 13 3. Twice daily (3 p.m./8 p.m): 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, oedema, exudation, blisters, bullae, scabs, scaling and lichenification. Secondary outcomes: serum cortisol and ACTH concentrations evaluated in all 3 patient groups at the beginning and end of the study period at 8 a.m. and 4 p.m. 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, 8 a.m./3 p.m.	Twice daily, 3 p.m./8 p.m.	*p*-Value
Age (mean) (years)	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, 8 a.m./3 p.m.	Twice daily, 3 p.m./8 p.m.	*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	

continued

Outcomes	Once daily	Twice daily, 8 a.m./3 p.m.	Twice daily, 3 p.m./8 p.m.	*p*-Value
Mean scores for severity of symptoms (estimated from figure)				
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 owing 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 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. Authors: Berth-Jones *et al*. Year: 2003. Country: UK, The 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 propionate cream 0.05% twice daily. 3. Fluticasone propionate ointment 0.005% once daily. 4. Fluticasone propionate ointment 0.005% twice daily Potency: potent. Duration of treatment: 4 weeks. 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 years 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. <u>Adverse events</u> 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 2 weeks in stabilisation phase. Questioned at each visit about adverse events, recorded by investigator. Regular examinations for visual evidence of skin atrophy.

continued

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) (years)	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	17 (18)	10 (11)	14 (14)	12 (13)	
>5 years	78 (82)	81 (89)	86 (86)	78 (87)	
Duration of current episode: no. (%)					
≤ 3 weeks	30 (32)	26 (29)	26 (26)	26 (29)	
>3 weeks	65 (68)	65 (71)	74 (74)	64 (71)	
Mean (SD) extent of atopic dermatitis (%)[a]	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)	

[a] 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

Adverse effect	**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[b]				
Telangiectasia	0	1	1	0
Striae	0	0	1	0

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

continued

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 end-point 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 and 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. Authors: Bleehen *et al*. Year: 1995. Country: UK. Study design: RCT. 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: 270, randomised: 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 and 65 years, referred to the hospital by their GP 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. Physician's overall assessment: cleared = 100% resolution, except for residual discoloration. Excellent = at least 75% improvement. Good = 50–75% improvement. Fair = 25–50% improvement. Little = <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.

continued

Characteristics of participants

	Once daily (n = 137)	Twice daily (n = 133)	p-Value
Mean age (SD, range) (years)	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)[a]	85% (113/133)	$p = 0.35$ (95% CI –14.2 to 5.0)
PP population analysis	79% (108/137)	83% (110/133)	$p = 0.42$ (95% CI –14.7 to 6.2)

[a] Numbers in parentheses 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%	$p = 0.72$
PP 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)	
PP 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

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

continued

Adverse effects (number of reports)	Once daily (n = 137)	Twice daily (n = 133)
Diseases of the respiratory system[b] (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	Exacerbation of eczema: 2
	Skin irritation following drug administration: 5	Skin irritation following drug administration: 2
	Exacerbation of itching: 4	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

[b] 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.

Withdrawals

Reason 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

continued

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 treatment and for which the two could be said to be equivalent. With respect to the investigators' 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 PP 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 and colleagues[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.) (years)	4.3 (2.9; 1, 12)	4.7 (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 (25th, 75th percentile; min., max.) (months)	36 (24, 60; 6, 144)	36 (24, 84; 3, 150)	
Duration current exacerbation, median (25th, 75th percentile; min., max.) (months)	6 (2, 16; 0.3, 72)	4 (1.5, 12; 0.5, 120)	
Concurrent illness			
Digestive system disorders	0	1	
Diseases and symptoms of nervous system	1	0	

continued

	Once daily	Twice daily	*p*-Value
Diseases of ear	1	1	
Diseases of the respiratory system	26	29	
Infectious and parasitic diseases	3	2	
Mental disorders	1	1	
Nutritional deficiencies and 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%) Last visit: 6/56 (11%)	Visit 2: 9/57 (16%) Visit 3: 4/52 (8%) Visit 4: 4/50 (8%) Visit 5: 3/44 (7%) 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:
OR (twice/once daily): 1.91 (95% CI 0.94 to 3.86).
Significance of treatment effect: $p = 0.072$.
Significance of age effect $p = 0.017$.

continued

Outcomes	Once daily	Twice daily	*p*-Value
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 (25th, 75th 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 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 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 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%)	

continued

Outcomes	Once daily	Twice daily	*p*-Value
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 effects

Adverse effects (number of reports)	Once daily	Twice daily
Digestive system disorders	0	4
Diseases and 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 impetiginisation	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 administration	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

continued

Withdrawals

Reason for withdrawal	Once daily	Twice daily
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 for withdrawal	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 propionate 0.005% ointment once daily and placebo ointment base once daily. 2. Fluticasone propionate 0.005% ointment twice daily. Potency: potent. Duration of treatment: 4 weeks or until eczema is cleared if sooner. Other interventions used: patients who had applied a 'very potent' topical corticosteroid during the previous 3 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) 50-g cartons of Eumovate® ointment to cover the treatment period. No dermatological medication other than study medication and emollients was allowed. If it was taken, it was recorded.	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 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.	Primary outcomes: physician's global assessment of response to therapy of the target area at the last visit attended compared with 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 discoloration. 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 with 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 with baseline. Signs and symptoms scale: 0.0 (absent); 0.5; 1.0 (mild); 1.5; 2.0 (moderate); 2.5; 3.0 (severe). 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 inpatient 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.

continued

Characteristics of participants[a]

	Once daily (n = 123)	Twice daily (n = 122)	p-Value
Age (years), median (min., max.; 25th, 75th percentile)	11 (1, 63; 3, 24)	14 (0, 65; 4, 30)	
Sex, no. (%)	M 62 (50%); F 61 (50%)	M 67 (55%); F 55 (45%)	
Ethnic origin, no. (%)			
Caucasian	104 (85%)	105 (86%)	
Asian	9 (7%)	6 (5%)	
Negroid	7 (6%)	6 (5%)	
Oriental	1 (1%)	3 (2%)	
Other	2 (2%)	2 (2%)	
Duration of 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 of 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)	
Concurrent disease			
Breast, female pelvic organs and genitals	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	
Ischaemic 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%)	

[a] 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.

continued

Results

Outcomes	**Once daily (*n* = 123)**	**Twice daily (*n* = 122)**	***p*-Value**
Investigators' global assessment scores, no. (%)[b]			
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 to 13.7), $p = 0.74$ –0.3% (–11.6 to 11.0), $p = 0.96$ 11.2% (–0.1 to 22.6), $p = 0.056$ 7.0% (–4.9 to 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 to 27.2), $p = 0.17$ *Evening vs twice daily:* 5.9% (–6.6 to 18.4), $p = 0.33$
1 (Cleared)	Visit 2: 4/116 (3%) Visit 3: 3/98 (3%) Visit 4: 9/94 (10%) Visit 5: 6/82 (7%) Last visit: 20/119 (17%)	Visit 2: 3/117 (3%) Visit 3: 7/106 (7%) Visit 4: 8/91 (9%) 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	

[b] Logistic regression model of investigator's unaggregated global assessment scores at last visit attended on treatment effect adjusting for age: OR for the treatment effect (twice daily/once daily) 1.76; (95% CI 1.10 to 2.81); (99% CI 0.95 to 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.

continued

Outcomes	Once daily (n = 123)	Twice daily (n = 122)	p-Value
Investigators' global assessment scores (proportion with success) by age[c]			
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%)	
[c] At last visit attended the percentage of patients who were classed as successes decreased as age increased in both groups.			
Patients' self-assessment scores, no. (%)[d]			
Self-assessment success			Difference (95% CI):
	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%)	1.7% (–10.2 to 13.6), p = 0.78 5.1% (–5.6 to 15.8), p = 0.35 4.4% (–7.4 to 16.2), p = 0.47 5.4% (–7.6 to 18.3), p = 0.42 10.0% (–1.1 to 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%)	

continued

Outcomes	Once daily (n = 123)	Twice daily (n = 122)	p-Value
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%)	

[d] OR for the treatment effect for self-assessment at last visit attended (unaggregated) twice daily/once daily: 1.26 (95% CI 1.07 to 1.45); (99% CI 1.01 to 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 2: 5.0 (0.0, 10.0; 3.0, 7.0)	1.16 (95% CI 0.71 to 1.90), $p = 0.55$[e]
	Visit 3: 4.0 (0.0, 10.0; 2.5, 5.5)	Visit 3: 4.0 (0.0, 10.0; 2.0, 5.5)	1.20 (95% CI 0.72 to 2.02), $p = 0.48$
	Visit 4: 3.5 (0.0, 9.5; 2.0, 5.5)	Visit 4: 3.0 (0.0, 9.5; 1.5, 5.0)	1.14 (95% CI 0.66 to 1.98), $p = 0.64$
	Visit 5: 3.0 (0.0, 8.5; 2.0, 5.0)	Visit 5: 2.5 (0.0, 11.0; 1.5, 4.5)	1.60 (95% CI 0.89 to 2.86), $p = 0.11$
	Last visit: 3.0 (0.0, 10.5; 1.5, 6.0)	Last visit: 2.3 (0.0, 11.0; 1.0; 4.5)	1.72 (95% CI 1.05 to 2.82), $p = 0.033$

[e] 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: OR for treatment effect (twice/once daily), (95% CI), significance of treatment effect.

Adverse events[f]

Adverse events (no.)	Once daily	Twice daily
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 Pruritus	 13 6	 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)

[f] 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).

continued

Adverse events (no.)	Once daily	Twice daily
Relationship to study medication (no. of reportings)		
Unrelated	44	47
Unlikely	21	14
Possibly[g]	6	8
Probably[g]	9	3
Almost certainly[g]	6	3
Total number of reasons	86	75
Total number of patients	54 (44%)	49 (40%)

[g] 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	Twice daily
Morning tube	Week 1: 15.9	Week 1: 15.4	Week 1: 15.0
	Week 2: 13.0	Week 2: 13.2	Week 2: 14.2
	Week 3: 10.6	Week 3: 13.9	Week 3: 11.1
	Week 4: 11.6	Week 4: 14.2	Week 4: 10.5
Evening tube	Week 1: 15.8	Week 1: 20.7	Week 1: 16.8
	Week 2: 13.8	Week 2: 18.7	Week 2: 14.8
	Week 3: 12.9	Week 3: 17.9	Week 3: 12.4
	Week 4: 11.3	Week 4: 15.8	Week 4: 10.3

Withdrawal

Reason for withdrawal	Once daily	Twice daily
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 number of reasons for withdrawal	45	47
Total number 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 software. All tests for the analyses were two-sided. All analysis was ITT. PP analysis reported if results different to ITT. Success rates compared using the normal approximation to the binomial distribution. For self-assessment an OR (twice daily/once daily) >1 favoured the twice-daily group and an OR <1 favoured the once daily-group.
- Sample size/power calculation: a total of 224 evaluable patients required to show once-daily treatment is as effective as twice-daily treatment within 15 percentage points, based on 80% power at the two-tailed 5% level of significance. A true 4-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.

continued

General comments
- Generalisability: patients aged between 1 and 65 years with moderate to severe atopic eczema.
- Outcome measures: investigators' and patients' 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). Year: 1999. Also published as abstract: Glazenburg *et al.*, 2000.[49]	Comparisons of different interventions: 1. Fluticasone propionate 0.005% ointment once daily. 2. Fluticasone propionate 0.005% ointment twice daily. Potency: potent.	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 patients classed as a success for patients' self-assessment score at last visit attended. 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'.

continued

Characteristics of participants

	Once daily (n = 63)	Twice daily (n = 57)	p-Value
Age last birthday (years), median (min., max.; 25th, 75th percentile)	3.0 (1, 12; 2.0, 6.0)	3.0 (0, 12; 2.0, 6.0)	
<1 year	n = 0	n = 1	
1–3 years	n = 37	n = 29	
4–7 years	n = 16	n = 15	
8–12 years	n = 10	n = 12	
Sex, no. (%)			
Female	28 (44%)	23 (40%)	
Male	35 (56%)	34 (60%)	
Ethnic origin, no. (%)			
Caucasian	49 (78%)	48 (84%)	
Asian	5 (8%)	3 (5%)	
Negroid	7 (11%)	4 (7%)	
Oriental	1 (2%)	1 (2%)	
Other	1 (2%)	1 (2%)	
Duration of current exacerbation (months), median (min., max.; 25th, 75th percentile)	8 (0.3, 72.0; 2.50, 24.00)	6 months (0.3, 120.0; 2.00, 12.00)	
Duration of eczema history (months) median (min., max.; 25th, 75th percentile)	30 (5, 144; 21.0, 60.0)	37 (6, 144; 23.0, 55.0)	
Concurrent diseases			
Congenital abnormalities	1	0	
Digestive system disorders	0	1	
Diseases and symptoms of nervous system	1	0	
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 number of disorders	34	37	
Total number of patients	29 (46%)	28 (49%)	

Results

Outcomes	**Once daily (n = 63)**	**Twice daily (n = 57)**	**p-Value**
Investigators' global assessment scores, no. (%)[a]			
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 to 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%)	

continued

Outcomes	Once daily (n = 63)	Twice daily (n = 57)	p-Value
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	
[a] Logistic regression model of investigators' global assessment scores at last visit attended on treatment effect adjusting for age: OR for the treatment effect (twice daily/once daily) 2.45 (95% CI 1.23 to 4.88); (99% CI 0.99 to 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%)	

continued

Outcomes	Once daily (n = 63)	Twice daily (n = 57)	p-Value
Patients' 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 to 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[b]			
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)	

[b] Comments: logistic regression model of total severity score on treatment effect adjusting for age and baseline severity: OR for the treatment effect (twice daily/once daily) 1.85, (95% CI 0.88 to 3.89); (99% CI 0.70 to 4.91); significance of treatment effect: p = 0.103; significance of age effect: p = 0.667; significance of baseline total severity score effect: $p < 0.001$.

continued

Adverse events

Adverse event (no.)	Once daily	Twice daily
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%)

Withdrawals

Reason for withdrawal	Once daily	Twice daily
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 number of reasons for withdrawal	22	30
Total number 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 the 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. Authors: 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: 3 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 0–3 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 1 week or systemic corticosteroids within 1 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 0–3 assigned by dermatologist for severity of erythema, infiltration and pruritus (3 = greatest severity). Global evaluation scores for effect of treatment: 1–6 (cleared to exacerbation). Atrophy scores: 0–4 (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 190–600 nmol/l).

Characteristics of participants[a]

Median age	**26 years**
Disease duration more than 1 year	92/96 (or possibly 92/94, denominator not clear)
Body surface area with dermatitis	2–50% of body surface area

[a] No further details reported.

Results

Outcomes	Once daily (mometasone furoate)	Twice daily (hydrocortisone 17-butyrate)	*p*-Value
Improvement in symptoms at 3 weeks[b]			
Pruritus	Significantly more improvement with mometasone 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

[b] Both groups experienced statistically significant improvement of erythema, infiltration and pruritus after 3 weeks.

continued

Outcomes	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 χ^2 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. Authors: Koopmans *et al.* Year: 1995 Country: Denmark, Norway, Finland, The Netherlands Study design: RCT. Number of centres: 4. 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. Once daily 75 2. Twice daily 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 (years) (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	

continued

Results[a]

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	
Clearance			
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%)	$p = 0.02$
Improvement[b]			
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)	

[a] 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 2 weeks). At 4 weeks $p = 0.08$. At 4 weeks, twice-daily group showed more pronounced reduction in ratings for erythema ($p = 0.03$).

[b] Analysis of the data showed an overall preference for twice-daily treatment for the investigators ($p = 0.01$) and patients ($p = 0.006$).

Adverse effects

Adverse effect	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

continued

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 pretreatment symptoms.
- Method of data analysis: pretreatment characteristics compared using Student's *t*-test for parametric data, Mann–Whitney *U*-test for non-parametric data and χ^2 tests for contingency tables for all other categorical data. Treatment data analysed using χ^2 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: three 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 three reported patients are missing.

General comments

- Generalisability: patients over the age of 12 years 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?	NA
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. Authors: Marchesi *et al*. Year: 1994. Country: Italy. Study design: RCT. Number of centres: 1. 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. Betametasone 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: 60, randomised 1. Once daily 30 2. Twice daily 30 Inclusion criteria for study entry: the disease condition was stable or worsening for more than 1 week; patients showed all three symptoms (erythema, induration and pruritus) in target area; total severity score at entry at least 6 or more (score 0–3); 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 on days 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. Laboratory tests checked at beginning and end of the treatment (no further information).

Characteristics of participants[a]

	Once daily (mometasone furoate) (n = 30)	Twice daily (betametasone dipropionate) (n = 30)	p-Value
Mean age (years) (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 disease (months), mean (SD)	28.3 (34.2)	37.1 (48.1)	
Disease status at entry (%)	Stable: 6.7 Worsening: 93.3	Stable: 3.4 Worsening: 96.6	
Percentage 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	

continued

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

[a] No baseline difference was seen between drugs for the three symptoms ($p > 0.05$).

Results

Outcomes	**Once daily (mometasone furoate) ($n = 30$)**	**Twice daily (betametasone dipropionate) ($n = 30$)**	***p*-Value**
Percentage reduction of signs and symptoms severity score (estimated from figure)[b]			
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
Physician's global evaluation of response to treatment, number of patients/response[c]			
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	

continued

Outcomes	Once daily (mometasone furoate) (n = 30)	Twice daily (betametasone dipropionate) (n = 30)	p-Value
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	

[b] Mean score values were significantly reduced at all visits compared with 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.
[c] More than one-third of patients started 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 betametasone dipropionate group were completely cleared.

Adverse effects[d]

Adverse effects (no. of reports)	Once daily	Twice daily
Telangiectasias of mild severity in last 2 weeks of treatment	4	5
Loss of skin marks and reduced elasticity	0	1

[d] 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. 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. Authors: Rajka *et al*. Year: 1993. Country: Norway, Denmark, Sweden. Study design: RCT Number of centres: 4. Study setting: dermatological centres. Funding: Schering Plough A/S, Norway.	Comparisons of different interventions: 1. Mometasone furoate fatty cream 0.1% (Elocon®) once daily. 2. Betametasone 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 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 25–50% of body surface. Exclusions: pregnant women, subjects with drug or alcohol abuse, subjects who had received systemic steroids within 4 weeks or topical corticosteroids 1 week before study. Patients with allergic contact dermatitis also included, data not extracted.	Primary outcomes: percentage improvement in total atopic dermatitis scores. The following outcomes are listed in the methods, but data are not presented for atopic dermatitis separately. Severity of erythema, induration and pruritus. Global evaluation of involved 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.

continued

Characteristics of participants
Not reported for atopic dermatitis separately.

Results[a]

Outcomes	Once-daily mometasone	Twice-daily betamethasone	*p*-Value
Percentage 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%	$p < 0.01$ $p < 0.01$ $p < 0.01$ $p < 0.01$

[a] The difference for atopic dermatitis patients was statistically significant ($p < 0.01$) in favour of once-daily mometasone for all visits according to the ANOVA. The diary cards of patients showed the same tendency, showing significant improvement after 3 to 4 days. The effect of twice-daily betametasone 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 non-compliant 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 4 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 (75–99% improvement) 3 = good (50–74% improvement) 4 = fair (25–49% 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 0–3. 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.

continued

Characteristics of participants[a]

	Once daily (n = 79)	Twice daily (n = 79)	Vehicle (n = 80)	p-Value
Age, (years) 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	55 (70)	50 (63)	57 (71)	0.543
Black	15 (19)	11 (14)	11 (14)	
Asian	4 (5)	6 (8)	5 (6)	
Other	5 (6)	12 (15)	7 (9)	
Disease status (%)				
Worsening	51 (65)	50 (64)	51 (64)	0.994
Stable	28 (35)	28 (36)	29 (36)	
History of eczema (years), median (range)	13 (0.4–70)	10.5 (0–60)	10.5 (0–71)	0.701
Duration of current episode (weeks), 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

[a] 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[b] (% 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 daily vs twice $p < 0.014$ (other visits p = ns).
Severity of symptoms and signs (day 29)[c]				
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

continued

Outcomes	Once daily	Twice daily	Vehicle	*p*-Value
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%)	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%)	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%)	Both treatments superior to vehicle at each visit ($p < 0.0001$)
	End of treatment: 1.7	End of treatment: 1.4	End of treatment: 4.5	End of treatment: $p = 0.9$
Patients' subjective assessment (percent rating treatment excellent or good)[d]				
	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)

[b] 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.

[c] At end of treatment, both treatments had significantly greater improvements compared with vehicle for all signs and symptoms ($p \leq 0.005$). 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 ($p \geq 0.07$).

[d] A differential trend ($p = 0.093$) favoured twice-daily over once-daily treatment at the end of treatment.

Adverse effects[e]

Adverse effect, no. of patients (%)	Once daily ($n = 77$)	Twice daily ($n = 77$)	Vehicle ($n = 78$)
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)

[e] None of the adverse events was judged to be serious or unexpected.

Withdrawals

Withdrawals	Once daily ($n = 79$)	Twice daily ($n = 79$)	Vehicle ($n = 80$)
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)
Non-compliant/personal	4 (5.1)	1 (1.3)	3 (3.8)

continued

Methodological comments

- Allocation to treatment groups: states random, but method not described.
- Blinding: states double-blind. Study medications packaged in identical 30-g 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, a greater proportion of patients in the twice-daily group had their arms evaluated.
- Method of data analysis: all statistical tests were two-sided and at the 5% significance level. Comparison of the three treatments were made at baseline and at each post-baseline evaluation. With the exception of the mean change (decrease) in the total severity score, the *p*-values for the group comparisons (once-daily or the twice-daily treatment vs vehicle and once-daily vs twice-daily treatment) 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, 60 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. Authors: Sudilovsky *et al.* Year: 1981. Country: USA. Study design: RCT (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: the 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 1 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, oedema, 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[a]

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%)	$p < 0.05$

continued

Outcomes	Once daily	Twice daily	*p*-Value
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

[a] Comparison of the rate of increase in numbers of responses judged satisfactory over the 3-week treatment period revealed no statistically significant difference between regimens (i.e. no evidence of tachyphylaxis). No significant relationships to severity of episode of prior chronicity were observed.

Adverse effects
States that side-effects were generally of a mild nature, the most common being burning, pruritus 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 treatment) 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 mentioned (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 observed results were related to pretreatment 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, i.e. 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 pretreatment 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?	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 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. *Br J Dermatol* 1995;**133**: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**:433–5. [Not RCT]

Bigby M. A thorough systematic review of treatments for atopic eczema. *Arch Dermatol* 2001;**137**:1635–6. [Editorial, not a systematic review]

Chu AC, Munn S. Fluticasone propionate in the treatment of inflammatory dermatoses. *Br J Clin Pract* 1995;**49**: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. *Curr Ther Res Clin Exp* 1990;**48**:128–39. [Different potencies]

Eaglstein WH, Farzad A, Capland L. Editorial: topical corticosteroid therapy: efficacy of frequent application. *Arch Dermatol* 1974;**110**: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. *Clin Exp Dermatol* 1989;**14**: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. *Br J Dermatol* 1980;**102**:575–7. [Patients not limited to atopic eczema]

Garretts M. Controlled double-blind comparative trial with fluprednylidene acetate cream and its base. *Arch Dermatol Forsch* 1975;**251**: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. *J Int Med Res* 1984;**12**: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 Med J* 1999;**40**:341–4. [Different potencies]

Haneke E. The treatment of atopic dermatitis with methylprednisolone aceponate (MPA), a new topical corticosteroid. *J Dermatol Treat* 1992;**3** (Suppl. 2):13–15. [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. (in German). *Schweiz Rundsch Med Prax* 1983;**72**: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. *J Int Med Res* 1982;**10**: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. *Curr Med Res Opin* 1984;**9**:259–64. [Patients not limited to atopic eczema, potency unclear]

Lawless JF, Stubbs SS. Comparative efficacy of once-a-day diflorasone diacetate and t.i.d. hydrocortisone in treating eczematous dermatitis. *Cur Ther Res Clinical Exp* 1978;**23**:159–65. [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. *Int J Dermatol* 1999;**38**: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. *Cur Med Res Opin* 1977;**5**: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. *Pediatr Dermatol* 1997;**14**:321–4. [CCT, groups not comparable]

Meenan FO. The treatment of atopic dermatitis with clobestasol propionate. *Ir Med J* 1977;**70**: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. *J Pak Assoc Dermatol* 2002; **12**(April/June):64–8. [Not RCT]

Rafanelli A, Rafanelli S, Stanganelli I, Marchesi E. Mometasone furoate in the treatment of atopic dermatitis in children. *J Eur Acad Dermatol Venereol* 1993;**2**:225–30. [Different potencies]

Reidhav I, Svensson A. Betamethasone valerate versus mometasone furoate cream once daily in atopic dermatitis. *J Dermatol Treat* 1996;**7**:87–8. [Both products once daily]

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

Squires DJ, Masson EL. An evaluation of once-daily applications of diflorasone diacetate in eczematous dermatoses. *J Int Med Res* 1981;**9**: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. *J Am Acad Dermatol* 1991;**24**: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. *J Int Med Res* 1990;**18**:460–7. [Patients not limited to atopic eczema]

Wishart JM, Lee I-S. Mometasone versus betamethasone creams: a trial in dermatoses. *N Z Med J* 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. *J Am Acad Dermatol* 1998;**39**:226–31. [Different potencies]

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol

Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford

Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine

Dr Jeffrey Aronson
Reader in Clinical Pharmacology, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

Professor Ann Bowling, Professor of Health Services Research, Primary Care and Population Studies, University College London

Professor Andrew Bradbury, Professor of Vascular Surgery, Department of Vascular Surgery, Birmingham Heartlands Hospital

Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health & Related Research, University of Sheffield

Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York

Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen

Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Peter Jones, Head of Department, University Department of Psychiatry, University of Cambridge

Professor Sallie Lamb, Research Professor in Physiotherapy/Co-Director, Interdisciplinary Research Centre in Health, Coventry University

Professor Julian Little, Professor of Epidemiology, Department of Medicine and Therapeutics, University of Aberdeen

Professor Stuart Logan, Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter & Plymouth

Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol

Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Professor Mark Sculpher, Professor of Health Economics, Centre for Health Economics, Institute for Research in the Social Services, University of York

Professor Martin Severs, Professor in Elderly Health Care, Portsmouth Institute of Medicine

Dr Jonathan Shapiro, Senior Fellow, Health Services Management Centre, Birmingham

Ms Kate Thomas, Deputy Director, Medical Care Research Unit, University of Sheffield

Professor Simon G Thompson, Director, MRC Biostatistics Unit, Institute of Public Health, Cambridge

Ms Sue Ziebland, Senior Research Fellow, Cancer Research UK, University of Oxford

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Dr John Fielding, Consultant Radiologist, Radiology Department, Royal Shrewsbury Hospital

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), Department of Health, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre

Professor Imti Choonara, Professor in Child Health, University of Nottingham, Derbyshire Children's Hospital

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Stan Kaye, Professor of Medical Oncology, Consultant in Medical Oncology/Drug Development, The Royal Marsden Hospital

Ms Barbara Meredith, Project Manager Clinical Guidelines, Patient Involvement Unit, NICE

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Dr Aileen Clarke, Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, Institute of Community Health Sciences, Queen Mary, University of London

Mr Matthew William Cooke, Senior Clinical Lecturer and Honorary Consultant, Emergency Department, University of Warwick, Coventry & Warwickshire NHS Trust, Division of Health in the Community, Centre for Primary Health Care Studies, Coventry

Dr Carl E Counsell, Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of Orthopaedic Surgery, South Tees Hospital NHS Trust

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint

Ms Maryann L. Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Professor James Neilson, Professor of Obstetrics and Gynaecology, Dept of Obstetrics and Gynaecology, University of Liverpool, Liverpool Women's Hospital

Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust

Dr Vimal Sharma, Consultant Psychiatrist & Hon Snr Lecturer, Mental Health Resource Centre, Victoria Central Hospital, Wirrall

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns,
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Mary Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Stephen Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum,
Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs,
Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss,
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Jon Nicholl,
Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick,
National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry, University Mental Health Group, Royal South Hants Hospital, Southampton

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge,
Director, College of Health, London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278