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Review

Systematic review of treatments for atopic eczema

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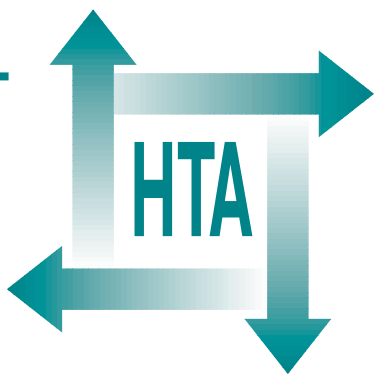
NHS R&D HTA Programme



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Systematic review of treatments for atopic eczema

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NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 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.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('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. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

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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 editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report. They would like to thank the referees for their constructive comments on the draft document.

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Contents

List of abbreviations and glossary

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.

List of abbreviations

ADASI	Atopic Dermatitis Area Severity Index
b.d.	twice daily*
BIT	biophysical information therapy
CCT	controlled clinical trial*
CCTR	Cochrane Controlled Trials Register
CI	confidence interval
DSCG	disodium cromoglycate
EDEN	European Dermato-Epidemiology Network
ETAC	Early Treatment of the Atopic Child (study)
GLA	gamma-linoleic acid
IgE	immunoglobulin E
ISAAC	International Study of Asthma and Allergies in Childhood
ITT	intention-to-treat*
NS	not significant
o.d.	once daily*
PAF	platelet-activating factor
PP	per protocol*
PUVA	psoralen plus UVA
q.d.s.	four times daily*
RCT	randomised controlled trial
RoNAA	Rule of Nines area assessment*
SCG	sodium cromoglycate
SCORAD	Severity Scoring of Atopic Dermatitis
SEM	standard error of the mean*
t.d.s.	three times daily*
UVR	ultraviolet radiation
VAS	visual analogue scale*

*Used only in tables

Glossary

Atopic dermatitis Synonymous with atopic eczema.

Bayesian approach An approach to data analysis first developed by Thomas Bayes, which tests the likelihood of something occuring in the light of prior knowledge and belief about what is likely to happen. This is different from traditional 'frequentist' statistics, which seeks to disprove the null hypothesis of no difference between the things being compared.

Demarcated Lacks boundary.

Erythema Redness.

Inverse proportion A relation between two quantities such that one increases in proportion as the other decreases.

ITT analysis A method of analysis for RCTs whereby all patients randomly allocated to oneof the treatments in a trial are analysed

continued

continued

together irrespective of whether or not they completed or received that treatment.

Lichenification Thickening of the skin as a result of chronic scratching.

Morphology Form.

Pruritus Itching.

Rebound phenomenon The tendency for atopic eczema to flare up immediately on stopping a treatment that suppresses the disease process.

Recombinant Reformed by recombination.

Rule of Nines A method for estimating extent of eczema based on dividing the body into multiples of 9%.

Serological (serology) The scientitic study of blood sera and their effects.

Spongiosis Excess fluid between the cells in the epidermis.

Tracker studies A type of experimental design suggested by Lillford for testing technologies that are rapidly changing, for example prosthetic devices. In the duration of a 3-year trial, the types of devices that were originally tested might have already been improved upon, thereby limiting the extent to which one could generalise from the findings. Tracker studies are more flexible by permitting the use of the technology as it evolves within the trial.

Wiskott–Aldrich Syndrome A genetic defect affecting a gene on the x chromosome. Generally passed from mother to son. Main symptoms are proneness to infections, thrombocytopenia (low platelet counts) and eczema of differing severity.

Executive summary

Background

Atopic eczema is the commonest inflammatory skin disease of childhood, affecting 15–20% of children in the UK at any one time. Adults make up about one-third of all community cases. Moderate-to-severe atopic eczema can have a profound effect on the quality of life for both sufferers and their families. In addition to the effects of intractable itching, skin damage, soreness, sleep loss and the social stigma of a visible skin disease, other factors such as frequent visits to doctors, special clothing and the need to constantly apply messy topical applications all add to the burden of disease. The cause of atopic eczema is unknown, though a genetic predisposition and a combination of allergic and non-allergic factors appear to be important in determining disease expression. Treatment of atopic eczema in the UK is characterised by a profusion of treatments aimed at disease control. The evidential basis of these treatments is often unclear. Most people with atopic eczema are managed in primary care where the least research has been done.

Objectives

The objectives of this scoping review are two-fold.

- To produce an up-to-date coverage 'map' of randomised controlled trials (RCTs) of treatments of atopic eczema.
- To assist in making treatment recommendations by summarising the available RCT evidence using qualitative and quantitative methods.

Methods

Data sources

Data sources included electronic searching of MEDLINE, EMBASE, the Cochrane Controlled Clinical Trials Register, the 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/exclusion criteria

Only RCTs of therapeutic agents used in the prevention and treatment of people with atopic eczema of any age were considered for inclusion. Only studies where a physician diagnosed atopic eczema or atopic dermatitis were included.

Data extraction

Data extraction was conducted by two observers onto abstraction forms, with discrepancies resolved by discussion.

Quality assessment

The quality assessment of retrieved RCTs included an assessment of:

- a clear description of method and concealment of allocation of randomisation
- the degree to which assessors and participants were blinded to the study interventions, and
- whether all those originally randomised were included in the final main analysis.

Data synthesis

Where possible, quantitative pooling of similar RCTs was conducted using the Cochrane Collaboration's methods. Where statistical heterogeneity was found, sources of heterogeneity in terms of study participants, formulation or posology of intervention, and use of co-treatments were explored. Where pooling was not deemed to be appropriate, detailed descriptions of the study characteristics and main reported results were presented along with comments on study quality.

Results

A total of 1165 possible RCTs were retrieved in hard copy form for further scrutiny. Of these, 893 were excluded from further analysis because of lack of appropriate data. The 272 remaining RCTs of atopic eczema covered at least 47 different interventions, which could be broadly categorised into ten main groups.

Quality of reporting was generally poor, and limited statistical pooling was possible only for oral cyclosporin, and only then after considerable data transformation.

There was reasonable RCT evidence to support the use of oral cyclosporin, topical corticosteroids, psychological approaches and ultraviolet light therapy.

There was insufficient evidence to make recommendations on maternal allergen avoidance for disease prevention, oral antihistamines, Chinese herbs, dietary restriction in established atopic eczema, homeopathy, house dust mite reduction, massage therapy, hypnotherapy, evening primrose oil, emollients, topical coal tar and topical doxepin.

There was no RCT evidence to support any clear clinical benefit on the use of avoidance of enzyme washing powders, cotton clothing as opposed to soft-weave synthetics, biofeedback, twice-daily as opposed to once-daily topical corticosteroids, topical antibiotic/steroid combinations versus topical steroids alone and antiseptic bath additives.

There was complete absence of RCT evidence on short bursts of potent versus longer-term weaker topical steroids, dilution of topical corticosteroids, oral prednisolone and azathioprine, salt baths, impregnated bandages, wet-wrap bandages, water softening devices, allergy testing, and different approaches to organisation of care.

Conclusions

Coverage

The evidence base for the prevention and treatment of atopic eczema has many limitations. It is characterised by a profusion of short-term trials of 'me too' products, a lack of common outcome measures which measure things that are important to patients, poor standards of clinical trial reporting, and a lack of data on questions that physicians and people with atopic eczema deem to be important. Little research has evaluated commonly used treatments compared with each other or in combination. This mismatch is probably due to a combination of the questions not being asked coupled with a lack of independent investment in primary atopic eczema research.

Recommendations for research

Urgent **primary research** priorities include RCTs of wet-wrap treatments, the clinical benefit of allergy testing, the use of water softeners, the role of specialist nurses, comparisons of tacrolimus and ascomycin against topical corticosteroids, studies of disease prevention, and the use of emollients in preventing disease relapse. Such RCTs should ideally be pragmatic and simple in design, with a few outcome measures that doctors and patients find easy to understand. They should ideally be of 4 months' or more duration in order to capture the chronicity of disease as well as short-term effects. If such trials are intended to inform primary care, where patients may have milder disease, then they should be conducted in a primary care setting.

This review suggests that there is some scope for further **secondary research** by systematically reviewing some of the major treatment groups such as antihistamines and essential fatty acids in more detail, and some of these are already underway within the Cochrane Skin Group.

Future **methodological research** is needed to increase the clinical relevance and reliability of outcome measures for atopic eczema. The RCT database contained within this report also provides a good opportunity to conduct some general research into the relationship between study quality and treatment benefit. There is much scope for improving the standard of clinical trial reporting in atopic eczema by dermatology journals adopting rigorous checks on clinical trial reporting and by registering ongoing trials with the Cochrane Skin Group.

Chapter 1

Background and aims

The problem of atopic eczema

What is atopic eczema?

Atopic eczema is a chronic inflammatory skin condition characterised by an itchy red rash that favours the skin creases such as folds of elbows or behind the knees. The eczema lesions themselves vary in appearance from collections of fluid in the skin (vesicles) to gross thickening of the skin (lichenification) on a background of poorly demarcated redness. Other features such as crusting, scaling, cracking and swelling of the skin can occur.[1] Atopic eczema is associated with other atopic diseases such as hay fever and asthma. People with atopic eczema also have a dry skin tendency, which makes them vulnerable to the drying effects of soaps. Atopic eczema typically starts in early life, with about 80% of cases starting before the age of 5 years.[2]

Is atopic eczema 'atopic'?

Although the word 'atopic' is used when describing atopic eczema, it should be noted that around 20% of people with otherwise typical atopic eczema are not **atopic** as defined by the presence of positive skin prick test reactions to common environmental allergens, or through blood tests, which detect specific circulating immunoglobulin E (IgE) antibodies.[3] The word 'atopic' in the term atopic eczema is simply an indicator of the frequent association with atopy and the need to separate this clinical phenotype from the ten or so other forms of **eczema** such as irritant, allergic contact, discoid, venous, seborrhoeic and photosensitive eczema, which have other causes and distinct patterns. The terms **atopic eczema** and **atopic dermatitis** are synonymous. The term atopic eczema or just eczema is frequently used in the UK, whereas atopic dermatitis is used more in North America. Much scientific energy has been wasted in debating which term should be used.

How is atopic eczema defined in clinical studies?

Very often, no definition of atopic eczema is given in clinical studies such as clinical trials. This leaves the reader guessing as to what sort of people were studied. Atopic eczema is a difficult disease to define as the clinical features are highly variable. This variability can be in the skin rash morphology (e.g. it can be dry and thickened or weeping and eroded), in place (e.g. it commonly affects the cheeks in infants and skin creases in older children) and time (it can be bright red one day and apparently gone in a couple of days). There is no specific diagnostic test that encompasses all people with typical eczema and which can serve as a reference standard. Diagnosis is therefore essentially a clinical one.

Up until the late 1970s, at least 12 synonyms for atopic eczema were in common usage in the dermatological literature, and it is not certain if physicians were all referring to the same disease when using these terms. A major milestone in describing the main clinical features of atopic eczema was the Hanifin and Rajka diagnostic criteria of 1980.[4] These are frequently cited in clinical trial articles, and they at least provide some degree of confidence that researchers are referring to a similar disease when using these features. It should be borne in mind however that these criteria were developed on the basis of consensus, and their validity and repeatability is unknown in relation to physician's diagnosis.[3] Some of the 30 or so minor features have since been shown not to be associated with atopic eczema, and many of the terms, which are poorly defined, probably mean something only to dermatologists. Scientifically developed refinements of the Hanifin and Rajka diagnostic criteria, mainly for epidemiological studies, have been developed by a UK working party, and these criteria have been widely used throughout the world.[5] According the these criteria,[6] in order to qualify as a case of atopic eczema, the person must have:

- an itchy skin condition

plus three or more of:

- past involvement of the skin creases, such as the bends of elbows or behind the knees
- personal or immediate family history of asthma or hay fever
- tendency towards a generally dry skin
- onset under the age of 2 years
- visible flexural dermatitis as defined by a photographic protocol.

Binary or continuous disease?

It is unclear whether atopic eczema is an 'entity' in itself or whether it is part of a continuum when considered at a population level. Some studies have suggested that atopic dermatitis score is distributed as part of a continuum.[3] Although it may be appropriate to ask the question: "How much atopic eczema does he/she have?" as opposed to "Does he/she have atopic eczema – yes or no?", most population and clinical studies require a categorical cut-off point and tend to include well-defined and typical cases.

Is it all one disease?

It is quite possible that there are distinct subsets of atopic eczema, for example those cases associated with atopy and those who have severe disease with recurrent infections. Until the exact genetic and causative agents are known, it is wiser to consider the clinical disease as one condition. Perhaps sensitivity analyses can be done for those who are thought to represent distinct subsets (e.g. those who are definitely atopic with raised circulating IgE to allergens, or those with severe disease and associated asthma).[3]

The prevalence of atopic eczema

Atopic eczema is a very common problem. Prevalence studies in the last decade in Northern Europe suggest an overall prevalence of 15–20% in children aged 7–18 years.[7] Standardised questionnaire data from 486,623 children aged 13–14 years in the International Study of Asthma and Allergies in Childhood (ISAAC) suggest that atopic eczema is not just a problem confined to Western Europe, with high prevalence found in many developing cities undergoing rapid demographic change.[8] There is reasonable evidence to suggest that the prevalence of atopic eczema has increased two- to three-fold over the past 30 years, the reasons of which are unclear.[9] No reliable incidence estimates are available for atopic eczema.

Age

Atopic eczema is commoner in childhood, particularly in the first 5 years of life. One study of 2365 patients who were examined by a dermatologist for atopic eczema in the town of Livingston, Scotland, suggested that atopic eczema is relatively rare over the age of 40, with a 1-year period prevalence of 0.2%.[10] Nevertheless, adults over 16 years made up 38% of all atopic eczema cases in that community. Adults also tend to represent a more persistent and severe subset of cases.

Severity distribution

Most cases of childhood eczema in any given community are mild. One recent study by Emerson and colleagues found that 84% of 1760 children aged 1–5 years from four urban and semi-urban general practices in Nottingham were mild, as defined globally by the examining physician, with 14% of cases in the moderate category and 2% in the severe category.[11] Disease severity was not the only determinant of referral for secondary care, however. This severity distribution was very similar to another recent population survey in Norway.[12]

How does atopic eczema affect people?

Direct morbidity has been estimated in several studies using generic dermatology quality-of-life scales. It has been found that atopic eczema usually accounts for the highest scores when compared with other dermatological disease. Specific aspects of a child's life that are affected by atopic eczema are:

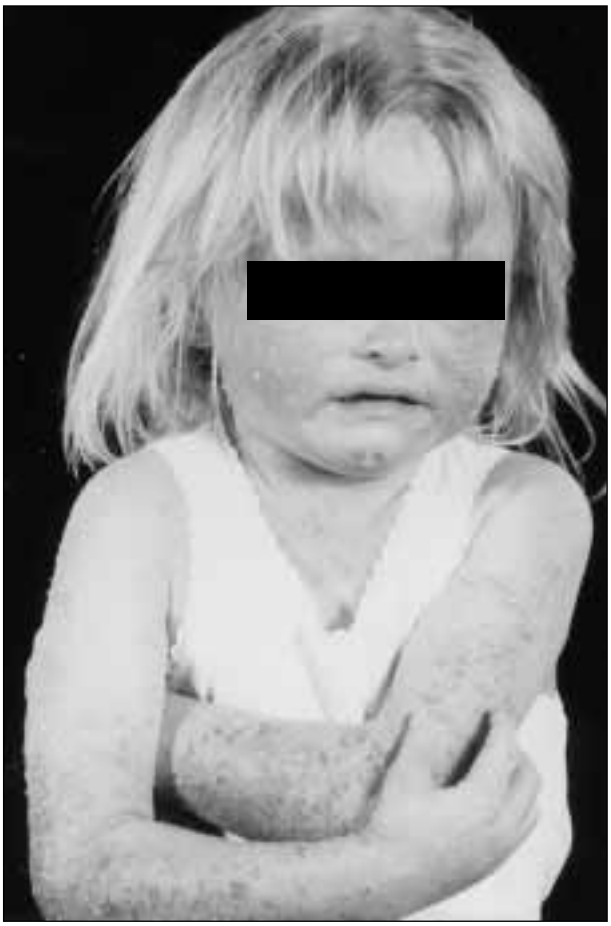
- itch and associated sleep disturbance (*Figure 1*)
- ostracism by other children and parents
- the need for special clothing and bedding
- avoidance of activities such as swimming, which other children can enjoy, and
- the need for frequent applications of greasy ointments and visits to the doctor.

Family disturbance is also considerable with sleep loss and the need to take time off work for visits to healthcare professionals.[7]

Economic costs

In financial terms, the cost of atopic eczema is potentially very large. One recent study of an entire community in Scotland estimated the mean personal cost to the patient at £25.90 over a 2-month period with the mean cost to the health service of £16.20.[13] If these results were extrapolated to the UK population, the annual personal costs to patients with atopic eczema based on lower prevalence estimates than recent studies suggest would be £297 million. The cost to the health service would be £125 million and the annual cost to society through lost working days would be £43 million making the total expenditure on atopic eczema £465 million per year (1995 prices). Another recent study from Australia found that the annual personal financial cost of managing mild, moderate and severe eczema was Aus$330,818 and $1255, respectively, which was greater than the costs associated with asthma in that study.[14]

FIGURE 1 *Despite the public's tendency to trivialise skin disease, the suffering associated with the intractable itching of atopic eczema can be greater than other illnesses such as asthma and heart disease.*[7]



What causes atopic eczema?

Genetics

There is strong evidence to suggest that genetic factors are important in the predisposition to atopic eczema. In addition to family studies, twin studies have shown a much higher concordance for monozygotic (85%) when compared with dizygotic twins (21%).[15] Preliminary work has suggested that a marker for IgE hyper-responsiveness might be located on chromosome 11q, but this has not been consistent. It is possible that the tendency to atopic eczema might be inherited independently from atopy.

Environment

While genetic factors are probably a very important factor for disease predisposition, there are numerous general and specific clues that point strongly to the crucial role of the environment on disease expression.[16] It is difficult to explain the large increase in atopic eczema prevalence over the past 30 years, for instance, in genetic terms.[9] It has been shown that atopic eczema is commoner in wealthier families.[17] It is unclear whether this positive social class gradient is a reflection of indoor allergen exposures or whether it reflects a whole constellation of other factors associated with 'development'. Other studies have shown an inverse association between eczema prevalence and family size.[18] This observation led to the 'hygiene hypothesis', that is that children in larger families were protected from expressing atopy because of frequent exposure to infections.[19] Some evidence for this protective effect of infections on atopic eczema has been shown in relation to measles infection in Guinea Bissau.[20]

Migrant studies also point strongly to the role of environmental factors in atopic eczema. It has been shown that 14.9% of black Caribbean children living in London develop atopic eczema (according to the UK diagnostic criteria) compared with only 5.6% for similar children living in Kingston, Jamaica.[21] Other migrant studies reviewed elsewhere have consistently recorded large differences in ethnic groups migrating from warmer climates to more prosperous cooler countries.

Further work has suggested that the tendency to atopy may be programmed at birth and could be related to factors such as maternal age.[22] The observation that many cases of atopic eczema improve spontaneously around puberty is also difficult to explain in genetic terms alone.[2] Specific risk factors for eczema expression in the environment are still not fully elucidated. Allergic factors such as exposure to house dust mite may be important but non-allergic factors such as exposure to irritants, bacteria and hard water may also be important.[23]

Pathophysiology

A number of mechanisms and cells are thought to be important in atopic eczema and these are reviewed in detail elsewhere.[1,24] Microscopically, the characteristic appearance of eczema is that of excess fluid between the cells in the epidermis (spongiosis). When severe, this fluid eventually disrupts the adjacent cells in the epidermis to form small collections of fluid, which are visible to the naked eye as vesicles. In the chronic phase, atopic eczema is characterised by gross thickening of the epidermis (acanthosis) and an infiltrate of lymphocytes in the dermis. The theory that unifies the various abnormalities of atopic eczema suggest that blood stem cells carrying abnormal

genetic expression of atopy cause clinical disease as they infiltrate and remain in the mucosal surfaces and skin. There appears to be a failure to switch off the natural predominance of Th2 helper lymphocytes, which normally occurs in infancy, and this leads to an abnormal response of chemical messengers called cytokines to a variety of stimuli. The underlying mechanism of disease may be either abnormalities of cyclic nucleotide regulation of marrow-derived cells or allergenic over-stimulation that causes secondary abnormalities. Some studies have suggested a defect in lipid composition and barrier function of people with atopic eczema – a defect that is thought to underlie the dry skin tendency and possibly enhanced penetration of environmental allergens and irritants, leading to chronic inflammation.

Does atopic eczema clear with time?

Although the tendency towards a dry and irritable skin is probably lifelong, the majority of children with atopic eczema appear to 'grow out' of their disease, at least to the point where the condition no longer becomes a problem in need of medical care. A detailed review of studies that have determined the prognosis of atopic eczema has been reported elsewhere.[2] This review suggested that most large studies of well-defined and representative cases suggest that about 60% of childhood cases are clear or free of symptoms from disease in early adolescence. Many such apparently clear cases are likely to recur in adulthood, often as hand eczema. The strongest and most consistent factors that appear to predict more persistent atopic eczema are early onset, severe widespread disease in infancy, concomitant asthma or hay fever and a family history of atopic eczema.

How is atopic eczema treated?

The management of atopic eczema in the UK was summarised in a paper jointly produced by a British Association of Dermatology and Royal College of Physicians Working Party in 1995.[25] The article described the management of atopic eczema in three stages. The first line of treatment involved providing an adequate explanation of the nature of disease as well as advice on avoiding irritants. The role of emollients in adequate quantities was emphasised, as well as prompt treatment of secondary infections. Topical steroids were highlighted as the mainstay of treatment, though care regarding the duration of treatment, site and age of the person treated was emphasised. Antihistamines were only recommended for their sedative action. Cognitive behavioural techniques were also mentioned as being important to some families. Allergen avoidance, for example the reduction of house dust mite or dietary intervention, was described as a second-line treatment, as was treatment with ultraviolet light under specialist care. Third-line treatment (always under the care of a specialist) included such treatments as short bursts of systemic corticosteroids, cyclosporin A, evening primrose oil and Chinese herbal medicines.

These recommendations were made on the basis of consensus from a wide range of practitioners and patient advocates. Although some recommendations were based on RCTs, many were not. It is unclear, therefore, how many of these recommendations are truly beneficial to patients. New developments since the publication of these recommendations include increased use of a double layer of protective bandages ('wet-wraps') with or without topical steroids, 'newer' once-daily topical corticosteroids such as mometasone and fluticasone, and possibly some increased use of potent systemic agents such as cyclosporin A. Other new potent topical preparations such as tacrolimus and ascomycin derivatives are probably going to become available in the near future.[26]

How is care organised in the UK?

Most children with atopic eczema in the UK are probably managed by the primary care team. This includes advice from pharmacists, health visitors, practice nurses and family practitioners. About 4% of children with atopic eczema are referred to a dermatologist for further advice.[11]

The quality of service provided by secondary care for eczema sufferers has recently been audited by the British Association of Dermatologists. Although most departments provided a high-quality service, some aspects of care, such as the administration of simple standardised record forms could be improved.[27,28]

Compliance (or more correctly, concordance) seems to be a major cause of apparent treatment failures and a recent study suggested that this was often due to a poor understanding of the chronic nature of the disease, a fear of topical corticosteroids and the belief that all atopic eczema is caused by a specific allergy. A survey in Nottingham has found that most mothers worry that topical steroids cause adverse effects, though

many were not able to distinguish between weak and strong ones.[29]

The National Eczema Society is the UK's self-help organisation for atopic eczema sufferers and people with other forms of eczema. It has a well-organised information service and national network of activities geared to help eczema sufferers and their families. Sources of alternative care for atopic eczema sufferers abound in the community ranging from the highly professional to elaborate expensive diagnostic and therapeutic measures of dubious value.

How are the effects of atopic eczema captured in clinical trials?

Outcome measures used in trials have recently been reviewed by Finlay.[30] Most outcome measures have incorporated some measure of itch as assessed by a doctor at periodic reviews or patient self-completed diaries. Other more sophisticated methods of objectively recording itch have been tried. Finlay drew attention to the profusion of composite scales used in evaluating atopic eczema outcomes. These usually incorporate measures of extent of atopic eczema and several physical signs such as redness, scratch marks, thickening of the skin, scaling and dryness. Such signs are typically mixed with symptoms of sleep loss and itching and variable weighting systems are used. It has been shown that measuring surface area involvement in atopic eczema is fraught with difficulties,[31] which is not surprising considering that eczema is, by definition, 'poorly-defined erythema'. Charman and colleagues recently performed a systematic review of named outcome measure scales for atopic eczema and found that of the 13 named scales in current use, only one (Severity Scoring of Atopic Dermatitis, SCORAD) had been fully tested for validity, repeatability and responsiveness.[32] Quality-of-life measures specific to dermatology include the Dermatology Quality of Life Index[30] and SKINDEX.[33] The Children's Dermatology Life Quality index has been used in atopic eczema trials in children.

The authors are aware that most clinical trials of atopic eczema have been short term, that is about 6 weeks. This seems inappropriate in a chronic relapsing condition. Very few studies have considered measuring number and duration of disease-free relapse periods. It is impossible to say whether modern treatments have increased chronicity at the expense of short-term control in the absence of such long-term studies.

Why is a systematic review needed?

The authors suspect that little research has been done into primary and secondary prevention of atopic eczema. Research is also probably very limited in non-pharmacological areas of treatment such as psychological approaches to disease management. Even for traditional pharmaceutical preparations, the choice of treatments for atopic eczema by patients or their practitioners is complicated by a profusion of preparations whose **comparative** efficacy is unknown.[5] Thus, the current *British National Formulary* lists 19 classes of topical corticosteroids available for treating atopic eczema and a total of 63 preparations that combine corticosteroids with other agents such as antibiotics, antiseptics, antifungals and keratolytic agents.[34] How can a family practitioner make a rational choice between so many preparations?[35]

Systemic treatments for severe atopic eczema have only been partially evaluated. There are plenty of trials, for instance on expensive drugs such as cyclosporin A (which may have serious long-term adverse effects), yet to the best of our knowledge, there is not a single controlled trial on oral azathioprine – a much cheaper and possibly safer and more effective treatment that is currently widely used by British dermatologists.[36] In other areas, there is a profusion of small studies, which do not have the power to adequately answer the therapeutic questions posed.

The authors are also aware that many clinical trials have not asked patients enough of what they think about the various treatments under test. There is an opportunity in a systematic review, therefore, to redress the balance of outcome measures used in clinical trials towards the sort of measures that are clinically meaningful to patients and their carers.

Public concern over long-term adverse effects such as skin thinning and growth retardation from use of topical corticosteroid preparations has not been matched by long-term studies on atopic eczema sufferers. Individuals with atopic eczema often resort to self-prescribed diets, which can be nutritionally harmful, or they may turn to 'alternative' tests and treatments which may turn out to be beneficial or expensive and harmful.

Thus, there is considerable uncertainty about the effectiveness of the prevention and treatment of atopic eczema. This combination of high disease prevalence, chronic disability, high financial costs, public concerns regarding adverse effects, lack of evaluation of non-pharmacological treatments,

concern regarding the clinical relevance of trial outcome measures and the profusion of treatments and care settings of unknown effectiveness is why a scoping systematic review of atopic eczema treatments is needed. It is hoped that the review will form the basis for identifying, prioritising and generating further primary, secondary and methodological research.

Summary of the problem of atopic eczema

- The terms atopic eczema and atopic dermatitis are synonymous.
- The definition of atopic eczema is a clinical one based on itching, redness and involvement of the skin creases.
- About 20% of people with clinically typical atopic eczema are not 'atopic'.
- The word 'atopic' in atopic eczema serves to distinguish it from the ten or so other types of 'eczema'.
- Atopic eczema affects about 15–20 % of UK schoolchildren.
- About 80% of cases in the community are mild.
- Adults form about one-third of all cases in a given community.
- Disease prevalence is increasing for unknown reasons.
- The constant itch and resultant skin damage in atopic eczema can lead to a poor quality of life for sufferers and their families.
- The economic costs of atopic eczema to both State and patient are high.
- Genetic and environmental factors are both critical for disease expression.
- Non-allergic factors may be just as important as allergic factors in determining disease expression and persistence.
- Imbalances of T-lymphocytes and skin barrier abnormalities are both important in explaining the pathological processes of atopic eczema.
- About 60% of children with atopic eczema are apparently clear or free of symptoms by adolescence.
- Early onset, severe disease in childhood and associated asthma/hay fever are predictors of a worse prognosis.
- Current first-line treatment in the UK includes emollients, topical corticosteroids, and sedative antihistamines.
- Second-line treatments include allergen avoidance and ultraviolet light.
- Third-line treatments include systemic immunomodulatory treatments such as cyclosporin A and azathioprine.
- Most people with atopic eczema are managed by the primary care team.
- Some people with atopic eczema seek alternative treatments.
- A systematic review is needed to map out where high quality research has been conducted to date with the aim of resolving some areas of uncertainty and in order to identify knowledge gaps to be addressed by further primary research.

Research questions asked in this review

The remit of this project is to provide a summary of RCTs of atopic eczema with the main aim of informing the NHS R&D Office and other research commissioners of possible research gaps for further primary, secondary or methodological research. It is also hoped that the review will be of some use to healthcare providers, physicians involved in the care of people with atopic eczema and also to atopic eczema sufferers and their families by placing current treatments in context with their evidence base. The main research questions asked in this review are therefore:

- What therapeutic interventions have the RCTs of atopic eczema covered so far? The main output of this **coverage** question is a summary of research gaps for further research, with research commissioners, charities and researchers as the main target audience.
- What treatment recommendations can be made by summarising the available RCT evidence using qualitative and quantitative methods? The main output for this question are detailed summaries of available RCT evidence for different interventions for atopic eczema along with the authors' interpretation of the data based on the quality, magnitude of treatment effect, and clinical relevance of that evidence.

An impossible task?

It is unrealistic to attempt to summarise the entire 'treatments of atopic eczema' into a single Cochrane-style systematic review, as such a task would take years and cover several volumes. Atopic eczema is a complex disease with at least 40 different treatment approaches and specific questions that can be asked of each treatment group. What is more realistic is to produce a 'sketch' or 'map' of RCTs of atopic eczema, to quantitatively summarise a few areas of conflicting studies where possible, and to qualitatively review

the others in a form that would be helpful to clinicians and patients. Such an approach could also act as 'seed reviews' for subsequent, more detailed Cochrane systematic reviews.

A question or data-driven review?

The very broad-ranging scoping nature of this review implies that it cannot be hypothesis-driven. Even in just one area of atopic eczema management such as dietary prevention, there are at least six separate systematic reviews that can be asked of the available data:

- Does maternal avoidance of certain potentially allergenic foods prevent atopic eczema and if so, by how much in offspring at high risk (i.e. family history of atopy) versus those at normal risk?
- Does dietary manipulation in pregnancy reduce the **severity** of atopic eczema in offspring?
- Does exposing infants to allergens at an early stage of their immune development help by making them tolerant to substances that they will inevitably encounter in later life?
- Does **exclusive** breastfeeding protect against atopic eczema?
- Does **prolonged** breastfeeding with supplementation protect against atopic eczema?
- Does the early introduction of solids bring on atopic eczema?

Trying to answer similar questions for each of the 40 or so interventions used for the treatment of atopic eczema would be impossible in one short report.

This review is therefore unashamedly a data-driven one. It is a review that aims to map out what has been done in terms of RCTs in atopic eczema to date and to reflect and comment on the coverage of already researched areas in relation to questions that are commonly asked by physicians and their patients.

The authors are aware that there is a danger that a data-driven review can serve to amplify and perpetuate current trends in evaluating minor differences between a profusion of similar pharmacological products. The authors have mitigated against this inevitable hazard by drawing attention to gaps that have not been addressed when summarising the reported studies, and also by including a comprehensive section on 'unanswered questions' in chapter 14 of this report, based on the views of contemporary researchers, physicians and patients.

Chapter 2
Methods

General methods structure

This review has been prepared along the guidelines developed by the University of York[37] and those issued by the NHS Health Technology Assessment (HTA) programme[38] and uses methods developed by the Cochrane Collaboration[39] where possible.

Types of studies included in the review

Only RCTs of treatments for atopic eczema were included in the data summaries as other forms of evidence are associated with higher risks of bias. In order to be included as an RCT, a randomisation procedure was described, the study compared two or more treatments in human beings, and the study was prospective. In addition, the RCTs had to be concerned with therapeutic issues in relation to the prevention or treatment of atopic eczema. Thus, RCTs that involved evaluating cellular or biochemical responses of patients with atopic eczema after testing or injecting them with substances such as histamine were not included. Although they might inform future therapy, they were not therapeutic trials. Studies of possible increased incidence of drug adverse effects in atopic people compared with non-atopic people were also excluded. Studies also had to include at least one clinical outcome. Therefore, studies that only reported changes in blood tests or cellular mechanisms were excluded.

Study participants

Studies were included if participants were babies, children or adults who have atopic eczema (syn. atopic dermatitis) according to Hanifin and Rajka diagnostic criteria,[4] or as diagnosed by a physician. Terms used to identify trial participants with definite, possible and definitely not atopic eczema are shown in *Table 1*. Those studies using terms in the 'definitely not atopic eczema' category such as allergic contact eczema were excluded. Those studies using terms in the 'possible atopic eczema' category, such as 'childhood eczema' were scrutinised by one of the authors and only included if the description of the participants clearly indicated atopic eczema (i.e. itching and flexural involvement).

Main outcome measures

Changes in patient-rated symptoms of atopic eczema such as itching (pruritus) or sleep loss were used where possible. Global severity as rated

TABLE 1 *Terms used to identify trial participants with definite, possible and definitely not atopic eczema*

Definite atopic eczema (include if study was an RCT)	**Possible atopic eczema** (implies original paper must be obtained and read before a judgement is made to include or exclude by one of the authors based on additional features such as a good clinical description of atopic eczema with atopy)	**Not atopic eczema** (implies that the authors did not accept this term as representing atopic eczema)
Atopic eczema	Periorbital eczema	Seborrheic eczema
Atopic dermatitis	Childhood eczema	Contact eczema
Besnier's prurigo	Infantile eczema	Allergic contact eczema
Neurodermatitis atopica (German)	'Eczema' unspecified	Irritant contact eczema
Flexural eczema/dermatitis	Constitutional eczema	Discoid/nummular eczema
	Endogenous eczema	Asteatotic eczema
	Chronic eczema	Varicose/stasis eczema
	Neurodermatitis	Photo-/light-sensitive eczema
	Neurodermatis (German)	Chronic actinic dermatitis
		Dishydrotic eczema
		Pompholyx eczema
		Hand eczema
		Frictional lichenoid dermatitis
		Lichen simplex
		Occupational dermatitis
		Prurigo

by patients or their physician were also sought. If these were not available, then global changes in composite rating scales using a published named scale, or where not possible, the author's modification of existing scales or new scales developed within the study were summarised. Adverse events were also included if reported. The selection of outcome measures was explored in more detail in a focus group of consumers held by one of the authors.

Secondary outcome measures

Secondary outcomes measures were changes in individual signs of atopic eczema as assessed by a physician, for example:

- erythema (redness)
- purulence (pus formation)
- excoriation (scratch marks)
- xerosis (skin dryness)
- scaling
- lichenification (thickening of the skin)
- fissuring (cracks)
- exudation (weeping serum from the skin surface)
- pustules (pus spots)
- papules (spots that protrude from the skin surface)
- vesicles (clear fluid or 'water blisters' in the skin)
- crusts (dried serum on skin surface)
- infiltration/oedema (swelling of the skin), and
- induration (a thickened feel to the skin).

Search strategy

Electronic searching

In order to retrieve all RCTs on atopic eczema treatments in accordance with inclusion criteria, a systematic and mainly electronic search strategy was carried out. The Cochrane Collaboration Handbook[39] and the Centre for Reviews and Dissemination guidelines for systematic reviews[37] were used as templates.

The following electronic databases have been searched:

- MEDLINE[40] (1966 to end of 1999)
- EMBASE[41] with its higher yield of non-English reports (1980 to end of 1999)
- The Cochrane Controlled Trials Register (CCTR)[42] and
- The Cochrane Skin Group Specialised Trials Register.[43]

Disease terms for atopic eczema (as a textword and MeSH term) are shown in appendix 1.

Possible **trials** were identified from each of the four databases by:

- MEDLINE (*Index Medicus* online): the Cochrane Collaboration 'highly sensitive electronic search string' for RCTs was used (appendix 1). Years 1966–December 1999 were searched and yielded over 3000 references using the disease search terms in appendix 1. An iterative approach was used with retrieved papers. Once trials on specific drug types were obtained, an additional MEDLINE search was carried out employing these specific drug terms (e.g. tacrolimus) or their developmental names (e.g. FK506) combined with a general skin search (appendix 1). References were checked for possible additional RCTs of atopic eczema. Review articles were also retrieved in hard copy form and references were checked for further RCTs.
- EMBASE (*Excerpta Medica* online): due to the different format of this database, an alternative search strategy was employed which was developed by the BMJ Publishing Group for its *Clinical Evidence* series (appendix 1).[44] Years 1980–December 1999, (the only years fully searchable on OVID), were searched. This yielded over 1000 references using the same eczema terms as for MEDLINE in *Table 1.* Trials that might have been on the EMBASE database from 1974 to 1979 would have been picked up by CCTR (see below), which has compiled its search of the entire EMBASE database since its inception in 1974.
- CCTR: the Cochrane Library, Issue 4, 1999 was searched for controlled trials within the CCTR section by exploding the disease-specific search terms separated by the boolean 'AND' with the advanced search option. These include clinical controlled trials (quasi randomisation) and RCTs (randomisation).
- Cochrane Skin Group Specialised Register: this was searched with the disease-specific terms and kind help of the Cochrane Skin Group Trials Search Coordinator.

Handsearching

As there are over 200 specialist dermatology journals and none specific to atopic eczema, separate handsearching was not done for this report. Some trials published in journals not listed in the main bibliographic databases or published within the body of a letter to the editor might therefore have been missed. However, results of handsearching of specialist dermatology journals by the Cochrane Skin Group are kept on the Cochrane Skin Group Specialised Register of trials, which was searched. This included results of handsearching the following dermatology journals as at July 2000:

- *Acta Dermato-Venereologica Supplementum* 1970–91
- *Archives of Dermatology* 1976–98
- *British Journal of Dermatology* 1991–97
- *Clinical & Experimental Dermatology* 1976–99
- *Cutis* 1967–99
- *International Journal of Dermatology* 1985–98
- *Journal of Investigative Dermatology* 1991–97
- *Journal of the American Academy of Dermatology* 1987–99.

In addition, conference proceedings of previous symposia such as the Atopic Dermatitis Symposium, held every 3 years (initially set up by Professor Georg Rajka), and all meeting abstracts for the annual meetings of the Society of Investigative Dermatology, European Academy of Dermatology and British Association of Dermatologists have been handsearched by one of the authors and the results made available to the Skin Group Specialised Register. Furthermore, one of the authors has been prospectively handsearching five dermatology journals (*Clinical Experimental Dermatology, British Journal of Dermatology, Journal of the American Academy of Dermatology, Journal of Investigative Dermatology* and *Paediatric Dermatology*) since January 1998, and any possible atopic eczema trials were accessed further by the team.

Other trial source

In addition to checking citations in retrieved RCTs and review articles, additional trials were sought by personal contact with atopic eczema researchers, and by writing to 37 pharmaceutical companies with a product or developing product in the area of atopic eczema.

Filtering

With the 3899 references yielded from the initial searches of MEDLINE, EMBASE and CCTR a filtering process began. This was carried out manually to assess whether the reference fitted the preliminary labels of 'trial' and 'atopic eczema'.

Not all references had abstracts; therefore, 'titles only' had to be included as possible trials to avoid premature judgement. Where doubt existed from the abstract or title, the full paper was requested and scrutinised further by two of the authors. Papers labelled as 'rejects' were categorised with another label to specify why they were not suitable for inclusion. This was carried out by one reviewer and checked by a second reviewer in any cases of possible uncertainty.

All papers were catalogued on a specialised ProCite database.[45]

Non-English studies

Studies published in non-English languages were screened by international colleagues (listed in the acknowledgement section) to see if they were possible RCTs with full data abstraction if this proved to be the case.

Data assessment

After assessment of retrieved papers for inclusion/exclusion criteria, the final list of included RCTs were subject to data abstraction with view to pooling or qualitative summary. Data abstraction forms were developed and used for those treatment groups where pooling appeared likely. Data for pooling were abstracted by two authors with discrepancies checked by a third if required. Data for qualitative summary were abstracted by one author and checked by a second.

Study quality

Methodological quality of each study was assessed using a previously described scheme where the three potential sources of bias were evaluated,[46] namely:

- the quality of the randomisation procedure
- the extent to which the primary analysis included all participants initially randomised (i.e. an intention-to-treat analysis)
- the extent to which those assessing the outcomes were aware of the treatments of those being assessed (blinding).

These three factors have been consistently shown to predict possible bias in effect estimates.[47]
A descriptive component, rather than a score-based system, was used to quality rate the studies so that readers can see which aspects of the study reporting were deficient. Due to the sheer size of this scoping review, report authors were not blinded to the identity of the RCT authors when quality rating or data abstracting. Such blinding would have needed to be very thorough (to the point of having to conceal the interventions) as many of the RCTs are well known to one of the abstracting authors.

Quantitative data synthesis

Where pooling made sense clinically in terms of the interventions, study participants and common clinical outcomes, a meta-analysis was performed using both a fixed- and random-effects model depending on whether there was evidence of statistical heterogeneity. Odds ratios of improvement compared with the comparison intervention was used in the pooling exercises. The inverse of

the variance of the outcome measures was used as weights for pooling the data from different trials. Sources of heterogeneity, such as differences in patients or formulation of interventions, were explored within the meta-analysis.

Methods of presenting qualitative results

Summarising the evidence of treatment and harm from 283 RCTs covering at least 47 different interventions in a way that would be helpful to healthcare commissioners, providers, physicians and users is challenging. There is always a conflict in such a situation of providing too much information resulting in loss of the general picture or of omitting important details in some specific areas. Readers are therefore encouraged to read the original studies for themselves where doubt occurs as to the reported data or author's conclusions in this paper.

For qualitative data summaries, the authors have adopted two systems.

- Where six or more RCTs are identified, these are summarised in tabular form, noting the interventions and comparator plus any other treatments permitted concurrently during the study (co-treatments), study population and sample size, study design and duration, outcome measures used in the study, main reported results, quality of reporting and specific comments relating to the study. The table is introduced with a brief summary of the rationale for use of the drug and the way it is used, and appended by any additional general comments and a summary of key points.
- Interventions with five or fewer RCTs have been summarised in text form in a way similar to that used in the BMJ Publishing Group's *Clinical Evidence* series.[44] After a brief introduction, the evidence of **benefits** from included RCTs is presented for each study, followed by a section on **harms** of treatment, followed by a section on author's interpretation of the data.

In many of the studies, over ten outcome measures have been reported, and it would have been impractical to document every one when presenting the reported results in the above two formats. In deciding which results to highlight in the 'main reported results' sections therefore, the authors have adopted a systematic approach of:

- patient-rated global improvement or itch or sleep loss, then
- global severity score based on several skin signs, or
- individual skin sign scores,

in that order of preference. In many studies evaluating multiple clinical signs of atopic eczema, only those that were statistically significant (*post-hoc*) were highlighted in the paper's conclusions or abstract. The authors have mitigated against this *post hoc* bias by reporting results relating to excoriations, erythema, extent or lichenification (in order of preference) if global or other more clinically meaningful summary measures were not reported.

If pre-existing systematic reviews were identified for any of the interventions, these were highlighted at the beginning of the results sections and described in more detail. Help in deciding which outcomes were important to patients was obtained by running a focus group of four participants recruited through the Cochrane Skin Group Consumer Network.

Separating trial data from authors' opinions

Throughout the report, the authors of the current review have been careful to make a clear distinction between the facts abstracted from individual studies and the respective author's interpretation of what those results or lack of results mean. Thus, actual data on efficacy and possible harms have been clearly separated from the author's 'comment' section. In the comment sections of the tables, the authors have commented on issues such as clinical relevance, quality of reporting, possible sources of bias, generalisability of the study, clinical implications and research gaps.

Identifying treatments with no RCTs and future research priorities

Given the inescapable fact that a data-driven review can only identify treatments for which some evidence exists, the authors sought to list those other treatments that are currently used throughout the world in atopic eczema which are not necessarily supported by RCTs. This was done by mailing colleagues through professional networks, requesting them to add any interventions that were missing from a list of treatments supported by RCTs drawn up by the authors. Eighteen out of 23 physicians from six different countries responded to this request.

In order to help the authors identify future research priorities, another sample of colleagues

was approached asking them to indicate the top five 'unanswered' questions in atopic eczema therapy today. Three purposive samples were sent this question on a personal letter: 12 colleagues internationally renowned for clinical atopic eczema research in the UK and abroad, four general practitioner colleagues with a known interest in skin disease, eight consultant dermatologists in England, Wales, Scotland and Ireland working in district general hospitals who did not have a declared special interest in atopic eczema, six consumer members of the Cochrane Skin Group and the seven Steering Group members of the European Dermato-Epidemiology Network (EDEN). Responses were collated by the authors and new themes were added as they became apparent.

Chapter 3
Results

Included studies

A total of 283 trials were finally included. In order to help summarise the interventions, groupings were constructed on the basis of: whether treatments dealt with prevention of new disease or treatment of established disease, and similar pharmacological drug type (e.g. topical steroids), similar intervention type (e.g. dietary measures) or convenience (e.g. non-pharmacological treatments) (*Table 2*).

Excluded studies

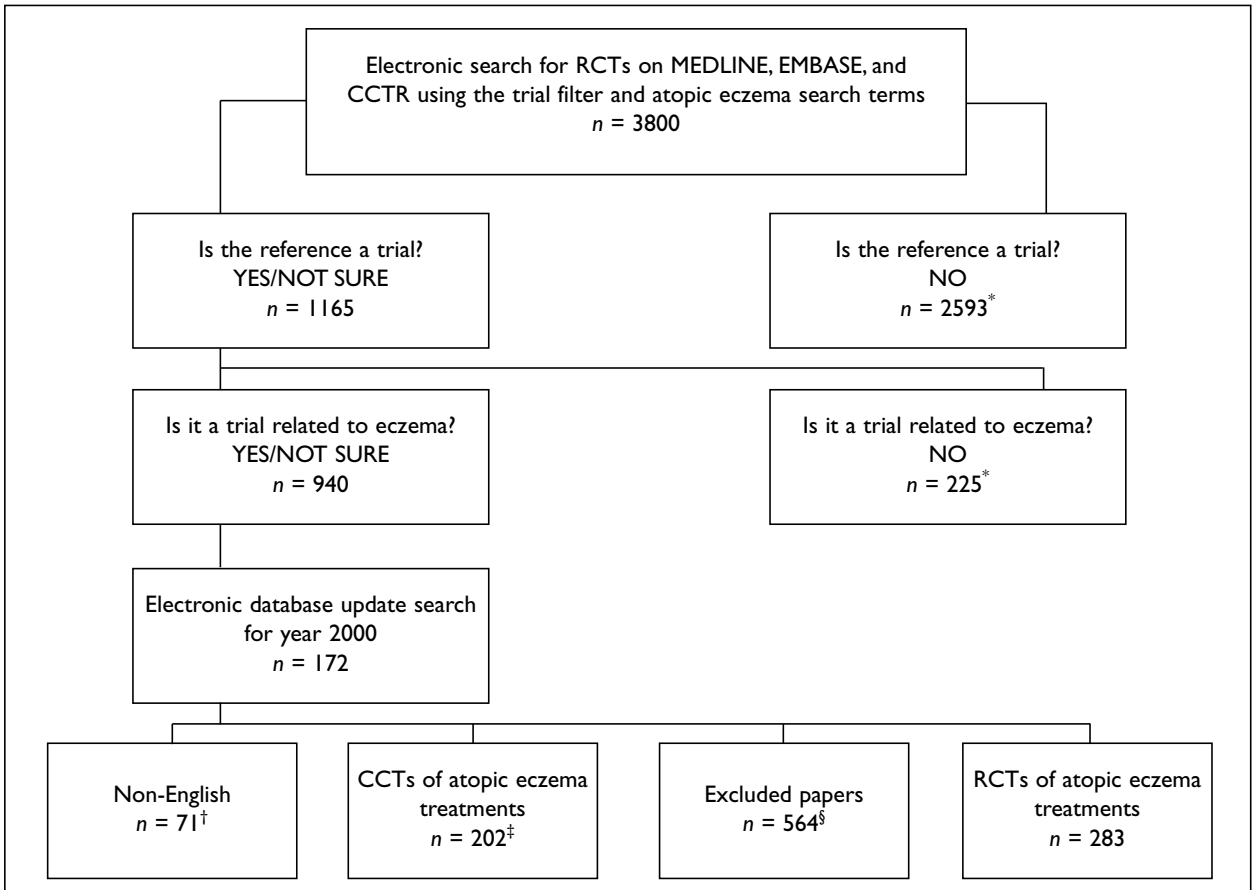
Details of excluded studies are shown in *Figure 2*. Further details on the 146 RCTs that included atopic eczema participants and which were excluded in the final stages are shown in appendix 2. The commonest reasons for exclusion were 'eczema' unspecified and combining the results of atopic eczema patients with patients who had other dermatoses.

TABLE 2 *Summary of study groupings*

Intervention groupings	No. of studies	References
A. Prevention of atopic eczema	**20**	
Prevention by allergen avoidance during pregnancy	8	48–55
Prevention by allergen avoidance after birth	12	56–67
B. Established atopic eczema	**254**	
Topical corticosteroids	**83***	**68–150**
Other topicals	**12**	
Coal tar	1	151
Emollients	6	152–157
Lithium succinate	1	158
Tacrolimus	3	159–161
Ascomycin	1	162
Antimicrobial/antiseptics	**10**	**163–172**
Antihistamines and mast cell stabilisers	**51**	
Antihistamines	21	173–193
Chromone compound/ sodium cromoglycate	20	84, 194–121
Nedocromil sodium	3	213–215
Ketotifen	2	216,217
Doxepin	4	218–221
Tiacrilast	1	222
Dietary interventions	**37**	
Dietary restriction in established atopic eczema	9	223–231
Evening Primrose Oil	14*	232–245
Borage oil	5	246–250
Fish oils	4	251–254
Pyridoxine	1	255
Vitamin E and multivitamins	3	256–258
Zinc supplementation	1	259
Non-pharmacological	**18**	
House dust mite reduction	8*	260–267
Non-pharmacological *contd.*		
Avoidance of enzyme-enriched detergents	1	268
Specialised clothing	3	269–271
Salt baths	1	272
Nurse education	1	273
Bioresonance	1	274
Psychological approaches	3	106,275,276
Ultraviolet light	7	277–283
Systemic immunomodulatory agents		**30**
Allergen–antibody complexes of house dust mite	2*	284,285
Cyclosporin A	13*	286–298
Levamisole	1	299
Platelet activating factor antagonist	1	300
Interferon-gamma	3	301–303
Thymodulin	2	304,305
Thymostimulin	2	306,307
Thymopentin	4	308–311
Immunoglobulin	1	312
Transfer factor	1	313
Complementary therapies	**8**	
Chinese herbs	4	314–317
Homeopathy	1	318
Aromatherapy	1	319
Hypnotherapy/biofeedback	1	320
Massage therapy	1	321
Miscellaneous	**7**	
Nitrazepam	1	322
Ranitidine	1	323
Theophylline	1	324
Salbutamol	1	325
Papaverine	2	326,327
Suplatast tosilate	1	328
Total RCTs	**283**	

**Includes duplicate publications*

FIGURE 2 *Details of excluded studies and process involved*



* *Available from authors on request. Aetiology, biological laboratory tests, case reports, clinical evaluations, diagnostics, miscellaneous epidemiology, morphological studies, non-human studies, pathogenesis, retrospective studies, severity scores, observational studies, treatment studies, treatment investigations, surveys, adverse effects, non-atopic eczema, treatment commentaries, case series*

† *Non-English: 17 non-English RCTs already included (nine Japanese, six Spanish, two French), ten non-English RCTs require data abstraction (one Finnish, eight German and one Danish), ten non-English awaiting translation to see if RCT of atopic dermatitis (nine Italian, one Polish), Russian papers translated no RCTs found. The remaining 45 papers consisted of 32 CCTs, 13 excluded RCTs and seven excluded non-RCTs*

‡ *Non-randomised CCTs: available from authors on request*

§ *162 excluded RCTs see appendix 2, the rest excluded for same reason as* *

CCT, controlled clinical trial

Note: numbers are close approximates as duplicates of the same paper were deleted when identified and references located from other sources were added to the database

Prevention of atopic eczema

Given the high and rising prevalence of atopic eczema, prevention of atopic eczema has to be a desirable goal. It seems to be a far more logical one than treating sick individuals who present themselves after a long chain of pathological effects with potentially toxic and expensive medicines, which at best only ameliorate disease symptoms. Disease prevention can be considered at several levels: that of preventing allergen sensitisation at birth (which may or may not lead to atopic disease), prevention of manifest atopic eczema in childhood, the prevention of severe disease (without necessarily altering the total prevalence of disease) and the prevention of other atopic diseases such as asthma, which may follow atopic eczema.

When considering disease prevention, it is important to be clear about whether a high-risk approach (i.e. intervening with parents who have atopic disease) or a low-risk population-based approach is being used in order to try and prevent atopic eczema developing in their offspring. Although it may sound an obvious strategy to simply target children known to be at high risk of developing atopic eczema, it has been previously suggested that a high-risk approach would prevent about 31% of children from developing atopic eczema compared with about 50% if the entire population was targeted.[5] It is also important that studies that purport to prevent atopic eczema follow-up children for a long time (i.e. 4 years or more), to ensure that the programme does not just simply delay the onset of disease to a time when it

could have an even more damaging effect on the child's development.

Most prevention studies have focused on the role of allergen avoidance (mainly dietary) in early life, and these are summarised in the next sections. The authors were not able to find any RCT evidence of other forms of disease prevention such as avoidance of soaps, regular use of emollients or deliberate exposure to allergens at a critical time of thymic development during infancy to try to induce tolerance to allergens.

One small study[62] on 40 pregnant Venezuelan women with a history of atopic disease, randomised 20 mothers to an educational and nutritional programme (which was not clearly defined) and 20 to no intervention in an open fashion, and followed the offspring to evaluate the efficacy of the programme in preventing atopic disease. No cases of atopic eczema (definition based on the Hanifin and Rajka guide) were noted in the 20 intervention children aged 4 years, whereas ten out of 20 children in the non-intervention group had developed atopic eczema by this time. Similar beneficial differences were noted for bronchial hyper-reactivity and rhinitis. Randomisation was not described, and the study was unblinded.

One ambitious RCT of a cohort of 817 infants aged 1–2 years with atopic eczema, the Early Treatment of the Atopic Child (ETAC) study,[329] tested the hypothesis that long-term treatment with the non-sedating antihistamine cetirizine, at a dose of 0.25 mg/kg twice daily, could prevent the development of asthma. Although there was no overall difference in the incidence of asthma between the cetirizine and placebo intention-to-treat populations, there was a reduced risk for developing asthma in subgroups who were sensitised to grass pollen and house dust mite, who made up 20% of the study population. Data on the severity of atopic eczema in the two treatment groups have not been published to date.

Atopic eczema prevention by allergen avoidance during pregnancy

Dietary prevention

The idea of trying to prevent atopic eczema by avoiding potentially allergenic foods and other allergens such as house dust mite during pregnancy and early life is an attractive one. Parents often believe that foods are an important cause of atopic eczema and expectant mothers are often highly motivated to do what they can to prevent illness in their offspring, particularly if there is a strong family history of atopic disease.

Many questions can be asked in relation to such prevention, for example:

- Does avoidance of certain potentially allergenic foods prevent atopic eczema and if so by how much in offspring at high risk (i.e. family history of atopy) versus those at normal risk?
- Does exposing infants to allergens at an early stage of their immune system development help by making them tolerant to such substance, which they will inevitably encounter in later life?
- Does such a programme simply delay the onset of disease and does it decrease disease severity?
- Do the benefits to children outweigh the rigorous long-term measures needed to undertake such dietary exclusions?
- Does **exclusive** breastfeeding protect against atopic eczema or does **prolonged** breastfeeding protect against atopic eczema?
- Does the early introduction of solids bring on atopic eczema?

All of these questions require different studies. Most have been observational in nature. This is understandable for breastfeeding, as the decision to breastfeed is not something that can be easily subject to an RCT. The decision to breastfeed can also be inextricably linked to possible confounding factors such as social class and family history of atopy, rendering observational studies of such issues difficult to interpret. These have been reviewed by Kramer.[330]

A Cochrane systematic review[331] has evaluated three trials of maternal antigen avoidance during pregnancy for preventing atopic disease in general in infants of women at high risk of atopy.[48,52,53] Kramer's review[331] of 504 women showed that the combined evidence did not suggest a strong protective effect or maternal antigen avoidance during pregnancy on the development of atopic eczema and other allergic diseases in the first year of life of their children and some evidence that such avoidance could lead to lower birth weight. The trials also suggested a non-significant increase in pre-term birth in the intervention groups. Cord blood IgE levels were similar in both groups.

Seven RCTs[48–50,52–55] that have looked at dietary manipulation during and after pregnancy are summarised in *Table 3*. All included studies have involved children at high risk of developing atopic eczema because of atopic disease in close family members. Although some of the interventions are broadly similar, pooling is probably not justified in view of the differences in foods avoided, duration

TABLE 3 *RCTs of dietary manipulation during and after pregnancy aimed at preventing atopic eczema in offspring*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Chandra *et al.*, 1986[53] (Canada)	Dietary antigen avoidance of milk, dairy products, egg, fish, beef and peanuts throughout pregnancy and lactation vs no dietary restriction	121 women with a previous history of a child with atopic eczema	Prospective RCT with infants followed-up until age 1 year	Proportion of infants who developed atopic eczema and severity/extent of atopic eczema	Of 109 mothers who completed study, 17 out of 55 (30.9%) children born to the dietary restriction group had eczema by 1 year compared with 24/54 (44.4%) children in the control group ($p = 0.069$) Severity scores lower in intervention group	Concealment of allocation unclear Unblinded study No ITT analysis (12/121 drop-outs some of whom withdrew for undisclosed reasons)	Unclear if reported benefit was sustained after age 1 year Lack of blinding serious threat to validity of study findings More mothers in the control group formula-fed, which could explain increased eczema
Miskelly *et al.*, 1988[54] Wales	Pregnant mothers restricting their daily milk intake to half a pint during pregnancy and during lactation and addition of soya-based milk if needed vs no such restrictions	487 mothers with at least one family member suffering from atopic disease (238 intervention, 249 control)	Prospective RCT with infants followed-up until age 1 year	Atopic eczema, wheeze, nasal discharge and skin-prick tests	Eczema during first year in 41% of intervention group vs 34% in control group ($p > 0.05$) Similar for wheeze and nasal discharge	Clear description of method of randomisation and concealment in sealed envelopes Physician examining children reported to be unaware of allocation status Clear description of flow of study participants ITT analysis carried out	High-quality study that tested hypothesis that cows' milk in early life increase risk of allergic disease and found no evidence to support this Definition of atopic eczema vague
Lilja *et al.*, 1989[48] Sweden	Maternal diet low in hens' egg and cows' milk ('reduced diet') vs diet with one hen's egg and 1 l of milk in last 3 months of pregnancy	162 mothers with respiratory allergy to animal dander and/or pollens giving birth to 166 infants	Prospective randomised study with children followed-up to age 18 months of age	Proportion developing atopic diseases and positive skin-prick tests	Of 163 evaluable children, no difference in prevalence of asthma, rhinitis, urticaria or atopic eczema Proportion of obvious, probable and possible cases of atopic eczema in reduced group was 33% compared with 28% in other group	Method and concealment of allocation unclear Study assessors reported to be unaware of diet allocation No ITT analysis	Marked differences (64% vs 46%) in mothers with personal history of atopic eczema in the 'reduced' vs high dairy intake groups at baseline No definition of atopic eczema given

continued

TABLE 3 contd *RCTs of dietary manipulation during and after pregnancy aimed at preventing atopic eczema in offspring*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Zeiger & Heller, 1995,[49] 1993[51] USA	Mothers who avoided cows' milk, eggs and peanuts during last trimester of pregnancy and lactation and whose children avoided cows' milk until 1 year, egg until 2 years and fish until 3 years vs mothers and their children who followed standard feeding practices	288 children born to parents at high risk of atopic disease	Prospective randomised study with children followed-up to age 7 years	Proportion developing atopic eczema and other atopic diseases, food allergy and skin-prick tests	Of 165 children evaluable at age 7 years, no differences in atopic eczema prevalence, allergic rhinitis, asthma, serum IgE noted Period of prevalence for atopic eczema in intervention group at age 7 years (estimated from graph) = 7%, identical to control group	Concealment of allocation unclear Study patients were unblinded due to nature of intervention Investigators recording atopic eczema also probably not blinded No ITT analysis	Very large drop-out from original randomisation Bias mis-classification of outcome cannot be ruled out due to unblinding Some changes between the 2 groups that were apparent at age 2 years (food allergy and milk sensitisation) were no longer present at age 7 years Differences in eczema treatment not recorded
Falth-Magnusson & Kjellman, 1992[52] Sweden	Total abstinence of cows' milk and eggs from week 28 of pregnancy until delivery vs normal food throughout pregnancy	209 pregnant mothers from families with at least one allergic family member	Prospective randomised study with children followed-up to age 5 years	Prevalence of allergic disease including atopic eczema, skin-prick testing, and IgE	Of 209 evaluable children at age 5 years, 29% of children in the dietary group vs 24% in the control group had reported atopic eczema ($p > 0.05$) Proportion with asthma, hay fever and objective atopy very similar in both groups	Method and concealment of allocation unclear Study unblinded No ITT (hough very few drop-outs)	Similar limitation of unblinding to other studies, though similar proportion with objective atopy argues against bias by observers Atopic eczema mainly based on history with some physical examination Remarkably high follow-up rate for such a long study (95%)
Hide *et al.*, 1994,[50] 1996[55] England	Mothers during last trimester of pregnancy and during lactation excluded dairy products, egg, fish and nuts or soy-based milk plus measures to reduce house dust mite at home vs mothers whose infants were fed conventionally with no control of house dust mite	120 children identified before birth as being at high risk for atopy	Prospective randomised study with children followed-up to age 4 years	Atopic eczema (prevalence and severity), asthma, rhinitis and skin-prick tests	At age 2 years, 13.8% in the prophylactic and 24.2% in the control group had examined atopic eczema At age 4 years, this difference persists (8% and 15% with atopic eczema, respectively) No differences in eczema severity Atopy also significantly less common in intervention group	Method and concealment of allocation unclear Study participants unblinded but some attempt at blinding study assessor No ITT analysis	Promising and persistent difference in atopic eczema prevalence in intervention group Unclear if reported benefit was die to prenatal diet, feeding practices after birth or reduction in house dust mite

ITT, intention-to-treat

of avoidance after birth and whether the mother continued to avoid the foods during lactation. Some key points emerging from these five studies are as follows.

- Lack of blinding seriously threatens the validity of the studies. Even if assessors were reported to be blind to the dietary allocation, it is possible that unblinded parents revealed their allocation to assessors. Independent assessment of disease status (e.g. by using coded photographic records) is one way of reducing such a possibility.
- Disease definition is often quite vague or non-existent in these studies. Disease definition is particularly important in the first year of life to separate atopic eczema from simple irritant eczema and seborrhoeic dermatitis of infancy.
- Studies that have examined avoidance of potentially allergenic foods during pregnancy produce conflicting results with two suggesting benefit and four no benefit. The highest quality reported study[54] found no benefit.
- Methodological difficulties such as failure to comply with protocols, lack of blinding and complex interventions can probably be overcome by closer involvement with consumers and by use of more objective outcome measures.

Prevention of atopic eczema through allergen avoidance and dietary manipulation after birth

One Cochrane systematic review[331] of maternal antigen avoidance during lactation pooled three studies[53,61,332] and found some benefit on the prevention of atopic disease in offspring from maternal avoidance of allergenic foods while breastfeeding. Methodological shortcomings in all three trials (mainly loss of blinding) argue for caution in interpreting the results. RCTs that have examined the usefulness of manipulating the diet of lactating mothers and their infants after birth with a view to preventing atopic eczema[56–61,63–67] are summarised in *Table 4*. A further trial[332] has been excluded because no separate data on atopic eczema have been given. These studies share similar methodological concerns regarding disease definition and unmasking of blinding.

Other summary points are as follows.

- The Moore and colleagues[63] study illustrates the difficulty of trying to randomise mothers to breastfeed.
- There is no evidence to support the use of soya milk as opposed to cows' milk supplementation to children as a means of preventing or delaying onset of atopic eczema.
- There is some evidence to support the use of extensively hydrolysed cows' milk formulae over regular cows' milk formulae in preventing atopic eczema in high-risk families, though the extent to which these unpalatable formulations can be taken up in practice is unclear.
- There is some evidence that maternal avoidance of allergenic foods during lactation may reduce the incidence of subsequent atopic eczema and other allergic disease.
- Some studies (e.g. Chandra *et al.*,[61] Marini *et al.*,[65] and Porch *et al.*,[57]) mix up results of observational data with randomised participants in such a way as to render it difficult to make valid comparisons.
- Most of the studies refer to children born to families with atopic disease.

House dust mite

No RCTs evaluating the sole use of anti-house dust mite measures to prevent atopic eczema were identified. The study by Hide and colleagues[55] evaluated the combined effect of dietary allergen reduction and house dust mite reduction during pregnancy and after birth, but it is impossible to say from this study whether it was the diet, house dust mite reduction or both that was responsible for the observed benefit. Future studies evaluating a combination of interventions simultaneously should consider factorial designs in order to tease out which components of the intervention have been beneficial.

TABLE 4 *Studies looking at dietary manipulation of mothers or infants, diet after birth with the aim of preventing onset of atopic eczema*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Kjellman & Johansson 1979[56] Sweden	Supplementing breastfeeding with either soy or cows' milk from weaning to age 9 months	48 children whose parents both had atopic disease	Parallel study with children followed-up for 4 years	Obvious and probable atopic disease (atopic dermatitis, asthma, gastrointestinal allergy, urticaria and rhinitis)	13/25 infants in the soy group compared with 11/25 in the cows' milk group developed obvious or probable atopic dermatitis (NS) No significant differences in other allergic diseases between the two groups	Method of randomisation and concealment not specified Probably single-blind Two drop-outs with no ITT analysis	Small study, which did not provide any evidence to suggest that soy supplements had any benefit for a range of allergic diseases over cows' milk
Moore *et al.*, 1985[63] England	Breastfeeding for at least 3 months and avoidance of solids for this time with soya-based supplementation if required vs standard advice plus cows' milk formula if needed	525 mothers (250 in experimental and 275 in control group)	Prospective RCT with infants followed-up until aged 1 year	Prevalence of eczema at 3, 6 and 12 months	Because only 26% of mothers in experimental and control groups exclusively breast-fed their infants, results were not analysed as a randomised study but as an observational one	Method of randomisation and concealment of allocation unclear Person recording skin lesions reported to be unaware of feeding group No ITT analysis	An ambitious large study that illustrates the difficulty in randomising mothers to breastfeed
Chandra *et al.*,[67] 1989a Canada	Four different infant feeding formulae: hydrolysate cows' milk formula vs soy-based formula vs conventional cows' milk vs exclusive breastfeeding for 4 months or more	288 'high-risk' infants with family history of atopic disease among first-degree relatives. 72 children in each of the four intervention groups	Prospective RCT with infants followed up for 6 months	Atopic eczema development, eczema severity, wheezing illness, nasal discharge	Of 263 evaluable children, 7.4% in the hydrolysate group, 29.9% in the conventional milk group, 27.9% in the soya group and 18.3% in the exclusive breast-fed group had atopic eczema (not tested for statistical significance in paper) Eczema severity score did not differ between all four groups Incidence of any disease of allergic atopic eczematiology was lowest in hydrolysate group ($p < 0.005$)	No details on randomisation procedure or concealment thereafter Two examining physicians reported to be blind to formula status of child No ITT analysis	Unclear if all four groups were randomised and at what point Description I methods suggest that the exclusive breast-fed group were not randomised at all Atopic eczema notoriously difficult to separate from seborrhoeic eczema at up to age 6 months

continued

TABLE 4 contd *Studies looking at dietary manipulation of mothers or infants, diet after birth with the aim of preventing onset of atopic eczema*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Chandra *et al.*, 1989b[61] Canada	Two studies: i) mothers who planned to breastfeed allocated to either diet restricted (milk, dairy products, eggs, fish, peanuts and soybeans) or normal diet while breastfeeding ii) mothers who did not plan to breastfeed allocated to one of three formula feeds (hydrolysate, soy milk or conventional cows' milk)	97 mothers who chose to breastfeed and 124 who did not	Prospective RCT with infants followed-up for 18 months	Development of atopic eczema and eczema severity	Eczema less common and milder in severity in babies who were breast-fed and whose mothers were on a restricted diet (11/49 (22%) vs 21/48 (48%)) In infants fed hydrolysate, soy or cows' milk, 9/43 (21%), 26/41 (63%) and 28/40 (70%), respectively developed eczema	Method of concealment of allocation unclear No blinding of eczema in breast-fed groups Blinding of observers reported for formula-fed babies No ITT analysis	Unclear if blinding of assessors was successful Vague definition of atopic eczema, which could easily be confused with seborrhoeic eczema of infancy Several exclusion from each group after randomisation
Lucas *et al.*, 1990[60] England	Two trials: i) evaluated donor milk vs preterm formula as sole diet or (separately randomised) as a supplement to mother's expressed milk ii) infants allocated term vs preterm formula	777 preterm infants (birth weight < 1850 g) born to parents at no increased of atopic disease	Prospective RCT with infants followed-up for 18 months after term	Development of eczema, asthma or wheezing, and allergic food reactions	No difference in the incidence of allergic disease between dietary groups in either trial at 18 months after term In subgroup with a family history of atopy, early exposure to cows' milk increased risk of developing eczema (odds ratio 3.6 in those with a family history vs 0.7 in those without; $p < 0.05$)	Randomisation and concealment described Observers reported to be blind to infants' initial diet ITT analysis	Large study with high-quality reporting Description of atopic eczema based on 'characteristic distribution' unclear Finding of increased risk in atopic families *post hoc* and needs testing in other studies Validity of results to non-preterm infants unclear
Mallett & Henocq, 1992[59] France	Infants assigned to hydrolysate formula vs adapted cows' milk formula Both interventions were either alone or with breastfeeding for 4 months	177 infants (92 in hydrolysate group and 85 in adapted formula group) selected from a birth cohort whose immediate family had a history of allergic disease confirmed by medical records	Prospective RCT with infants followed-up for until aged 4 years	Atopic eczema occurrence and severity, asthma, food intolerance and objective tests of atopy (total IgE)	Eczema significantly more common at 4 months, age 2 and age 4 years At age years, 7.1% (5/70) of children had eczema in the hydrolysate group compared with 25.9% in the cows' milk group ($p < 0.001$) No evidence of protective effect of hydrolysate for asthma	No details on randomisation procedure or concealment thereafter No mention of blinding in study No ITT analysis with a 30% drop-out rate at age 4 years	Unblinded study No definition of eczema given Despite randomisation, 58% in hydrolysate group vs 33% in cows' milk group chose to breastfeed, which could confound results

continued

TABLE 4 contd *Studies looking at dietary manipulation of mothers or infants, diet after birth with the aim of preventing onset of atopic eczema*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Vandenplas *et al.*, 1995[66] Belgium	Assignment to partial whey-hydrolysate formula vs regular cows' milk during first 6 months of life	75 infants with atopic disease in at least two first-degree relatives and whose mothers chose not to breastfeed	Prospective RCT with infants followed-up for until aged 5 years	Cows' milk protein sensitivity, atopic eczema prevalence and severity, allergic rhinitis and asthma	Of 58 evaluable children at age 5 years, 7/28 children on whey had developed eczema vs 8/30 on cows' milk (NS) No difference in eczema severity Cumulative atopic disease of any type was 29% vs 60% in the whey vs cows' milk group	No details on randomisation procedure or concealment thereafter Some attempt at blinding of mothers and observers No ITT analysis with a 23% drop-out rate at age 5 years	No description of atopic eczema definition Due to the obvious taste difference to hydrolysate, unblinding highly likely
Marini *et al.*, 1996[65] Italy	Hydrolysed milk formula vs conventional cows' milk formula	Children born to mothers with high atopic risk participating in an allergen avoidance programme (n = 279) whose mothers had insufficient breast milk These mothers randomised to breastfeeding plus hydrolysate (n = 32) and breast plus cows' milk (n = 28)	Prospective RCT with infants followed-up for until aged 3 years	Atopic eczema, recurrent wheeze, rhinitis, urticaria and gut symptoms	Unclear which results refer to the randomised groups Of the 25 evaluable children on hydrolysate plus breast milk, three (12%) had eczema at 3 years vs 3/22 (13.6%) evaluable children in the breastfeeding plus cows' milk group (NS)	Randomisation procedure or concealment thereafter unclear Mothers unblinded; physicians reported to be unaware of dietary allocation No ITT analysis with a 22% drop-out rate at age 3 years	Small underpowered randomised study occurring within a large case control study Very difficult to relate results to original randomisation schedule as so many groups from the observational part of the study mixed together
Odelram *et al.*, 1996[64] Finland and Sweden	Hydrolysed cows' milk formula vs ordinary cows' milk formula	82 infants with at least two atopic family members or one atopic parent whose mothers exclusively breast-fed for 9 months Lactating mothers and their infants also avoided milk egg and fish until 12 months	Prospective RCT with infants followed-up for until aged 18 months	Atopic eczema occurrence, asthma, rhinitis and food allergy Also skin-prick tests and IgE analysis	Of the 82 randomised infants, 11 mothers chose to continue exclusive breastfeeding and these joined nine other children to form a non-randomised comparison group of 20 children Data for atopic eczema in the remaining 32 children randomised to hydrolysate and 39 to ordinary cows' formula, were not given, but reported as not statistically significant	Method of randomisation described Study not blinded No ITT analysis	Small study where there is loss of originally randomised groups due to mothers' preferences Authors point out the difficulties in randomising such a group and conclude that "we can spare high atopy-risk families this (hydrolysate) extra burden"

continued

TABLE 4 contd *Studies looking at dietary manipulation of mothers or infants, diet after birth with the aim of preventing onset of atopic eczema*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Oldaeus *et al.*, 1997[58] Sweden	Extensively hydrolysed vs partially hydrolysed vs regular cows' milk formula in infants at weaning stage	155 infants with a family history of allergy who avoided cows' milk for first 9 months and no eggs or fish until 12 months Breastfeeding mothers avoided same foods	Prospective RCT with infants followed-up for until aged 18 months	Cumulative prevalence of asthma, atopic eczema and rhinitis and IgE antibodies	In the 55 children randomised to extensively hydrolysed formula, 17% had developed eczema by 18 months vs 44% of the 51 children in the partially hydrolysed group and 41% of 49 children in the regular cows' milk group	Randomisation procedure or concealment thereafter unclear Mothers unblinded to cows' milk formula but some attempt at blinding between hydrolysate formulae Physicians reported to be unaware of formula No ITT analysis	Atopic eczema definition unclear Degree of success of blinding unclear
Porch *et al.*, 1998[57] USA	Three different infant feeding formulae: extensively hydrolysed casein formula, partially hydrolysed whey formula and soy formula	181 infants recruited before birth if one or both parents had a history of allergy Only those infants whose mothers decided not to breastfeed were randomly assigned to one of three feeding groups	Prospective, randomised, double-blind parallel study of 12 months duration Observational group of infants who were breast-fed	Development of atopic dermatitis in infants based on examination by a paediatrician nurse and/or physician, chronic or recurrent vomiting and diarrhoea in first year of life persisting longer than 3 weeks or recurring over 2 months or more	Of the 130 infants who completed the 1-year study, two out of 40 (5%) on soy formula, five out of 42 (12%) on partially hydrolysed whey formula and three out of 31 (10%) on the extensively hydrolysed formula developed atopic dermatitis by 1 year These differences were not statistically different Symptoms of food intolerance were similar in all groups	Clear description of method of randomisation and blinding: parents, hospital staff, physicians and investigators reported to be unaware of allocation status No ITT analysis carried out	Another study evaluating quite a select group of motivated parents with atopic disease who chose not to breastfeed their infants No statistical differences in atopic dermatitis were noted across the three randomised feeding groups, and the rate of atopic dermatitis (12%) was similar in the non-randomised breastfed group

NS, not significant

Chapter 4

Topical corticosteroids

Topical corticosteroids have been one of the cornerstones of treatment of atopic eczema for almost 40 years. Hydrocortisone was first developed in 1952 and improved various eczematous dermatoses when applied topically.[333] Since then, another 30 or so compounds have been developed, each in different formulations such as creams, oily creams or ointments, and often in combination with other ingredients such as antibiotics. They vary in strength (as measured by ability to constrict blood vessels rather than clinical anti-inflammatory or skin thinning effect) from very mild (e.g. hydrocortisone), to very strong fluorinated products (e.g. clobetasone propionate). Systemic adverse effects are rare and include suppression of the pituitary–adrenal axis and Cushing's syndrome. Local adverse effects include spread of untreated fungal infection, irreversible striae (stretch marks) and prominent fine blood vessels, contact dermatitis, perioral dermatitis and worsening of acne and mild loss of pigmentation. The adverse effect that undoubtedly causes the most concern is that of skin thinning.[334]

We located 83 RCTs on the use of topical steroids in atopic eczema.[68–150] Sixty-five other RCTs on use of topical steroids, summarised in appendix 2, had to be excluded as they did not give a sufficiently clear description of the patients, or the results of patients with atopic eczema and other inflammatory dermatoses were mixed up together. Due to the large number of studies, the 83 included RCTs are summarised in appendix 3 and separated into groups according to the sort of questions they address (though some RCTs straddle more than these categories). These groups will be commented on in turn. Some quantitative pooling of data was attempted for the question of once- versus twice-daily corticosteroid usage in view of the importance of this question to the NHS and patients.

Topical corticosteroids versus placebo

Quality of reporting of studies in the 1960s to 1980s was generally poor, and methodological details scant. Studies that only report patient preference data give us little idea of the magnitude of the benefit. Those studies that do report magnitude of benefit suggest a large treatment effect. We could not find one RCT comparing betamethasone 17-valerate and placebo, which is worrying as this is used as the 'standard' comparator for most new topical corticosteroids developed subsequently. Nearly all studies were less than 1 months' duration.

Topical corticosteroids versus other topical corticosteroids

This group of RCTs represents the largest in this section ($n = 40$). Most trials are again of poor quality, and have tended to mix atopic eczema patients with a whole range of other patients. In these studies, responses to the same topical corticosteroids for different conditions are in many cases quite different, though it is unclear how many of these observations are due to different sample sizes in the different groups. It is difficult to make any summary statement on this group of trials as there are no trials that compare all of the contenders for the most effective and safest topical corticosteroid together. Thus drug A has been compared with drug C, drug C against drug D, drug D against drug A, Drug B against drug C, but never all together. It is difficult therefore to make any ranking conclusions. Some batches of RCTs introducing a 'new' topical corticosteroid are oddly country-specific despite being marketed by international companies. Many of the RCTs introducing a 'me too' product claim equivalence against a standard preparation, erroneously making the assumption that no evidence of statistical difference is the same as evidence of equivalence.

Two newer topical corticosteroids (fluticasone propionate and mometasone furoate) have been introduced in the UK over the past 10 years and claim to have less systemic absorption and an efficacy profile that permits them to be used once as opposed to twice daily.[335] The RCTs that have compared these two substances have invariably compared the 'new' agents against twice-daily older agents and demonstrated reasonable equivalence. They have subsequently and rightly been marketed as 'once-daily'

treatments for atopic eczema, possibly giving the impression that once-daily application of other topical corticosteroids is not as effective as twice daily. The RCTs evaluating these newer agents have been careful therefore to only include a once-daily comparison of their product against a twice-daily comparator. This has occasionally introduced problems with patient masking. The absence of a once-daily comparator (e.g. beta-methasone 17-valerate) is thus a pity in these RCTs as it is possible that most of the 'older' established topical steroids can also be used once daily. This point becomes important when one considers that the cost of 100 g of cream is £3.95, £14.05 and £13.90 for beta-methasone, mometasone and fluticasone creams, respectively.

Topical corticosteroids versus other topical preparations

Only four RCTs are described in detail in this section, but probably many more described in other result sections could have been included as topical betamethasone and hydrocortisone are used as standard comparators. It is difficult to evaluate treatment efficacy in those studies without a placebo arm (e.g. the tar versus hydrocortisone study). There is one useful and well-described study, which does not provide any evidence of benefit of *hamamelis* above placebo, whereas some benefit for hydrocortisone was present. Blinding can be a problem for other topicals such as tar.

Topical corticosteroids plus additional active agents

Several RCTs have evaluated the possible benefit of adding in various antimicrobial/antiseptics to topical corticosteroids. Despite their widespread use, we located only one RCT comparing plain betamethasone 17-valerate against a combination of betamethasone 17-valerate plus fusidic acid,[111] which provided no evidence of improved efficacy of the combination product in patients with infected atopic eczema. Similarly, we found only one RCT that compared 1% hydrocortisone with fusidic acid against 1% hydrocortisone alone.[128] That study did not find any evidence to support a benefit of the combination product above plain hydrocortisone in patients with moderately severe atopic eczema. Another study[90] failed to demonstrate any additional benefit of adding in gentamicin to betamethasone.

Different formulations of the same topical corticosteroids

Two points are worthy of note in this section. The first is that there is some evidence that composition of vehicle can affect efficacy,[130] though long-term studies are needed to see whether these benefits are at the expense of adverse effects. The second point is that cosmetic preference may be very important even when equivalence is suggested in a comparison of two different formulations of the same preparation,[144] though this is not consistent between studies even in the same countries.[143]

Once-daily versus more frequent use of the same topical corticosteroids

Several trials have investigated whether single daily topical application of corticosteroid is as effective as more frequent applications. The question being addressed is important from several perspectives:

- the patient's perspective because this would make therapy much less burdensome and potentially safer because of the reduced risk of adverse effects of corticosteroid, and
- the NHS perspective because of reduced cost of therapy.

Results

Unfortunately few trials met our inclusion criteria and of the three that did, the methods of assessment were disparate. The response rate, defined as the proportion of patients who obtained at least a good response with treatment, allowed us to assess comparative efficacy. However, because of the disparate study designs, the estimates from the individual trials were not pooled.

Table 5 is a contingency table of the data from the three eligible trials. The estimated differences in response rates with once-daily versus more frequent applications, are also shown in *Table 5* and *Figure 3*. It is clear that in none of the studies were more frequent applications superior to once-daily application. While the point estimates suggest that a small difference in favour of more frequent applications cannot be excluded, it is doubtful whether this is practically meaningful. This was also the conclusion of a recent review that considered this question in relation to all inflammatory dermatoses.[336]

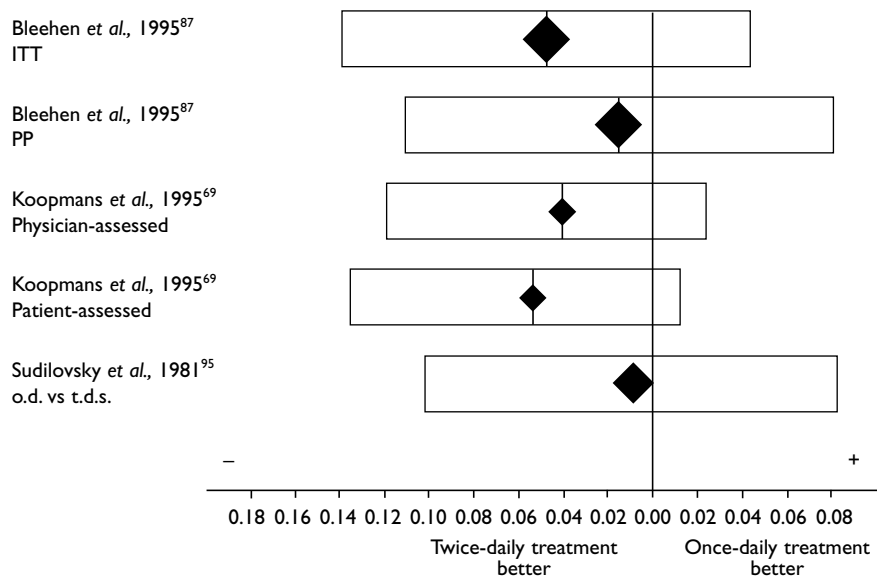
Koopmans and colleagues[69] concluded that the proportion of patients who were cleared of eczema in the twice-daily group was higher than that in the

TABLE 5 *Estimate of difference in response rate for topical corticosteroids*

Study and analysis	Stratum	Contingency table				Risk difference	95% CI (near exact)
		a	b	c	d		
Bleehen *et al.*, 1995[87] ITT	1	110	113	27	20	–0.047	–0.138 to 0.045
Bleehen *et al.*, 1995[87] PP	2	108	110	29	27	–0.015	–0.111 to 0.082
Koopmans *et al.*, 1995[69*]	3	71	74	4	1	–0.040‡	–0.118 to 0.025‡
Koopmans *et al.*, 1995[69†]	4	70	74	5	1	–0.053§	–0.136 to 0.013§
Sudilovsky *et al.*, 1981[95] o.d. vs t.d.s.	5	99	100	17	16	–0.009	–0.101 to 0.084

a = number who obtained at least a good response in the once-daily group; b = number who obtained at least a good response with more frequent application; c = number who did not obtain at least a good response in the once-daily group; d = number who did not obtain at least a good response in the more frequent application group
** ITT; † PP (per protocol); ‡ Physician-assessed; § Patient-assessed*

FIGURE 3 *Estimated risk difference for topical steroids*



once-daily group. Re-analysis of their data shows that this is the case, using doctors' assessment of clearance (rate difference –0.21; 95% confidence interval (CI) –0.36 to –0.06) but not the patients' assessments (rate difference 0.13; 95% CI –0.28 to 0.02). While the results of their trial do not exclude the possibility that Koopman and colleagues' claim may be true, theirs was the only trial that reported results in sufficient detail to test their claim.

Prevention of relapse using topical corticosteroids

One RCT has broken new ground by trying to evaluate the usefulness of topical corticosteroids in preventing relapse rather than the usual trend of just trying to demonstrate short-term efficacy. The study's methodological deficiencies and missing data discussed elsewhere[337] made it difficult to say whether prevention of relapse was due to application of steroids to previously healed sites or due to application to 'new' areas, in which case, the study has become a straightforward vehicle-controlled comparison. The study did however suggest a benefit of using intermittent topical corticosteroid to prevent relapse. Generalising from the 37.5% subsample of original study participants is also problematic. Nevertheless, this is one of the first studies to look at long-term outcomes of this chronic disease in a pragmatic way. The study also provided useful detailed data suggesting that topical corticosteroids do not produce any skin thinning when used in short bursts over a long period.

Trials that have specifically examined adverse effects of topical corticosteroids

RCTs are not the best studies to evaluate adverse effects. A more detailed search for other surveillance and case-control data is needed, which is beyond the scope of this review. Those RCTs that have specifically gathered data on skin thinning and suppression of the pituitary–adrenal axis have failed to find any evidence of harm, though these studies are very short term. The study on prevention of relapse[104] also found no evidence of skin thinning after 4 months, intermittent use of a potent topical corticosteroid. Four other RCT studies of topical corticosteroid use in healthy volunteers reviewed elsewhere[334] show skin thinning at 6 weeks, which reversed within 4 weeks of stopping. While there are undoubtedly occasional horror stories of individuals developing Cushing's syndrome, permanent skin thinning and striae after long-term use of potent topical corticosteroids in large areas, there is no evidence to suggest that they are a problem for typical clinical use characterised by bursts of 1–2 weeks' treatment followed by 'holiday' periods with emollients only. Nevertheless, steroid 'phobia' is now firmly established in the UK among both patients and doctors.[29]

Trials that evaluated oral steroids

Large treatment effects are observed in studies that compare systemic steroids versus placebo in terms of short-term disease response. We could not identify any longer-term studies evaluating the usefulness of oral prednisolone (continuous or intermittent) against other systemic agents such as cyclosporin in the treatment of severe atopic eczema.

Additional unanswered questions

Dilution of topical corticosteroids

This is widely practised in the UK on the basis that dilution might reduce adverse effects but maintain the same degree of efficacy.[338] We could find no RCT evidence to demonstrate this in patients with atopic eczema. The largest manufacturer of topical corticosteroids does not recommend dilution as there is a wide range of preparations currently available covering a wide range of potencies (Glaxo Wellcome, personal written communication, May 1998). Nevertheless, such a practice occurs with sufficient frequency to stimulate companies such as Glaxo Wellcome to provide ready diluted preparations such as Betnovate RD™ 1:4 ointment of known stability, purity and compatibility. The possibility of compromising on stability, compatibility and microbiological purity following extemporaneous dilution of topical corticosteroids seems unnecessary with the current range of products of different strength.[339–341] It is recognised that widespread use of diluted topical corticosteroids reflects a perceived increased safety margin compared with undiluted products by prescribers and their patients, though such a belief may be a false reassurance unless there are clear data to say otherwise. Use of diluted products by prescribers may also indicate the need for a wider range of products towards the less potent end of the spectrum, particularly for the very young.

What is the most effective and safest way of using topical corticosteroids?

Atopic eczema is most commonly a condition that comes and goes, and constant use of topical corticosteroids is unnecessary and indeed undesirable in view of long-term local and systemic adverse effects. Thus, most practitioners probably use topical corticosteroids in short bursts followed by 'holiday' periods of emollients only.[342] Others may start with a potent preparation and then decrease to a lower potency preparation as the condition improves (the step-down approach). We could find no RCT evidence to throw light on these important issues. A pragmatic RCT set up to compare short bursts of a potent steroid versus longer-term use of a weak preparation is currently being conducted in Nottingham with support from Trent Regional R&D.

Summary of topical corticosteroids

- RCTs of topical corticosteroids versus placebo are few, but suggest a large treatment effect.
- It is difficult to make recommendations about the 'best' topical corticosteroid as most trials have only compared one against another one, but seldom against the same one and never all together.
- The market is currently saturated with many different strengths and formulations of topical corticosteroids.
- Many older studies confuse absence of statistical evidence of superiority of one compound over another with evidence supporting therapeutic equivalence.
- Three RCTs have compared antibiotic/topical corticosteroid combinations versus corticosteroids alone in infected and non-infected atopic eczema.

- None have demonstrated superior clinical efficacy of the combination antibiotic/corticosteroid above corticosteroid alone despite their frequent use in clinical practice.
- There is some evidence to suggest that the type of vehicle used for a topical corticosteroid may enhance its efficacy.
- Patient preference on the basis of cosmetic acceptability may be important for long-term use even when equivalent effects are demonstrated between two treatments.
- There is no clear RCT evidence to support the use of twice-daily over once-daily topical corticosteroid administration.
- Based on this evidence, it would be justifiable to use once-daily corticosteroids as a first step in all patients with atopic eczema.
- Such a policy could halve the drug bill for topical corticosteroids overnight, and possibly increase compliance and reduce adverse effects, though changing well-engrained practice may be challenging.
- There is need for a cost-effectiveness study comparing betamethasone 17-valerate once daily with once-daily mometasone furoate and fluticasone propionate ointments.
- There is no RCT evidence to suggest that skin thinning is a problem for correct use of topical corticosteroids, though other non-RCT evidence should be considered before making firm conclusions.
- No RCTs have compared oral steroids with other systemic agents in patients with severe atopic eczema.
- There is no RCT evidence to support the notion that diluting topical corticosteroids reduces adverse effects while maintaining efficacy in people with atopic eczema.
- There are some concerns that extemporaneous dilution of topical corticosteroids could affect stability, compatibility and microbiological purity.
- Such a practice, although firmly established with some practitioners, seems unnecessary given the wide range of different preparations of different potencies currently available.
- We could find no RCT evidence to support different approaches to using topical corticosteroids such as comparing shorter bursts of strong preparations versus longer-term treatment with weaker preparations.
- A pragmatic RCT is currently underway by this research team which addresses this last question.

Chapter 5

Other topical agents

Topical coal tar

Although less commonly used today in Northern Europe, coal tar was used to treat chronic atopic eczema for many decades. We have located one RCT conducted by Niordson and Stahl,[151] which compared one type of coal tar preparation (Clinitar™, CHS, UK) versus conventional 1% crude coal tar in the same cream, in 27 patients (mainly children) with atopic eczema in a right/left comparison study of 4 weeks' duration. As the preparations were designed to be cosmetically different, only investigator blinding was possible. The title of the RCT is 'Treatment of Psoriasis…', which is clearly a misprint as the entire article refers to atopic eczema.

Benefits

Of the 23 evaluable patients after 4 weeks, infiltration, redness, skin thickening, scratch marks and dryness reduced by about 50% in both treatment groups. None of the differences were statistically significant. No statistically significant differences in parents preference for treatment was found. There was a statistically significant ($p < 0.001$) preference by patients or their parents for Clinitar cream compared with the crude coal tar cream, however, at the end of the study.

Harms

Four patients complained of stinging and itching, one on the site treated with Clinitar cream, two with coal tar cream and one with both. All were shown with patch testing to be an allergic reaction.

Comment

Although coal tar has been used for many years in atopic eczema, it is a pity not to discover any RCTs demonstrating its efficacy compared with vehicle alone. It is difficult to say from this study comparing two different preparations of coal tar whether both were vehicle effects or whether two active treatments were being compared. Both treatment groups improved equally during the study. Although cosmetic acceptability was higher for the Clinitar group, this was an unblinded assessment in patients who might have been eager to please the investigators. Method of randomisation was not described and no intention-to-treat analysis was performed. Further RCTs should compare the most cosmetically acceptable form of coal tar treatment versus vehicle alone and versus other common topical treatments such as topical steroids. There is a theoretical risk that tar is a possible carcinogen based on observational studies of occupational groups working with tar components.

Emollients

Skin dryness is a very common feature of atopic eczema, so much so that it is a diagnostic criterion.[3] Skin dryness can lead to inflammation, and vice versa, and which event occurs first has been debated over the years.[343] There is considerable biochemical evidence to suggest that there are specific abnormalities in skin lipids (ceramides) of atopic eczema skin. A dry skin is less supple than normal skin, and this can lead to painful cracks, particularly overlying joints. Another consequence of the atopic dry skin is impaired barrier function, both in terms of keeping undesirable things out (such as bacteria) and retaining useful things, such as water. *Staphylococcus aureus*, a common secondary pathogen in atopic eczema, is also known to exhibit enhanced adherence to the dry surface skin cells in atopic eczema.

Few would dispute that a dry skin is an important feature of atopic eczema, but the rationale for reversing this dryness with moisturisers (emollients) is less clear. One rationale is simply to relieve the feeling and appearance of 'dryness', which many eczema sufferers choose to do. Another rationale is that emollients may have a soothing effect on itching and soreness. Emollients are often purported to have a topical steroid-sparing effect. Another question to pose is whether emollients have any low grade anti-inflammatory activity without the use of additional topical steroids. Some have even advocated a form of 'total emollient therapy' for children with atopic eczema.[344] It is possible that emollients might play a role in decreasing the incidence and severity of secondary infections. It is also possible that emollients may prevent allergen sensitisation if used from a very young age in high-risk infants, or the opposite is possible (i.e. enhanced allergen penetration because of alteration of the skin barrier fat solubility characteristics). It is also possible that regular emollient use may reduce relapses.

There are thus many questions that need to be answered by RCTs in terms of the use of emollients. Emollients are almost universally recommended as first-line therapy for atopic eczema treatment in the UK.[25] Currently there are at least 30 different types of emollients listed in the *British National Formulary*, and this excludes different formulations (e.g. lotion, cream or ointment). A further group of ten bath additives are also available.[34] Emollients mainly act by either occluding water loss from the outer layers of the skin (e.g. white soft paraffin), by improving water binding of the skin (e.g. urea) or by directly adding water to the dry outer layers of the skin (e.g. aqueous cream).

Some are used as bath additives, and most are applied directly to the skin. It is often recommended to apply emollients after a bath so that water is retained in the skin. Some have advocated using emollients under damp cotton bandages at night in the 'wet-wrap' technique.

Despite our rigorous searching efforts, only five published RCTs[152,154–157] could be included in this section. Many other possible trials were excluded because they were not randomised (or randomisation was unclear), many included a range of skin conditions with no separate results for atopic eczema (e.g. Newbold[345]), and some (e.g. Pigatto *et al.*[153]) did not present any actual clinical data but instead concentrated on a host of biometric measurements, the clinical significance of which was unclear. The use of emollients with added antiseptics is discussed elsewhere in chapter 9 (*Non-pharmacological treatments*), where it was concluded that the addition of antiseptics did not show any benefit.

Benefits

The Kantor and colleagues study[154] compared the use of an oil-in-water emollient (Moisturel™, not available in the UK) versus a water-in-oil emollient (Eucerin™, Beiersdorf, UK) in 50 patients of all ages with symmetrical atopic eczema using a left/right comparison design for a period of 3 weeks. The study was split into two RCTs, which compared the two preparations in either a cream (Study 1) or lotion (Study 2). Test limbs affected by atopic eczema were treated once daily with the designated emollients and once daily with 2.5% hydrocortisone cream, and were assessed by an independent physician for redness, scaling/crusting, itching, burning/stinging and a global eczema severity on a scale of 0–3. Global severity reduced from 1.28 to 1.00 and 1.92 to 0.96 in the Eucerin and Moisturel cream groups. respectively ($n = 25$) and from 1.91 to 0.68 and 1.91 to 0.91 in the Eucerin and Moisturel lotion groups, respectively ($n = 22$). Although differences from baseline were statistically significant, there were no significant differences between the two emollients.

The Hanifin and colleagues study[156] compared the effects of adding an emollient called Cetaphil™ (manufactured by the study sponsor) applied three times daily to twice-daily application of 0.05% desonide lotion (a topical steroid) versus twice-daily topical desonide alone in 80 patients with atopic eczema for a 3-week period. The study was investigator-blinded only. Efficacy variables included seven symptoms and signs measured on a scale of 0–9, with a maximum score of 63. Global assessment by investigators was also recorded. At the end of 3 weeks, there was a 70% and 80% relative reduction in total score from a baseline of 24.23 and 24.13 for the desonide alone compared with the desonide/moisturiser side, respectively ($p < 0.01$). The sides treated by desonide alone showed complete clearing according to physician global evaluation in about 10% of people compared with 11% in the side treated with combination (data estimated from graph).

The Wilhelm and colleagues[157] and Andersson and colleagues[155] studies both evaluated the benefit of emollients containing urea preparations – a substance intended to improve water-binding capacity of the outer layer of skin. In the Wilhelm study, 80 patients with subacute atopic eczema and associated dry skin were randomised to apply a topical formulation containing 10% urea (manufactured by the study sponsors) versus the vehicle base as 'placebo' in a right/left forearm comparison for 4 weeks. Skin redness was improved in 70% of patients at the site of the 10% urea preparation compared with 30% on the vehicle site. Similar differences were noted for induration, but not for summary score. Measurement of outer skin moisture using a capacitance meter showed statistically increased hydration in the 10% urea group when compared with vehicle alone.

The Andersson and colleagues study[155] compared a 'new' cream containing 5% urea as the active substance with an established licensed cream containing 4% urea and 4% sodium chloride in a parallel double-blind study of 48 adults with atopic eczema in Sweden. Patients were asked to apply the creams at least once daily for 30 days to dry, eczematous areas. Clinical disease severity measured by a physician on scale with a maximum score of 1600, showed a significant benefit for both creams, but with no statistical differences between the preparations. Actual data were not given and

data were difficult to read from the figure as most data points were scrunched up towards the lower range of the large scale. Patient evaluation on a visual analogue scale (maximum of 14 meaning 'no dry skin') changed from 7.5 at baseline to 10 at Day 31 for those on the 'new' cream compared with a change from 7 at baseline to 9 at the end of treat-ment for the established cream (estimated from graph). There was no statistical difference between the two groups in terms of biometric measure-ments of water content or water loss through the outer layer of the skin.

Ammonium lactate is another substance thought to improve the water-binding capacity of the outer layer of the skin. This was the subject of Larregue and colleagues' study,[153] comparing 6% ammonium lactate with its cream base only, in 46 children aged 6 months to 12 years with atopic dermatitis. The study was a within-person comparison of two symmetrical sites on patients recruited from France and Italy. Outcome measure included pruritus, and clinical objective measures included redness, dryness (xerosis), desquamation, lichenification, hyperkeratosis, and presence of papules. These were graded on a scale of 0–3. Intensity items were only partially reported in the results section, and suggested a reduction in lichenification, hyper-keratosis and dryness in both groups but slightly more in the ammonium lactate group. This was reported to be statistically significant at Day 15 for lichenification and for erythema at Day 30 (the final evaluation point of the study). Tolerance, as evaluated by the patients, was very similar in both groups. Results for itching symptoms were not given.

Harms

No adverse effects were reported in the first two studies with the exception of one patient in the Kantor and colleagues study[154] experiencing a burning sensation when the oil-in-water emollient was applied. In the Hanifin and colleagues study,[156] 14% of the patients reported stinging or burning on the side treated with desonide compared with 12% on the side treated with a combination at week 1. Most patients (96% versus 4%) preferred the combination treatment. Transient burning was noticed in four and five patients when treated with urea and vehicle creams, respectively in the Wilhelm and Scholermann study.[157] No adverse effects were described in the Andersson and colleagues study.[155] Other adverse effects of emollients include an occlusion folliculitis on hair-bearing skin and accidents from slipping while climbing into the bath due to the use of emollient bath additives.

Comment

The first two studies were of extremely short duration and quality of reporting was generally poor with little description of randomisation method, limited blinding and no intention-to-treat analysis. The Kantor study failed to show any benefit of one emollient preparation over another (in the presence of a moderate potency topical steroid), and the Hanifin study suggested that regular use of an emollient with a topical steroid may result in a small increase in treatment response compared with a topical steroid alone. Very few physicians prescribe a course of topical steroids without an emollient, but it was good to see some RCT evidence that such a policy is justified. Neither study was designed to show a steroid-sparing effect for emollients.

The two studies on urea preparations showed a possible benefit of a urea-containing preparation compared with vehicle, and the other (which compared two preparations both containing urea in different concentrations) failed to show any benefit of a new preparation containing the higher concentration of urea. Quality of reporting on randomisation, blinding and intention-to-treat analysis was poor in both studies. Similar findings were present in the Larregue lactate study.

It is extremely disappointing, particularly in relation to the questions posed at the beginning of this section, to see a virtual absence of clinically useful RCT data on the use of emollients in atopic eczema. Many studies have been performed with emollients, but these have concentrated on 'objective' measurements such as transepidermal water loss and surface profilimetry. Despite their scientific ring, such measurements are often highly variable in terms of measurement reliability and more importantly, their clinical significance to a child with chronic atopic eczema is often completely unclear. In addition to measuring efficacy of emollients in treating mild atopic eczema lesions or the dry skin associated with atopic eczema, it is essential that future RCTs of emollients measure long-term tolerability, patient preferences and cosmetic acceptability as these are probably key determinants for successful long-term use.

The history of emollient use in atopic eczema is a good example of the inverse research law in dermatology, whereby the quality and quantity of evidence is inversely proportional to their frequency of use.[346] Emollients have become consecrated through usage and are firmly implanted in the treatment regimens of most

European healthcare practitioners. Although emollients many have many beneficial actions,[347] there is an urgent need to answer several basic questions about their use, preferably through industry-independent RCTs. Although other clinical and laboratory studies may continue to shed some light on the use of emollients in atopic eczema, RCTs are needed to address the unanswered clinical questions of most relevance to eczema sufferers and their carers. The top ten questions that need answering through RCTs with regard to use of emollients are as follows.

- Do some emollients have a useful therapeutic effect (with or without wet-wraps) for treating minor flares of atopic eczema when compared with other emollients or very mild topical steroids?
- Are some emollients effective in reducing itch and soreness associated with dry skin in atopic eczema compared with no emollients or other emollients?
- Do emollients have a topical steroid-sparing effect without loss of efficacy in the long-term management of atopic eczema?
- Does the regular use of emollients in between eczema flares treated by topical steroids help to reduce relapse rates?
- Does the use of emollients in children born to atopic parents reduce the incidence of allergen sensitisation and subsequent clinical disease?
- Does the regular use of emollients prevent painful cracks (fissures) on the hands of atopic eczema sufferers?
- Which emollients do children and adults prefer at different sites of their body?
- Does the pouring of an expensive emollient into a bath provide any additional benefit to having an ordinary bath and then applying an emollient directly to the skin afterwards?
- Does the use of regular emollients reduce the incidence and severity of secondary infection in atopic eczema?
- How common is clinically relevant sensitisation to emollient constituents such as lanolin?

It might be argued that because clinical opinion on the use of emollients is so deeply engrained that the position of clinical equipoise[348] for testing emollients passed some 20 years ago. On the other hand, patients and the NHS spend a vast amount on emollients and trials would be justified on the basis of potential economic savings alone. It is understandable that it is not in the interests of the pharmaceutical industry to invest much into RCTs of the comparative efficacy of established emollients.

Lithium succinate ointment

Based on observation for the possible benefit for lithium succinate ointment for the treatment of seborrhoeic dermatitis, Anstey and Wilkinson[158] conducted a small RCT of 8% lithium succinate versus inactive placebo ointment in a right/left comparison of flexural arm eczema for 2 weeks.

Benefits

Fourteen patients (mean age 16 years) with mild-to-moderate atopic eczema and symmetrical lesions were enrolled and three dropped out. One developed redness on both arms and subsequent patch testing confirmed a contact allergy to wool alcohol present in the ointment. At the end of 2 weeks, there was slight improvement for overall impression and global score compared with baseline and changes were virtually identical in the active and placebo group. None of the changes were statistically significant between the two groups.

Harms

No adverse effects were reported within this study apart from the contact allergy to wool alcohol. Patients given topical lithium should be monitored for lithium toxicity if large quantities are applied.

Comment

Although this was a very small study published in correspondence form only, the detailed results section is particularly informative as CIs around the treatment differences are presented. Because of the small standard deviations within patient differences, the study excluded moderate and large treatment effects. Method of randomisation and concealment of allocation and blinding was unclear and no intention-to-treat analysis was performed.

Tacrolimus

Tacrolimus or FK506 is a macrolide lactone isolated from the bacterium *Streptomyces tsukubaensis*. It is an effective immunosuppressant drug used for the prevention of rejection after kidney and liver organ transplantation. Because of its lower molecular weight and higher potency compared with cyclosporin, it was proposed as an effective topical agent for inflammatory skin conditions such as atopic eczema. Its use in dermatology has been reviewed elsewhere.[349] Two RCTs have been published on the use of tacrolimus ointment in atopic eczema – one in adults[161] and in children.[159] A further open study was published by Nakagawa and colleagues[350]

in 1994. We are aware of at least four other ongoing trials sponsored by the manufacturer, comparing tacrolimus with vehicle and hydrocortisone.

Benefits

In the adult study,[161] 215 patients with moderate-to-severe atopic eczema aged 13–60 years were randomised to a parallel group study of either 0.03%, 0.1% or 0.3% tacrolimus ointment or vehicle alone. No concurrent treatment except emollients were allowed and the study duration was 3 weeks. Compared with baseline, the percentage of patients with completely resolved or markedly improved skin lesions at the treatment site according to an overall assessment by a physician were 60%, 82%, 72% and 8% (data estimated from graphs) in the 0.03%, 0.1%, 0.3% tacrolimus ointment and vehicle groups, respectively. Results were similar for patients' overall assessments, though the data were not shown. Median percentage decrease in a summary score for redness, swelling and itch was markedly greater in the tacrolimus groups compared with vehicle (66%:83%) when compared with placebo (22.5%). All of the changes were statistically significant for comparisons of placebo versus the three tacrolimus concentrations, but there were no statistical differences between the three tacrolimus concentrations.

The tacrolimus ointment for children with atopic eczema study had the same four comparison groups as the adult study with 180 children of moderate-to-severe atopic eczema aged 7–16 years recruited from 18 study centres in North America. For the patients' (or parents') assessment of itching, the median percentage improvement from baseline to the end of the 3-week trial was 50.5% for vehicle, 88.7% for 0.03% tacrolimus, 73.6% for 0.1% tacrolimus, and 77.1% for 0.3% tacrolimus. Only the differences between vehicle and the different tacrolimus concentrations were statistically significant. Similar percentage improvements were seen for physician's global evaluation. The mean percentage improvement for a modified eczema area and severity index at the end of the treatment for each of the three tacrolimus groups (72% for the 0.03% preparation, 77% for the 0.1%, and 81% for the 0.3% preparation) was significantly better than the vehicle group (26%; $p < 0.001$).

Harms

There was a significantly higher sensation of burning at the site of application in the adult tacrolimus patients. Itching and redness were also reported in the adult study. Blood concentrations of tacrolimus remained very low throughout the adult study. No serious adverse effects were reported in the children's study, though again burning and increased itching at the site of application during the first 4 days of the study were reported in about a quarter of the patients. Only seven of the 254 blood samples evaluated contained more than 1 ng/ml of tacrolimus. To put this into context, increased toxicity in transplant patients has been associated with concentrations of greater than 20 ng/ml.

Another study of potential skin thinning of tacrolimus has been reported by Reitamo and colleagues,[160] whereby the authors evaluated the potential of 0.1% tacrolimus ointment versus vehicle control versus betamethasone valerate (a potent topical corticosteroid) applied in a randomised order to apparently normal areas of skin on the abdomen under occlusion for 7 days. They found no evidence of skin thinning as measured by ultrasound in the tacrolimus group (compared with 8.8% median decrease in skin thickness relative to a vehicle control for betamethasone). They did not find any increase in chemical markers for collagen breakdown in the tacrolimus group whereas these were present in the steroid group.

Comment

Both of these RCTs were well reported with a good description of randomisation, blinding and both with intention-to-treat analyses. The flow diagram of the trial profile in the Boguniewicz and colleagues[159] trial was particularly refreshing. Magnitude of the clinical benefit measured in a number of ways was moderately large in tacrolimus in both adults and children when compared with placebo, and little difference was observed between the different concentrations of tacrolimus. Although no more serious adverse effects have been reported to date, much larger numbers and experience with the drug is needed before topical tacrolimus can be declared safe for the widespread use of atopic eczema in the community. Both of the trials were of extremely short duration and longer-term trials are needed to evaluate the benefit of tacrolimus in managing the chronicity of atopic eczema. Both trials are placebo-controlled and therefore lack the crucial comparisons against short bursts of moderate-to-potent topical corticosteroids and also against the newly developed and very similar topical ascomycin derivatives. Such comparative trials should include cost-effectiveness, and they should also be pragmatic in order to capture the tolerability of the topical agents in the community, where transient burning may result in lower compliance than that in organised clinical trials. The lack of skin thinning is a potential

advantage of tacrolimus, along with ascomycin, though the evidence that serious skin thinning occurs with correct use of topical corticosteroids in the community is lacking. Both of these RCTs were sponsored by the manufacturer, Fugisawa USA Inc.

Ascomycin derivatives

Topical ascomycin (SDZ ASM 981, Novartis Pharma AG) is a cytokine inhibitor. It inhibits activation of T-lymphocyte cells by inhibiting T-cell proliferation antigen-specific activation. Based on some success in psoriasis, it has been tried on atopic dermatitis. Two RCTs on ascomycin have been found, one of which was published in full at the time of writing this report.[162]

Benefits

The van Leent and colleagues study of 1998[162] randomised 34 patients with moderate atopic eczema to a double-blind placebo-controlled right/left comparison study. Topical 1% ascomycin cream was applied twice daily ($n = 16$) or once daily ($n = 18$) and compared with a corresponding placebo cream base for symmetrical lesions on the arm on one or other side. The trial duration was 21 days, and all participants were adults. At the end of 21 days, those in the twice-daily group showed a 71.9% decrease in baseline severity score compared with 10.3% in the placebo group ($p < 0.001$). Changes were also beneficial in the once-daily ascomycin group, but the magnitude was not so impressive with a 37.7% reduction in atopic dermatitis severity index in the active versus a 6.2% reduction of score in the placebo group ($p = 0.002$). Three out of 15 patients showed total clearance of their lesion in the twice-daily ascomycin group compared with none in the placebo group. None of the patients in the once-daily group (neither active nor placebo) showed any clearance of their lesions.

The other study has been published in abstract form only[351] and preliminary results were shown at a recent satellite symposium sponsored by the manufacturers. The study randomised patients to one of four different concentrations of ascomycin, vehicle, or betamethasone 17-valerate cream. Results presented at the meeting suggested that the ascomycin cream was significantly more effective than the vehicle alone in a dose-dependent manner, but not as effective as the topical corticosteroid. Full publication of the study is awaited before further comments can be made.

Harms

None of the patients in the van Leent study were shown to have any skin irritation or other local adverse effects. Blood values of ascomycin remained low throughout the study. In another study published in abstract form only,[352] ascomycin 1% cream did not cause any thinning of the skin in 16 healthy volunteers who applied the cream to their forearm for 4 weeks.

Comment

This was a well-reported study, though the method of randomisation and concealment of allocation in randomisation was not described. Blinding was well described and intention-to-treat analysis was performed. The study showed large treatment effects when presented in terms of relative treatment difference of a composite severity system when compared with placebo. The magnitude of the benefit was almost twice as large in the twice-daily group compared with the once-daily group, though the percentages are not directly comparable as they were not derived from the same randomised population. Although the atopic dermatitis severity index scores were unequivocally beneficial in the active group, it was disappointing not to see any patients' views on efficacy for pruritus incorporated in the main outcome measures. The small placebo effect of the cream is also unusual for atopic eczema trials, and possibly points to unblinding of the interventions. The fact that only three out of 16 patients showed total clearing of their eczema lesion on the arm after twice-daily continual application for 3 weeks is also slightly disappointing, bearing in mind the clearance potential of moderately potent topical steroids. Nevertheless, this study suggests that topical ascomycin derivatives are effective in moderately severe atopic eczema in adults, and is a welcome addition to the treatment modalities available. More comparative trials are needed, particularly against intermittent use of potent topical steroids and tacrolimus ointment in order to evaluate the place of ascomycin therapy in atopic eczema. Longer-term safety studies are also needed to ascertain rare but serious adverse effects from systemic absorption.

Summary of other topical agents

Coal tar

- One small RCT has suggested no difference in efficacy between Clinitar cream and 1% crude coal tar, though parents preferred the Clinitar preparation. It is difficult to say whether the efficacy changes reported from baseline were

due to the vehicle or active drug. Further RCTs comparing the most cosmetically acceptable coal tar preparation versus other topical treatments and vehicle alone are needed.

Emollients

- Although the use of emollients has become established as one of the firmest rituals of atopic eczema treatment, the RCT evidence for its efficacy is very sparse.
- There is a reasonable rationale for using emollients in atopic eczema in terms of their steroid-sparing effect providing this is not accompanied by loss of efficacy.
- There is little RCT evidence to form a rationale for choosing between different emollients.
- As emollients vary tremendously between themselves in terms of greasiness and water content, and because they need to be used long term, patient preference is a crucial factor.
- The correct emollient is therefore the one that the patient will use regularly.
- There is little RCT evidence to support the use of emollients in atopic eczema.

Lithium succinate ointment

- One small RCT failed to show any benefit of lithium succinate ointment when compared with placebo for the treatment of flexural eczema on the upper arms.

Tacrolimus

- Topical tacrolimus has been shown to be an effective short-term treatment for atopic eczema in children and adults.
- Transient burning and redness at the site of application is a common adverse effect.
- Future trials of tacrolimus should compare it against short bursts of topical corticosteroids and against ascomycin derivatives in a cost-effectiveness analysis. Such studies should be of long duration (i.e. 4 months or more), in order to capture the effect on chronicity of disease.

Ascomycins

- Topical ascomycin derivatives have shown to be markedly effective in moderate atopic eczema when compared with placebo in the trial of 3 weeks of twice-daily applications.

Chapter 6

Antimicrobial and antiseptic agents

The relationship between secondary infection or skin colonisation with the bacterium *S. aureus* and atopic eczema disease activity has been debated for many years, and is still far from clear. People with atopic eczema carry *S. aureus* in about 90% of clinically involved areas and about 75% of clinically uninvolved areas.[353] *S. aureus* represents about 90% of the total aerobic bacterial flora of such individuals compared with 30% in normal skin.[354] The density of *S. aureus* tends to increase with the clinical severity of the atopic eczema lesions. It has been suggested that the dry skin of atopic eczema is deficient in certain inhibitory fatty acids, which may encourage growth of the organism, and the organism may also show enhanced adherence properties to skin cells obtained from atopic eczema sufferers compared with normal controls.[355]

Few clinicians would dispute that grossly infected atopic eczema with oozing and sore pus spots requires treatment with some form of antibiotic or antiseptic, and that the bacteria are contributing at least in part to that particular flare-up. The role of *S. aureus* in non-clinically infected atopic eczema skin or for borderline infection (e.g. with just redness and oozing) is far from clear however,[356] and the reliability of physicians to diagnose 'clinically infected atopic eczema' is probably poor. Skin swabs taken for bacteriological culture are of little use due to the almost universal colonisation of atopic eczema skin with *S. aureus*, though such swabs may reveal additional bacteria such as *Streptococci* spp.

If *S. aureus* does play a pathogenic role in atopic eczema, then this could be due to a direct chemical irritation, a non-specific reaction of the protein A component of the bacterium with immune cells, and by the production of specific exotoxins called superantigens, which are capable of large populations of T-lymphocytes distant from the site of colonisation, giving rise to widespread activation of eczematous lesions.[357]

Although in many cases of non-clinically infected atopic eczema, the presence of *S. aureus* could be considered as an 'innocent bystander', which has simply colonised a dry and broken skin surface, there is at least thus some rationale for considering a role of *S. aureus* in more acute forms of atopic eczema. This has led to the use of many antimicrobial compounds such as oral antibiotics active against *S. aureus* given in short or prolonged courses, topically applied antibiotics, and antiseptic agents applied directly or by mixing with emollients applied directly to the skin or within bath additives. Topical corticosteroid/antibiotic contributions have already been discussed in chapter 5 (*Other topical agents*).

A total of ten RCTs[163–172] evaluating the possible benefit of antmicrobial or antiseptic agents in atopic eczema were located and these are presented in *Table 6*. Three of the studies evaluated the use of oral antibiotics, one evaluated topical antibiotics, and five evaluated antiseptic agents. Another study evaluated the use of an anti-yeast preparation and this has also been included in this section for completeness. In view of the differences in the types of interventions (e.g. topical or oral) and different patient populations (e.g. those with clinically infected as opposed to uninfected eczema), it did not make sense to pool the studies quantitatively.

Comment

Table 6 shows quality of reporting was generally disappointing in the studies. Missing data and small sample sizes rendered interpretation difficult. The RCT results suggest that the potential role of *S. aureus* in atopic eczema may have been overstated in the past, and this combined with concerns of selecting resistant strains argue against the general use of antiseptics and antimicrobials in clinically uninfected atopic eczema. Normalisation of the affected eczematous skin by treatment with a topical steroid alone decreases *S. aureus* colonisation dramatically,[164] suggesting that topical steroids alone are an effective means of decreasing bacterial skin colonisation in atopic eczema.

Summary of antimicrobial and antiseptic agents

- Some patients with atopic eczema develop overt signs of clinical infection which is usually due to the bacterium *S. aureus*.
- Most atopic eczema patients' skins are colonised with *S. aureus*.

- There is no RCT evidence that oral antibiotics are of any benefit in clinically uninfected atopic eczema.
- There is some evidence that a short course of cefadroxil is of benefit in clinically infected atopic eczema.
- There is some evidence from a short-term study that topical mupirocin may improve atopic eczema activity as well as reduce bacterial counts, though there is concern regarding the emergence of resistant strains with such an approach.
- There is no evidence that antiseptics are of benefit in atopic eczema when applied directly to the skin or in the bath.
- One small study of 1-week duration in Japan suggested that spraying an acidic solution on babies with atopic eczema might result in an improvement of disease activity.
- A study of head and neck atopic eczema failed to show any benefit of antifungal creams and shampoos directed against the yeast *Pityrosporum ovale*.
- Topical steroids alone are an effective way of reducing skin colonisation by *S. aureus*.

TABLE 6 *RCTs that have evaluated antimicrobial or antiseptic agent in atopic eczema. (An additional RCT of the use of an antifungal agent has also been included for completeness)*

Study	Interventions (co-treatments)	Study population and sample size follow-up	Trial design, description and	Outcome measures	Main reported results	Quality of reporting	Comment
Salo *et al.*, 1988[169] Finland	Oral erythromycin acistrate (EA) 400 mg three times daily vs oral erythromycin stearate (ES) 500 mg three times daily for 5 to 12 days (topical steroids and emollients)	42 patients (aged 15 to 66 years) admitted with clinically infected atopic eczema Most had bacteriological isolates of *S. aureus* and four had combined *Staph*/*Strep* infection	Parallel group randomised double-blind study for 5 to 12 days	Investigator and patient assessment of treatment efficacy on a five-point Likert scale and adverse effects	Mean duration of treatment was 7.7 days and 7.5 days in the EA and ES groups, respectively At the end of treatment, 75% and 83% of those in the EA and ES groups, respectively, were noted to show 'good' or 'very effective' improvement Similar results according to patients Gastrointestinal adverse effects similar in both groups	Method of randomisation and concealment unclear No ITT analysis	Difficult to evaluate as two 'actives' were being compared in the presence of inpatient care and potent co-treatment The fact that seven patients with clinically infected eczema had no bacteriological evidence of infection confirms the difficulty understanding the link between disease and bacteria
Weinberg *et al.*, 1992[170] South Africa	Oral cefadroxil 50 mg/kg/day in two equal doses vs placebo for 2 weeks (no mention of co-treatments)	33 patients aged 6 months to 12 years with bacteriologically confirmed superinfected atopic eczema caused by either *S. aureus* or mixed *Staph*/*Strep* infection	Parallel group randomised double-blind study for 2 weeks	Clearance of superinfection (assessed clinically), eczema severity, number of patients with positive cultures and global improvement	Of 30 evaluable patients, all 13 in the cefadroxil group no longer had clinical evidence of superinfection at the end of the study compared with six out of 15 in the placebo group Number of patients with positive isolates fell from 13 to four and from 17 to nine in the cefadroxil and placebo groups, respectively Physician-rated global improvement recorded marked or moderate improvement in 84 of cefadroxil compared with 53% of placebo-treated patients	Method of randomisation and concealment unclear No description of blinding No ITT analysis	Results clearly in favour of cefadroxil for these children with infected atopic eczema Poor quality of reporting
Ewing *et al.*, 1998[163] England	Oral flucloxacillin 250 mg daily or matched placebo four times daily for 4 weeks (topical steroids, emollients and antihistamines)	50 children aged 1–16 years who did not have any signs suggestive of bacterial infection	Parallel group randomised double-blind study for 1 month with an 8-week follow-up period	Change in baceteriological count of *S. aureus*, patient compliance, and composite eczema severity scores	Although mean *S. aureus* counts decreased significantly in those treated with flucloxacillin, clinical efficacy scores did not change between the two groups in any systematic way The difference in bacteriological counts at 14 days after stopping treatment were no longer significant ($p = 0.32$) Methicillin-resistant strains were commoner in those on flucloxacillin	Good description of randomisation, blinding, but no ITT analysis (five drop-outs by week 4)	An important study that did not find any evidence to support prolonged use of anti-staphylococcal antibiotics in those with clinically uninfected atopic eczema Flucloxacillin only temporarily changed skin colonisation by *S. aureus*

continued

TABLE 6 contd *RCTs that have evaluated antimicrobial or antiseptic agent in atopic eczema. (An additional RCT of the use of an antifungal agent has also been included for completeness)*

Study	Interventions (co-treatments)	Study population and sample size follow-up	Trial design, description and	Outcome measures	Main reported results	Quality of reporting	Comment
Lever *et al.*, 1988[167] Scotland	Topical mupirocin ointment vs placebo for 2 weeks (topical steroids and emollients)	49 patients aged 2–56 years with relapsing atopic eczema without overt secondary skin infection	Double-blind randomised crossover period with a 2-week run-in, two 2-week crossover periods and a further 4-week follow-up	Type and counts of bacterial isolates, composite clinical severity score and extent involved by disease Patients' assessment of appearance, itch and sleep	Bacterial count for 45 evaluable patients was significantly reduced in those receiving topical mupirocin but not in the placebo group, although recolonisation occurred in the 4-week follow-up period (17% of whom had developed a 'new' strain that had not been previously isolated) For the first treatment period, total skin severity score fell from a mean of 69.9 to 68 in the placebo group compared with a fall from 59.5 to 37.6 in the mupirocin group ($p < 0.002$); changes for surface area were not so marked Patient assessments were statistically in favour of the mupirocin for the first treatment period	Method of randomisation and concealment unclear No ITT analysis; no analysis of period or carry over effect Results suggest a significant carry-over effect between 1st and 2nd periods	Crossover design not ideally suited to a study of antibiotics with delayed actions on the skin Some evidence of atopic eczema improvement in the first study period in favour of mupirocin Concern for selection of resistant strains
Stalder *et al.*, 1992[164] France	Proprietary brand of chlorhexidine solution compared against 1:20,000 dilution of potassium permanganate solution for 7 days in addition to topical desonide (a topical steroid)	20 children aged 5 months to 9 years No details given if they were clinically infected	Parallel double-blind randomised study of 1 week duration	Bacterial counts, composite clinical severity score and patient reported tolerance	Total severity score fell from 8.8 at day 0 to 5.7 at the end of the 7 days for chlorhexidine and from 11.1 to 8.8 for the permanganate group ($p = 0.63$) Intensity and number of affected sites also showed very little difference between the two groups Bacterial counts feel substantially in both groups but they were not statistically significant ($p = 0.37$) and baseline scores in the two groups were quite different Clinical tolerance was 'good' in both groups	Poor quality of reporting with very few methodological details	Difficult to interpret with such a tiny study and the comparison of two active treatments Scanty methodological detail The clinical tolerance data were the most useful

continued

TABLE 6 contd *RCTs that have evaluated antimicrobial or antiseptic agent in atopic eczema. (An additional RCT of the use of an antifungal agent has also been included for completeness)*

Study	Interventions (co-treatments)	Study population and sample size follow-up	Trial design, description and	Outcome measures	Main reported results	Quality of reporting	Comment
Sasai-Takedatsu *et al.*, 1997[171] Japan	Comparison of spraying infants with water twice a day for 1 week or an acid electrolytic water (pH < 2.7) using a spray gun (no co-treatment allowed in this period)	22 children aged 2 to 56 months with mild-to-moderate atopic eczema	Parallel randomised double blind study of 1 week duration	Colony counts of *S. aureus*, composite grading score, and scores for itching and sleep disturbance	Colony counts decreased by around 50% in the active but not in the water group (though baseline scores were quite different) Global severity scores fell from 9 to 5 in the active group compared with a rise from 7 to 8 in the water group; scores for itching and sleep also decreased in the active group but not in the water group Although the authors found a statistically significant change in all of these measures for the active group compared with baseline, they did not do the appropriate test of difference between the two groups	Although the study was described as randomised, there is serious cause to challenge this in the methods section whereby the authors state that the 22 patients were 'arbitrarily divided by a referee physician into two groups of 11'; blinding also seems unlikely due to the acidic taste and sensation of the acid	Difficult to interpret the clinical data as the correct statistical comparison has not been done and because of the short duration of the study Some serious concerns about the study quality The ethics of spraying an acid onto young infants is also a cause for concern
Harper, 1995[166] England	Comparison of a standard proprietary bath emollient (Oilatum™) vs the same with the two added antiseptics 6% w/w benzalkonium chloride and 2% triclosan (Oilatum Plus™) used daily at a dose of 15 ml to the bath for 4 weeks (topical steroids)	30 children aged 1–9 years with recurrent infections and/or frequent exacerbation	Randomised crossover study of two 4 week treatment periods with a 2-week washout period in between	Composite sign and symptom score (max. 100), patient recorded global overall impression and global change scales	Based on 26 evaluable patients, the change from baseline score (baselines scores not given) was 9.0 for those using the antiseptic emollient compared with 2.7 for those with regular emollient at 4 weeks Patient rated scores did not show any significant differences between the two treatments (data not shown)	Method of randomisation was described, but no ITT analysis Only statistical tests of change in scores from baseline for each treatment separately rather than the appropriate test of the difference in score changes between the two treatments	Both this study and the Holland study are published in a 'round table' discussion document sponsored by the manufacturer Difficult to interpret in view of the wrong statistical tests being used and missing patient-reported data Re-analysis of data comparing the change in score between the two treatments at 4 weeks did not confirm any superiority of the antiseptic emollient

continued

TABLE 6 contd *RCTs that have evaluated antimicrobial or antiseptic agent in atopic eczema. (An additional RCT of the use of an antifungal agent has also been included for completeness)*

Study	Interventions (co-treatments)	Study population and sample size follow-up	Trial design, description and	Outcome measures	Main reported results	Quality of reporting	Comment
Holland *et al.*, 1995[165] England	Comparison of a standard proprietary bath emollient (Oilatum) vs the same with the two added antiseptics 6% w/w benzalkonium chloride and 2% triclosan (Oilatum Plus) used daily for 4 weeks (co-treatments not mentioned)	15 patients aged 4–34 years with moderate-to-severe atopic eczema with *S. aureus* on their skin	Parallel randomised double-blind study of 4 weeks' duration	Clinical scores of signs, symptoms and extent and bacterial counts	At the end of 4 weeks' treatments, clinical scores in the emollient/antiseptic group had fallen more than those in the emollient only group, but these were statistically significant There was no statistically significant difference in *S. aureus* counts between the two groups at the end of the treatment period Five drop-outs in the emollient only group	No description of randomisation process or ITT analysis Although described as a parallel study, patients were paired for matching pre-treatment *S. aureus* population densities	Difficult to interpret the lack of demonstration of efficacy in such a tiny study with high drop-outs
Hizawa *et al.*, 1998[172] Japan	Daily povidone-iodine solution to one arm vs nil else on opposite side (emollients only)	16 volunteers with atopic eczema aged 12–29 years with similar eczema lesions in each elbow fold	Right/left investigator-blinded comparison study of 1 week duration	Physician-assessed before and after photographs and colony counts of *S. aureus*	Of 15 evaluable patients, physicians reported an improvement in the povidone-treated sites ($p < 0.01$), but not on the control sites Bacterial colonisation was significantly reduced on the treated but not untreated site No summary data of differences between treatments reported	Unclear method and concealment of randomisation Investigator masking suspect as iodine stains the skin	Worth pursuing in a larger double-blind study as povidone-iodine is a cheap antiseptic with good anti-staphylococcal properties This is study is inconclusive in view of threat of unblinding, short duration, and failure to perform the appropriate statistical tests
Broberg & Faergemann, 1995[168] Sweden	After a course of antibiotics, patients were allocated to a combination active against *Pityrosporum* yeasts (a cream containing the antifungal miconazole plus hydrocortisone applied twice daily to the head and neck and ketoconazole shampoo twice weekly) vs plain hydrocortisone cream and shampoo base (emollients)	60 patients aged 14–53 years with atopic eczema affecting the head and neck of whom 83% were positive for *P. ovale* on culture at start	Parallel randomised double-blind trial of 6 weeks' duration	Modified SCORAD (a composite sign and symptom score) and reduction in *P. ovale* counts	Of 53 evaluable patients, severity score fell from 58.6 at baseline to 33.2 after 4 weeks in the antifungal group compared with 60.1 at baseline to 22.9 in the standard group (NS) *P. ovale* colonisation rates fell significantly in the antifungal group but not in the standard treatment group	No description of randomisation method, allocation concealment and no ITT analysis	Despite widespread use of antifungals for atopic eczema affecting the head and neck, this RCT does not suggest that there is any additional benefit over conventional treatment and that colonisation by the yeast *P. ovale* may be a secondary phenomenon

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Chapter 7

Antihistamines and mast cell stabilisers

Antihistamines

Itching is the central and often most distressing feature of atopic eczema. Antihistamines have long been prescribed for atopic eczema in the belief that they reduce itching by blocking the action of histamine on its receptors in the skin. The role of histamine in the itch of atopic eczema is unclear, and it may only play a small part. Histamine receptors are of two types, named H_1 and H_2, respectively. Both types are found in the skin. Most antihistamines that have been tried in atopic eczema are of the H_1 type. These H_1 antihistamines can be further subdivided into those with a sedating (e.g. chlorpheniramine) and those with a less-sedating action (e.g. cetirizine). Although lack of sedation may be desirable in the daytime, it is often stated that oral antihistamines are only effective in atopic eczema if they are sedative.[25] It is suggested that sedating antihistamines are effective because of their central sedating effect rather than any action on peripheral histamine blockade.[178]

Regardless of **how** antihistamines might work in atopic eczema, it is useful to consider the evidence of whether they help at all. We located 21 RCTs of antihistamines of various types in the treatment of atopic eczema,[173–193] and these are summarised in *Tables 7–9*. A further study[358] was excluded as data on atopic eczema patients were not separated from patients with urticaria.

Comment

Quality of studies

Generally, the quality of study reporting was very poor, with some (e.g. Hjorth[186] and Foulds & MacKie[184]) not containing any clinical effective-ness data at all. At least eight of the studies used a crossover study design, which, as others have noted,[359] is perhaps not the best design in view of potential carry-over and period effects. Such effects were only formally tested for in one study,[178] and in the absence of such testing, only comparisons for the first treatment period can be evaluated with confidence. Atopic eczema is also a very unstable disease, with flares occurring within 24 hours, making it an unsuitable condition for evaluation by crossover design. The clinical usefulness of small but statistically significant changes in mean itch scores between treatment groups is also very difficult to judge from the papers.

Ongoing systematic review

No statistical pooling has been attempted in this review as there is an ongoing, more detailed Cochrane Skin Group systematic review of antihistamines in atopic eczema which includes the authors of this report.[360] This is likely to be published later in 2000. Although the outcome data in *Table 8* suggests that some pooling for itch might be possible for most studies, the ongoing Cochrane Skin Group review of antihistamines in atopic eczema is already encountering difficulty in pooling due to missing vital information such as baseline data, type of scale used, and standard errors.

Sedative antihistamines

Those studies that have evaluated sedating antihistamines against placebo[176,182,184,185] do not show any evidence of a clear benefit for itch or global improvements. All the studies are quite small however.

H_2 antihistamines

Similarly, those studies[182,184] that have evaluated the benefit of the H_2 antihistamine, cimetidine, alone or in combination with H_1 drugs have not shown any benefit of the H_2 agents, though both studies were under-powered to detect even a modest improvement.

Less-sedative antihistamines

Those studies that have included comparative data on less-sedating antihistamines versus placebo[177–179,187–190,192] show mixed results. The largest study of 817 children followed-up for 18 months as part of the ETAC study,[329] has only published safety data to date, but the authors are aware that preliminary data presented at a previous meeting (Diepgen T, oral communication, 1999) on SCORAD scores[361] between the placebo and cetirizine groups did not show any differences. The full publication of the ETAC atopic eczema outcome data is eagerly awaited. The second largest (n = 187) and relatively well-reported study by Hanuksela and colleagues[190] compared three different doses of cetirizine with placebo. They showed a possible benefit with cetirizine, but only at four times the normal recommended dose and at the expense of some sedation. The remaining studies show a mixture of no effect and some effect, but need to be interpreted cautiously in

the absence of baseline data and other missing important data in the reports.

Studies that have compared different antihistamines or doses against each other are very difficult to interpret in the absence of a clear demonstration of benefit in placebo-controlled studies.

Other systematic reviews

One systematic review on the use of antihistamines in atopic eczema has recently been published.[362] That study missed nine of the RCTs identified in this report[173–175,180,185–187,192,193] and also evaluated non-randomised studies in their qualitative analysis based on study quality. The authors suggested that the best-quality evidence did not support a useful effect of antihistamines in relieving the itch of atopic eczema.

Sodium cromoglycate

Sodium cromoglycate (SCG) is used widely in the management of bronchial asthma and allergic rhinitis. Its effectiveness is thought to be at least partly due to inhibition of release of inflammatory mediators from mast cells following antigen encounter.[203] The drug has an impressive safety record and as immunological mechanisms are known to be important in atopic eczema, several investigators have evaluated its use for this condition. In addition, increased intestinal permeability to macromolecules is thought to be one of the predisposing factors to food allergy in children with atopic dermatitis, and orally administered SCG is thought to reduce intestinal permeability.[211] Opinions remain divided over the value of SCG in atopic eczema. We therefore undertook a systematic review of relevant RCTs.[84,194–212]

Results and discussion

A summary of the studies retrieved, their characteristics and the outcomes used are presented in *Tables 10–17*. The studies using oral SCG generally reported little or no beneficial effect for the drug compared with placebo. From those results it is probably safe to conclude that orally administered SCG is of little value in atopic eczema.

The results of trials of topical disodium cromoglycate (DSCG) are conflicting. Most of the studies that have reported positive effects were from the same laboratory[84,194,201] and have used solutions of the drug rather than semi-solid formulations. While differences in product formulation may have accounted for the differences in observed responses, it is possible that the study populations may also have had an effect. One of the Kimata studies[201] also included oxatomide in both the control and treatment arms so that treatment effects from his two studies cannot be quantitatively compared. The other two studies provide estimates which suggest that at 2 weeks, the itch scores decreased to a comparable extent with both DSCG and beclomethasone dipropionate (*Table 18*). The magnitude of change in itch scores obtained with those two drugs were somewhat higher than the difference seen between DSCG and placebo.

The study by Moore and colleagues[198] also suggests that SCG was effective in atopic eczema with severity scores substantially reduced within 1 month of initiation of therapy. However, the individual symptom scores are not reported so that quantitative comparison with the Kimata studies is not possible.

Nedocromil sodium

Nedocromil sodium, a mast cell stabiliser, is the disodium salt of pyranoqiunoline dicarboxylic acid and is similar to SCG in pharamcological action. Its mode of action prevents the release of inflammatory mediators from mucosal mast cells, blocking the late cutaneous reactions in mast cell-dependent allergic reactions.

Three RCTs[213–215] that evaluated nedocromil sodium in atopic eczema were identified. Two studies[213,214] evaluated nedocromil cream versus placebo cream and the other[215] evaluated oral nedocromil versus placebo.

Benefits

The study by Kemmett and Barnetson[213] (abstract only) evaluated topical 4% nedocromil sodium cream versus matching placebo, in 32 atopic eczema patients over a 4-week period. There were no significant differences between treatment and control groups as determined by clinical assessment and IgE levels (no data given). Patient-assessed relief of itch, redness and weeping was recorded but no data were given.

The paper by van Bever and Stevens[214] evaluated topical 4% nedocromil sodium cream versus vehicle only, in 26 adults and children with atopic eczema over a 4-week period. Patients and clinicians could not detect any difference between the two treatments as determined by daily score card for itch, sleep and overall severity of skin lesions and clinical examination for severity of skin lesions.

The study by Benton and colleagues[215] evaluated oral nedocromil sodium 100 mg three times daily versus placebo, in 22 adults with moderate-to-severe atopic eczema over a 4-week period. Patient diary cards for itch, redness and weeping and clinician's overall opinion showed no significant differences between active treatment and placebo.

Harms

Benton and colleagues performed full blood counts and tests of renal and hepatic function each month to determine any drug toxicity. The authors report no abnormalities were found in the laboratory data, and the drug was well tolerated apart from one patient who developed persistent diarrhoea, which ceased on withdrawal of the drug. Van Bever and Stevens report 17 episodes of flaring of symptoms, nine were in the nedocromil sodium group. One other patient reported dryness of skin and another furunculosis.

Comment

All three studies were randomised but method and concealment of randomisation was unclear, all described as double blind. The Kemmett and colleagues study was in abstract form only so little information was available and no data were given for results. The van Bever and Stevens study did not specify whether daily score card was patient- or doctor-assessed, and no actual data were given. It was unclear how many people were enrolled in the Benton and colleagues study. The results do not show any evidence to support benefit of nedocromil sodium, though the studies were relatively small and over short periods of time.

Ketotifen

Ketotifen is a benzocycloheptathiophene with antihistaminic and anti-anaphylactic properties. Its action is said to resemble SCG.

Benefits

We located two RCTs reporting the use of ketotifen for atopic eczema[216,217] one on adults and one on children. The study in children[217] evaluated ketotifen 1–2 mg twice daily versus placebo on 42 atopic children with asthma and allergic rhinitis (15 had eczema) for a period of 4 months. Parent-assessed diary cards of asthma symptom scores plus night itch, day itch and redness of skin were the primary outcome measures. No statistically significant beneficial effect of ketotifen was shown in asthma, allergic rhinitis or eczema.

Falk[216] evaluated ketotifen 1 mg twice daily versus placebo in 60 adults with atopic eczema over a 3-month period. The eczema was assessed for itch, sleep loss, erythema, lichenification and overall efficacy of treatment. Improvement of itch over baseline on a scale of 1–3 was 2.40 reduced to 1.20 for ketotifen ($p < 0.01$) versus 2.30 reduced to 1.60 for placebo ($p < 0.05$).

Harms

Apart from slight drowsiness no other adverse effects were reported.

Comment

The White and colleagues study[217] was primarily evaluating ketotifen for asthma; however, 15 of the children also had eczema. Being a small sub-group the authors conclude the number of patients with eczema was too small for meaningful analysis. The method and concealment of randomisation were unclear, though the study was described as double-blind. Withdrawals or drop-outs were not mentioned.

The Falk study[216] showed no appropriate test of differences between the two treatments and no standard errors were given, therefore the results are difficult to interpret. The method and concealment of randomisation were unclear, though the study was described as double-blind. Four dropped out, and there was no intention-to-treat analysis.

Topical doxepin cream

Doxepin is a tricyclic antidepressant drug, which also has powerful antihistamine properties by antagonising both H_1 and H_2 histamine receptors. On the basis of the putative role of histamine in the itch of atopic eczema and potent antihistamine antagonising effects of doxepin, topical preparations of doxepin have been tried in people with atopic eczema and other itchy skin conditions.

Benefits

Four RCTs[218–221] that evaluated topical doxepin in atopic eczema patients were identified. A further study of weal response in atopic eczema patients was excluded because no atopic eczema outcomes were reported.[363] One trial[364] was excluded as it was only published in abstract form with few data. Of the remaining four RCTs, two evaluated topical doxepin versus vehicle cream[218,219] and the other two evaluated the possible additional benefit of topical doxepin to treatment with topical corticosteroids.[220,221] Statistical pooling of the Breneman and colleagues[219] and Drake and colleagues[221] studies was not possible because separate data on atopic eczema were not given in the latter study.

Pooling was not attempted in the Berberian and colleagues[220] and Drake and colleagues[221] studies because different strengths of topical triamcinolone were used.

The study by Drake and colleagues[218] evaluated topical 5% doxepin cream versus vehicle only, applied four times daily, in 270 patients with atopic eczema over a 7-day period. Relief of itch (as recorded by a physician) was reported in 85% of doxepin and 57% of vehicle-treated patients by Day 7. A statistically significant relief in itch as recorded by patients on a 100 mm visual analogue scale (where 0 = no relief and 100 = complete relief) was also noted in the doxepin versus vehicle groups (68.6 versus 54.6, respectively after 7 days with baseline of 0 for both groups). Physician-reported eczema severity was also reported to be better in the doxepin group, though no data were given.

The paper by Breneman and colleagues[219] is more difficult to asses as the RCT reported within this paper included a mixture of 47 patients with atopic eczema and 49 with lichen simplex (another form of localised eczema), and results were not presented separately. There was no clinically or statistically significant difference in patient-assessed itch relief at the end of the 7-day RCT.

The study by Berberian and colleagues[220] evaluated the possible additional benefit of adding 5% doxepin to commonly used topical steroids in an 8-day study of 349 patients with atopic eczema. Four groups were randomly allocated to 2.5% hydrocortisone, 0.1% triamcinolone acetonide, 2.5% hydrocortisone plus 5% doxepin or 0.1% triamcinolone acetonide plus 5% doxepin, applied four times daily. At the end of 8 days, the mean visual analogue scale value for patient-recorded itch in the doxepin/hydrocortisone group versus hydrocortisone group was 77.8 and 68.3, respectively (where 100 = complete relief from itching). For the doxepin/triamcinolone versus triamcinolone groups, the relief scores were 94.9 versus 90.5, respectively ($p < 0.05$). Baseline scores were not reported. Statistically significant effects were noted in the groups containing the doxepin from Day 1 onwards, but the magnitude of these effects diminished with each consecutive day. Physicians' global evaluation of eczema severity at the end of the 8 days was not clinically or statistically significantly different.

The Drake and colleagues study[221] was mainly a pharmacokinetic study comparing doxepin hydrochloride 5% cream alone with doxepin plus 0.025% triamcinolone acetonide in 24 adults for 7 days. Only limited efficacy data were given. The paper stated that there were no significant differences in severity of atopic eczema between the two treatments at any point throughout the course of treatment. Pruritus severity scores (one of six itching assessment methods used in this study) demonstrated statistically significant greater improvement in the doxepin/triamcinolone group at 8 days ($p = 0.001$), though actual data for this and the other pruritus outcomes were not given.

Harms

Transient stinging or burning was commoner in doxepin-treated patients (e.g. 16 versus three in the Drake study). Drowsiness was also a problem (37 for doxepin versus three in the vehicle-treated patients in the Drake study), resulting in 16 drop-outs from the doxepin arm versus three in the vehicle arm. Somnolence was also noted in four out of 22 participants in the Drake study.[221]

Comment

The quality of reporting in the studies was quite good – methods of randomisation (though not subsequent concealment of allocation), a description of blinding and an intention-to-treat analysis were present in all three studies above. The fact that many patients developed drowsiness and stinging resulting in differential drop-outs in study arms raises concerns regarding the success of blinding in these studies. All four RCTs were sponsored by the manufacturer and were conducted by the same group of US investigators. Two of the above studies suggest that there is some evidence that topical doxepin produces some additional relief for itching in the short term (24–48 hours) when compared with vehicle. Whether this initial relief is clinically useful is doubtful, particularly when problems of drowsiness are taken into account. These short-term effects on itch become clinically insignificant over a 1-week period. None of the studies have demonstrated a clinically useful benefit of doxepin on atopic eczema severity or control even over the very short 1-week assessment periods. The studies have also used outcome measures scales that include itch as a prominent feature, or they have used several methods to assess itch, thereby increasing the likelihood of demonstrating a significant difference between the groups for itch. Longer-term independent studies (i.e. at least 6 months) evaluating combinations of doxepin plus other commonly used topical agents in atopic eczema are needed.

Tiacrilast

Tiacrilast is an important mast cell degranulation inhibitor in *in vitro* and in animal studies. As mast

cells and their mediators are possibly involved in atopic eczema, it has been tried in a topical preparation in atopic eczema. One RCT[222] compared 3% tiacrilast in the hydrogel formulation with vehicle alone in a multicentre study of 37 adults.

Benefits

In this right/left comparison study of 28 days, a lesion of atopic eczema was rated as responding if the sum of its rating (a composite scale of signs and itching) decreased by at least 33% from baseline to the end of treatment. Of 32 evaluable patients, 78% were noted to respond on the active drug versus 75% compared with a vehicle ($p = 0.614$). Median changes of efficacy parameters from baseline to end of treatment were also very similar between the two groups.

Harms

Treatment was well tolerated except for one patient who experienced burning at the site of drug application (site not specified).

Comment

This is one of the few RCTs in atopic eczema to pre-specify a measure of 'success' of its complex efficacy ratings scale. Method of randomisation was unclear and no intention-to-treat analysis was performed. Although this study was under-powered, the complete lack of difference between active and vehicle argues against a large treatment effect.

Summary of antihistamines and mast cell stabilisers

- There is no RCT evidence to suggest that sedating oral antihistamines have a clinically useful benefit in atopic eczema.
- There is limited and conflicting RCT evidence that less-sedating oral antihistamines have a clinically useful benefit in atopic eczema.
- It is possible that any benefit can only be achieved with doses much higher than is currently recommended.
- The largest and highest quality study of antihistamines in 817 children followed for 18 months has yet to report its outcome data on atopic eczema severity.
- The current RCT evidence does not support the routine use of antihistamines in atopic eczema.
- There is no evidence to support the use of oral SCG in atopic eczema.
- The results of trials of topical DSCG are conflicting.
- Most of the studies that reported positive results are from the same study laboratory and need to be repeated elsewhere.
- There is no RCT evidence to support the use of nedocromil sodium treatment in atopic eczema.
- There is no RCT evidence that shows any benefit to oral ketotifen in atopic eczema.
- Two RCTs suggest that topical doxepin might produce some additional relief of itching compared with vehicle alone in the first 48 hours.
- None of the studies of topical doxepin have demonstrated a clinically useful benefit on eczema severity.
- Drowsiness may occur with topical doxepin.
- All of the studies of topical doxepin have been conducted by the same research team – sponsored by the manufacturer.
- Longer-term independent RCTs of topical doxepin are needed.
- There is no evidence to support the benefit of topical tiacrilast in atopic eczema.

TABLE 7 *Patient characteristics and interventions of included studies of antihistamines*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawals and drop-outs
Berth-Jones & Graham-Brown, 1989[178]	Crossover RCT	28	11–67	1 week	Stable	Terfenadine 120 mg b.d.	Placebo	Topical steroid Emollients	Four: failure to comply
Doherty *et al.*, 1989[179]	Parallel RCT	49	16–58	2 weeks	Clinical diagnosis of atopic eczema	Acrivastine 8 mg t.d.s. vs Terfenadine 60 mg t.d.s.	Placebo	Twice daily 0.05% clobetasone butyrate and aqueous cream	Four active, one placebo
Foulds & MacKie, 1981[184]	Multiple crossover RCT	21	14–29	3 x 2 weeks	Life-long atopic eczema	Cimetidine + placebo vs Sedative H_1 + placebo vs Cimetidine + H_1	Placebo Placebo H_1	Ichthammol + emulsifier + 25 mg promethazine hydrochloride	One loss to follow-up
Frosch *et al.*, 1984[182]	Multiple crossover RCT	18	14–43	3 x 4 weeks	3-year history of atopic eczema	Cimetidine + chlorpheniramine vs Chlorpheniramine + Placebo vs Placebo + placebo	Placebo	Bland greasy ointment 0.1% betamethasone	Two personal reasons
Hamada *et al.*, 1996[192] (Japanese translation)	Parallel RCT	64	7–?	6 weeks	Mild to severe	Terfenadine 60 mg b.d. + alclometasone propionate (0.1%) ointment b.d.	Betamethasone valerate 0.1% b.d.	None	Five
Hannuksela *et al.*, 1993[190]	Parallel RCT	178	18+	4 weeks	Moderate to severe	Three different doses of cetirizine 10 mg, 20 mg and 40 mg daily	Placebo	Emollients 1% hydrocortisone	51 total 20 adverse effects, 19 non- compliers
Henz *et al.*, 1998[187]	Parallel RCT	74 with atopic eczema 244 total including urticaria	17–67	2 weeks	Moderate to severe pruritus	Azelastine 4 mg vs Cetirizine 10 mg	Placebo	*	37 total but unclear how many in atopic eczemagroup
Hjorth, 1988[186]	Crossover RCT	30	*	2 weeks	Atopic eczema with history of contact urticaria	Terfenadine 60 mg b.d.	Placebo	*	*

continued

TABLE 7 contd *Patient characteristics and interventions of included studies of antihistamines*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawals and drop-outs
Ishibashi *et al.*, 1989(a)[174] (Japanese translation)	Parallel RCT	157 GIR* 168 OSR 159 GUR	1–15	4 weeks	Mild to severe	E-0659 (azelastine hydrochloride) 0.017 /kg/day	0.07mg/kg/day and 0.13mg/kg/day azelastine hydrochloride	White vaseline	15 11 Nine
Ishibashi *et al.*, 1989(b)[193] (Japanese translation)	Parallel RCT	169 GIR/ GUR* 179 OSR	6–?	4 weeks	Mild to severe	E-0659 (azelastine hydrochloride) 4 mg/day and 2 mg/day	Ketotifen 2mg/day	White vaseline and topical hydrocortisone	11 One
Klein & Galant, 1980[191]	Parallel RCT	20	2–16	1 week	Acute exacerbations of atopic eczema	Hydroxyzine 1.25 mg/kg/day	Cyproheptadine 0.25 mg/kg/day	Lubriderm lubricating cream	*
Langeland *et al.*, 1994[188]	Six consecutive crossover RCTs	16	19–37	12 weeks	Moderate-severe	Loratadine 10 mg	Placebo	Emollients Mild topical steroid	*
La Rosa *et al.*, 1994[189]	Parallel RCT	23	6–12	8 weeks	Hanifin and Rajka	Cetirizine 5 mg/day for 30 kg and under 10 mg/day for over 30 kg	Placebo	*	One voluntary withdrawal
Monroe, 1992[176]	Parallel RCT	41 out of 59	18–65	1 week	*	10 mg loratadine o.d. placebo b.d. 25 mg hydroxyzine t.d.s.	Placebo t.d.s.	Topical treatment but not specified	None
Patel *et al.*, 1997[180]	Parallel RCT	118	12–65	2 weeks	At least moderate severity	10 mg/day loratadine	Cetirizine 10 mg/day	*	Ten failure to meet entry criteria or report for follow-up
Savin *et al.*, 1979[185]	Unclear if parallel or crossover RCT	12	23–38	3 nights over 4 weeks	Severe atopic eczema	Trimeprazine tartrate 20 mg Trimipramine maleate 50 mg	Placebo	Yes but not specified	*
Savin *et al.*, 1986[181]	Multiple crossover RCT	10	*	10 days	Long standing atopic eczema	LN2974 15 mg	Placebo	Routine topical treatment but not specified	*
Simons, 1984[183]	Crossover RCT	12	1–14	4 days	Severe widespread	Hydroxyzine 1.4 mg/kg	Hydroxyzine 0.7 mg/kg	*	Unclear

continued

TABLE 7 contd *Patient characteristics and interventions of included studies of antihistamines*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawals and drop-outs
Simons, 1999[175]	Parallel RCT	817	12–24	18 months	Atopic eczema with family history	Cetirizine 0.25 mg/kg b.d.	Placebo	Yes but no details given	99
Wahlgren *et al.*, 1990[177]	Crossover RCT	25	17–42	3 days	Persistent atopic eczema	Terfenadine 60 mg b.d. Clemastine 2 mg b.d.	Placebo	1% hydrocortisone	None
Zuluaga de Cadena *et al.*, 1989[173] (Colombia translated)	Parallel RCT	52	2–6	4 weeks	Not specified	Hydroxyzine 25 mg daily in three divided doses Terfenadine 10 mg daily in two divided doses vs Astemizole 5 mg daily in one dose	Three active treatments	Emollients only	Eight total (six on hydroxyzine and two on Astemizole treatment)

**No data*
GIR, general improvement rating; OSR, overall safety rating; GUR, general usefulness rating
b.d., twice daily
t.d.s., three times daily

TABLE 8 *Outcome measures signs and symptoms of antihistamines*

Study	Erythema	Purulence	Excoriation	Dryness	Xerosis	Scaling	Lichenification	Cracking	Fissuring	Exudation	Vesiculation	Pustules/papules	Oozing/weeping	Oedema	Inflammation	Crusts	Infiltration	Induration	Patient itch	Doctor itch	Patient sleep loss	Physician global severity assesssment	Patient global severity assessment	Area assessment (method used)	Scale named (if modified specify)
Berth-Jones & Graham-Brown, 1989[178]			●																●						
Doherty *et al.*, 1989[179]																			●	●					
Foulds & MacKie, 1981[184]	●		●																●			●	●	● % body surface area	
Frosch *et al.*, 1984[182]							●												●			●	●		
Hamada *et al.*, 1996[192]	●		●			●	●					●											●		
Hannuksela *et al.*, 1993[190]	●		●			●					●								●	●	●	●	●		
Henz *et al.*, 1998[187]	●					●													●			●			
Hjorth, 1988[186]																			●						
Ishibashi *et al.*, 1989(a)	●		●				●					●	●							●					
Ishibashi *et al.*, 1989(b)	●		●				●					●	●							●					
Klein & Galant, 1980[191]	●		●																●	●		●			
Langeland *et al.*, 1994[188]																			●						
La Rosa *et al.*, 1994[189]	●		●			●	●				●	●							●	●					
Monroe, 1992[176]	●																		●						
Patel *et al.*, 1997[180]	●		●				●												●	●	●	●	●		
Savin *et al.*, 1979[185]																					●				
Savin *et al.*, 1986[181]																			●						
Simons *et al.*, 1984[183]																				●					
Simons, 1999[175]	Safety study: drop-outs and serious events																								
Wahlgren *et al.*, 1990[177]																			●						
Zuluaga de Cadena *et al.*, 1989[173]	●						●				●	●	●	●											

Note: Frosch et al.,[182] *impetiginisation; Henz* et al.,[187] *whealing; Klein & Galant,*[191] *hives, macules, plaques; Monroe,*[176] *number and size of hives or lesions; Savin* et al.,[185] *scratching; Savin* et al.,[181] *scratching; Zuluaga de Cadena* et al.,[173] *also desquamation and extent of eczema*

TABLE 9 *Results*

Study	Main reported results	Authors' conclusions	Comment and quality
Berth-Jones & Graham-Brown, 1989[178]	There was no evidence of any difference between terfenadine and placebo. The mean scores for itch over the last 4 days of treatment (and standard errors of the means) were 23.95 (±4.9) for the terfenadine phase and 25.13 (±5.1) for the placebo phase. There was no evidence of carry-over or period-effect when pruritus scores were assessed	There was no benefit from terfenadine	Method and concealment of randomisation unclear, study described as double-blind. Four withdrawals for failure to comply, not clear at which point and in which initial arm. No ITT analysis. Low power to detect carry-over effect in only 20 patients. No data in graphical form. First and last period data not presented separately. Terfenadine double normal dose
Doherty *et al.*, 1989[179]	Acrivastine significantly reduced itching when compared with placebo according to the doctor's assessment ($p = 0.021$). Both acrivastine ($p = 0.026$) and terfenadine ($p = 0.037$) improved the patient's condition significantly more than placebo according to the patient's assessment of the degree of benefit obtained. No significant differences were found between the two active treatments	Acrivastine and terfenadine can partially relieve itching in atopic eczema	Method and concealment of randomisation unclear, study described as double-blind. Visual analogue data only given for Day 7. Five drop-outs (four active, one placebo), no ITT analysis. Unclear what was being assessed and what was meant by 'careful examination of the skin'
Foulds & MacKie, 1981[184]	Although it was found that there was a significant difference between individual patients for patient-assessed day pruritus ($p < 0.001$) and night pruritus ($0.01 < p < 0.025$) there was no difference between the treatment periods	This study does not demonstrate any significant advantage in adding an H_2 receptor antagonist to the H_1 receptor antagonist commonly used in young adults with severe chronic atopic eczema	Method and concealment of randomisation unclear, study described as double-blind. Only one loss to follow-up, no ITT analysis carried out. No actual data given for clinical outcomes – only *p*-value for statistical comparisons
Frosch *et al.*, 1984[182]	Analysis of cimetidine plus chlorpheniramine results for weeks 2, 3 and 4 for both day- and night-time patient-assessed itch compared with chlorpheniramine and placebo failed to show any significant difference	The combined administration of H_1 and H_2 receptor antagonists is of no benefit in the treatment of atopic eczema	Randomisation was conducted according to a Latin square, study described as double-blind. Baseline itch not given, therefore unable to calculate change. No standard errors given. Missing baseline data. Two drop-outs, no ITT analysis carried out
Hamada *et al.*, 1996[192]	Itching score and scratch marks were improved significantly. Physician 'improved' and 'markedly improved' was 89.3% in antihistamine and steroid group compared with 50% in the topical steroid only group	Combination of terfenadine ingestion and topical alclometasone application is more effective than betamethasone application only	Used different topical steroids in each intervention and no oral placebo. No ITT
Hannuksela *et al.*, 1993[190]	There was a non-significant difference between groups in patient-assessed pruritus intensity at baseline. All groups improved significantly ($p = 0.005$). This improvement was significantly more pronounced for cetirizine 40 mg compared with placebo	The sedation observed probably was partly responsible for pruritus relief, authors suggest that cetirizine has other properties responsible for skin lesion healing	Method and concealment of randomisation unclear. A high drop-out rate of 51, 20 for side-effects (mainly sedation) and 19 non-compliers, doesn't specify drug group. No ITT analysis carried out. Possible benefit of cetirizine when used at four times normal dose, but at the expense of sedation
Henz *et al.*, 1998[187]	Mean overall % response rate based on physician's global score was 36.4%, 25.0% and 27.3% in the azelastine, cetirizine and placebo groups, respectively. Baseline data and exact numbers of atopic eczema patients in each group were not stated. Mean itching score dropped from 2.2 to 1.4 in the cetirizine group and from 2.2 to 1.2 in both azelastine and placebo groups (estimated from graphs)	The data underline the low efficacy of antihistamines in atopic eczema	Neither drug reduced itching significantly more than placebo. Statistics not given for atopic eczema patients, no description of what constituted a response, placebo looks very impressive, clearly no difference in atopic eczema patients. High drop-out rate of 37, no ITT analysis carried out
Hjorth, 1988[186]	Terfenadine reduced severity of itch in approximately 52% of patients, 34% reported no change and 14% reported increased severity of itch. No data given for placebo	Terfenadine is if value in some patients with atopic eczema and a history of contact urticaria	No outcome data given and no information whatsoever on placebo response. Method and concealment of randomisation unclear, study described as double-blind. Unclear if any drop-outs or withdrawals. Author since deceased

continued

TABLE 9 contd *Results*

Study	Main reported results	Authors' conclusions	Comment and quality
Ishibashi *et al.*, 1989(a)[174] (Japanese translation)	No significant difference in general improvement rating, overall severity rating and general usefulness rating among the three dose groups. A significant difference in improvement ratio was found among three dose group in the signs if itch, papules, erythema and lichenification	No translated data available	No translated data available
Ishibashi *et al.*, 1989(b)[193] (Japanese translation)	No difference in final general improvement rating or general usefulness rating among the three groups. The effectiveness and usefulness in the treatment of atopic eczema were considered similar for the three groups. There was a significant difference in overall safety rating between the 4 mg/day and 2 mg/day groups. The safety rating was higher in the 2 mg/day group than in the 4 mg/day group. The overall safety rating showed no significant difference between the 4 mg/day and ketotifen groups or the 2 mg/day and ketotifen groups	No translated data available	No translated data available
Klein & Galant, 1980[191]	The group receiving hydroxyzine had a daytime percentage improvement of 32.14 ± 4.98 (mean ± SEM) over their baseline pruritus for the entire week, which is significantly greater ($p < 0.001$) than the percentage improvement for the cyproheptadine group of 6.21 ± 4.90	This study suggests that hydroxyzine is more effective than cyproheptadine for the management of pruritus associated with atopic eczema in children	Unstable data shown on a graph with inflationary % scale but no actual data given. Method and concealment of randomisation unclear, study described as double-blind. Not clear if any drop-outs or withdrawals
Langeland *et al.*, 1994[188]	The study detected a significant effect of loratadine, as compared with placebo, on patient-assessed pruritus during the day and night and severity of rash	Loratadine may be tried as an adjuvant therapy in the management of severe and moderate atopic eczema, in patients complaining of pruritus	Complex design, six consecutive crossovers. Changes in pruritus on VAS all small differences. No data for period or carry over effects shown. Method and concealment of randomisation unclear, study described as double-blind (block randomised)
La Rosa *et al.*, 1994[189]	Patient diary card scores showed a statistically significant decrease in erythema and other cutaneous symptoms such as lichenification, in the cetirizine group. Improvement over baseline total mean global score of 230 for cetirizine reduced to 155 after 8 weeks treatment, and 205 baseline for placebo reduced to 180 ($p > 0.05$) after 8 weeks treatment (estimated from graph)	The results of this preliminary study suggest that cetirizine can effectively control pruritus and other cutaneous symptoms in children suffering from atopic eczema without noticeable adverse effects	Method and concealment of randomisation unclear, study described as double-blind. Only one drop-out (voluntary withdrawal). Higher baseline scores in those on active treatments suggest that regression to the means could partly amount for results
Monroe, 1992[176]	The daily pruritus score decreased 57% in the 14 patients treated with loratadine, 38% in the 14 patients treated with hydroxyzine, and 33% in the 13 placebo patients	Loratadine demonstrates a significant antipruritic effect in atopic eczema	Patients excluded if unresponsive to antihistamines. No baseline values given. Method and concealment of randomisation unclear, study described as double-blind. Very short study at 1 week
Patel *et al.*, 1997[180]	Loratadine reduced patients perceived severity of their overall condition by 20.8% at endpoint. Incidence of somnolence was 9% with cetirizine and 3% with loratadine	In the management of symptoms of atopic eczema, loratadine is as effective as cetirizine and is less sedating	Study excludes non-responders before study started but not told how many. The report suggests ITT but fails to carry it out. Unclear if either drug is of benefit in absence of placebo group. Method and concealment of randomisation unclear, study described as double-blind
Savin *et al.*, 1979[185]	Neither of the drugs altered the likelihood of scratching bout beginning in wakefulness or in any stage of sleep. However, both drugs, especially trimeprazine, made sleep less broken, and the reduced time spent in stage 1 of sleep accounted for a modest reduction in the overall amount of scratching during the night	Both trimeprazine and trimipramine sleep becomes less broken, with a lessening of the time awake and in stage 1 sleep, and that these actions, which may be helpful to some patients, were associated with a modest reduction in the number and length of scratching bouts	Unclear if parallel or crossover study. Length of study unclear. Method and concealment of randomisation unclear, study described as double-blind. Withdrawals or drop-outs not mentioned in this study. Unclear if the changes in sleep pattern helped the patient's eczema

continued

TABLE 9 contd *Results*

Study	Main reported results	Authors' conclusions	Comment and quality
Savin *et al.,* 1986[181]	No significant difference was detected between the limb movement times on placebo and on active treatment with LN2974. The difference between the mean scores of the visual analogue assessment of itching on placebo and on LN2974 did not reach statistical significance although tending to favour LN2974	No significant suppression of scratching, as measured by limb movement meters, or of itching, recorded on VASs, could be demonstrated	No actual data given. Method and concealment of randomisation unclear, study described as double-blind. Unclear if any withdrawals or drop-outs
Simons *et al.,* 1984[183]	The scores for atopic eczema severity and distribution were significantly reduced at the end of treatment for both doses of hydroxyzine ($p \leq 0.05$)	Hydroxyzine 0.7 mg/kg three times daily was as effective as hydroxyzine 1.4 mg/kg three times daily in relieving pruritus and promoting resolution of the skin lesions	This trial was buried in the middle of a case-series. Only presented mean score at end of treatment rather than mean change in score. Itch data and baseline scores not given. Sample size unclear. Point of randomisation was after the single dose study. Method and concealment of randomisation unclear, study described as double blind. Unclear of any withdrawals or drop-outs. Far too small a study to establish equivalence effects
Simons, 1999[175]	During the 18 month long study, only 48 children treated with cetirizine and 51 treated with placebo dropped out 'for any reason' ($p = 0.737$); of these, only 11 and 15 children, respectively, dropped out because of symptoms or events ($p = 0.421$). Serious events were reported in 37 children (9.3%) receiving cetirizine and in 54 children (13.6%) receiving placebo. Hospitalisations were reported in 36 children receiving cetirizine and in 47 receiving placebo ($p = 0.189$). Fatigue and insomnia were slightly, but not statistically significantly, raised in cetirizine group. No difference in somnolence between cetirizine and placebo. No efficacy data given	The safety of cetirizine has been confirmed in this prospective study, the largest and longest randomised, double-blind, placebo-controlled, safety investigation of any H_1 antagonist ever conducted in children and the longest of prospective safety study of any H_1 antagonist conducted in any age group	Good description of randomisation and blinding. Well reported study. 99 drop-outs, no ITT analysis carried out. Clinical efficacy outcome data eagerly awaited.
Wahlgren *et al.,* 1990[177]	No significant difference in itch intensity between the three treatment periods was detected with Pain-Track, nor was there any difference in time awake without pruritus. No significant changes in itch magnitude appeared during each period (Days 0–3)	The antipruritic effect of 3 days of treatment with terfenadine (non-sedative) and clemastine (sedative) did not differ from that found with placebo	Very short trial of only 3 days. Method and concealment of randomisation unclear, study described as double blind. No withdrawals or drop-outs. Underpowered
Zuluaga de Cadena *et al.,* 1989[173] (Colombia) translated	At the end of the 4-week evaluation period, eight out of 15 patients on terfenadine compared with eight out of 17 patients on astemizole and six out of 8 patients on hydroxyzine had improvement in itch. Global improvement was noticed in 14 out of 15 cases on terfenadine, 15 out of 17 cases on astemizole and seven out eight cases on hydroxyzine. Improvements in other outcome measures was similar between all three groups. Other laboratory measures were also recorded	Antihistamines may be beneficial in atopic eczema with astemizole conferring a prolonged benefit	Outcome measures and their combination were quite complex. Method and concealment of randomisation unclear. Study described as single (investigative)-blind. No ITT analysis. Small numbers and no placebo group

SEM, standard error of the mean; VAS, visual analogue scale

TABLE 10 *Design, patient characteristics and interventions of included studies: oral SCG*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawals and drop-outs
Atherton *et al.*, 1982[203]	Crossover, double-blind, randomised	29	2–10	4 weeks	Varying severity	Oral SCG 100 mg q.d.s.	Placebo	Emollients, corticosteroids, antihistamines	One due to systemic cortico-steroids
Birkeland *et al.*, 1981[208]	Parallel, double-blind, randomised	28	19–48	6 weeks	*	Oral DSCG 6 mg q.d.s.	Placebo	All stopped	*
Burks & Sampson, 1988[207]	Crossover, double-blind, randomised	10	3–15	1 week	*	Oral cromolyn 30–40 mg/kg/day	Placebo	*	None
Businco *et al.*, 1986[205]	Crossover, double-blind, randomised, ITT	31	0.5–10	8 weeks	Severe enough to require continuous treatment	Oral aqueous solution SCG	Placebo	Other treatment kept to a minimum, no steroids allowed	Six
Graham *et al.*, 1984[197]	Crossover, double-blind, randomised, no ITT	29	3–12	6 weeks	Chronic	Oral SCG 100 mg q.d.s. for 3 weeks 200 mg q.d.s. for 3 weeks	Placebo	Hydrocortisone and antihistamines Antibiotics if infected	Eight
Kavli & Larsen, 1981[204]	Crossover, double-blind, randomised, no ITT	35	15–42	2 weeks	*	FPL 57787 (chromone carboxylic acid) 18 mg q.d.s.	Placebo	1% hydrocortisone	18
Larsen & Larsen, 1979[206]	Parallel, double-blind, randomised	14	18+	6 weeks	*	FPL 57787 6 mg q.d.s.	Placebo	1% hydrocortisone	*
Larsen & Jacobsen, 1980[195]	Crossover, double-blind, randomised	23	18–41	6 weeks	*	FPL 57787 18 mg q.d.s.	Placebo	1% hydrocortisone	Three (one due to adverse effects)
Lindskov & Knedsen, 1983[210]	Crossover, double-blind, randomised	24	4–37	6 weeks	Severe widespread	Oral DSCG 200 mg q.d.s (adults) 100 mg q.d.s. (children)	Placebo	Moisture cream, oil bath and hydrocortisone butyrate	None
Ventura *et al.*, 1996[211]	Parallel, double-blind, randomised	83	0.1–1.5	4 weeks	*	Oral DSCG 100–120 mg/kg/day q.d.s.	Placebo	Corticosteroids (Locoidon, hydrocortisone butyrate) emollients	*

Locoidon™ = Locoid™, Yamanouchi, UK
q.d.s., four times daily

TABLE 11 *Design, patient characteristics and interventions of included studies: topical SCG*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawals and drop-outs
Ariyanayagum *et al.*, 1985[202]	Parallel, double-blind, randomised	46	16–65	12 weeks	*	4% SCG	Placebo	Hydrocortisone 1% Terfenadine (adults) Clemastine (children)	Seven withdrew: three SCG, four placebo
Croner *et al.*, 1981[200]	Parallel, double-blind, randomised	22	2–16	6 weeks	Moderate to severe	10% SCG w/w in white soft paraffin	Vehicle	Antihistamines if required	*
Haider, 1977[196]	Parallel, double-blind, randomised	44	0.42–14	12 weeks	Chronic	10% SCG in white soft paraffin	Placebo	None	20: treatment ineffective
Hiratsuka *et al.*, 1996[84]	Parallel, double-blind, randomised	43	5.2–14.6	2 weeks	*	Topical SCG (concentration not given	Betnovate	None	*
Kimata & Igarashi, 1990[194]	Parallel, double-blind, randomised	45	0.8–3	4 weeks	Moderate to severe	Cromolyn nebulizer solution	Placebo	None	None
Kimata & Hiratsuka, 1994[201]	Parallel, double-blind, randomised	53	4.1–14.2	4 weeks	Moderate to severe	SCG nebulizer plus oxatomide (1.5 mg/kg/day)	Placebo (water solution plus oxatomide)	Oxatomide	Four: two from placebo group: ineffective two from active group: incorrect use of treatment
Kjellman & Gustafsson, 1986[209]	Parallel, double-blind, randomised	40	1–18	12 weeks	*	SCG 4% oil in water	Placebo	1% hydrocortisone antihistamines emollients and potent topical steroids	Three: one from SCG group lack of compliance two from placebo group deterioration of eczema
Moore *et al.*, 1998[198]	Crossover, randomised, not blinded	26	0.5–18	4 weeks	Moderate to severe	Cromolyn sodium inhalation solution 0.21%	Placebo	0.1% triamcinolone, 1% hydrocortisone	Five
Pike & Atherton, 1988[212]	Parallel, double-blind, randomised	36	1–14	12 weeks	*	SCG oil in water cream	Placebo	*	
Thirumoorthy & Greaves, 1978[199]	Right/left comparison, double-blind, randomised	11	1–1.5	4 weeks	Moderate to severe	DSCG 10% in white soft paraffin	Placebo	None	Five drop-outs no data given

TABLE 12 *Outcome measures: oral SCG*

Study	Outcome measure	Scale
Atherton *et al.*, 1982[203]	Parent diary card for day-time itch and night-time sleep loss	0–3 scale
	Clinical evaluations 20 areas of skin surface for erythema, vesiculation and/or crusting, excoriation and lichenification	
	At end of study general well-being and severity of eczema	+2 to –2 (very much better to very much worse)
Birkeland *et al.*, 1981[208]	Clinical assessments of 14 regions for colour, scaling, infiltration, itching of the three most active eczematous regions	1–3 scale (1 = none, 2 = slight, 3 = marked)
	Total serum IgE and reduction in disease activity	
Burks & Sampson, 1988[207]	Parent symptom diary cards: rash distribution, pruritus, urticaria	0–3 scale
Businco *et al.*, 1986[205]	Clinician-assessed body divided into ten areas for redness, weeping, vesiculation, crusting, excoriations, lichenification	0–3 score total body score 60, max score for all parameters 240
	Parent-assessed diary card for itching and sleep disturbance due to itching, weeping, redness of skin	0–3 scale max score 12
Graham *et al.*, 1984[197]	Patient diary card for pruritus, sleeplessness, severity and area of eczema	0–4 scale
	Clinical assessment on a homunculus for severity and area.	0–4 scale
	Dryness and excoriation also noted	
Kavli & Larsen, 1981[204]	Clinician-assessed disease extent and severity.	
	Patient diary cards for itching and sleep loss and severity for lichenification, excoriation, redness	0–3 scale (none-severe)
Larsen & Larsen, 1979[206]	Scaling, colour, lichenification, general assessment of the eczema and severity of itch	*
Larsen & Jacobsen, 1980[195]	Clinician-assessed dryness, lichenification, excoriation	0–3 scale
Lindskov & Knudsen, 1983[210]	Clinician-assessed lichenification, eczema, and overall disease	Scales 0–2, 0–3 and 0–4, respectively
	Patient- or parent-assessed day- and night-time itching and general severity of eczema	0–5mm VAS
Ventura *et al.*, 1996[211]	Clinician-assessed erythema, exudation, lichenification, eczema extension and itch	*

* *No scale*

TABLE 13 *Outcome measures: topical SCG*

Study	Outcome measure	Scale
Ariyanayagam *et al.,* 1985[202]	Patient diary card for pruritus, sleeplessness, severity of eczema and use of concomitant therapy	0–3 point scale patient-assessed signs and symptoms
	Severity assessed on erythema, lichenification, vesiculation, dryness and excoriation over four main areas	0–6 point scale physician-assessed over four main areas for signs
Croner *et al.,* 1981[200]	Patient diary cards for itching (day and night), sleep disturbance and severity of eczema on face, trunk, arms and legs	0–3 score where 0 = no symptoms and 3 = severe symptoms
Haider, 1977[196]	Physician-assessed inflammation, lichenification and cracking of the arms and legs	0–2 point scale physician-assessed signs over two areas
	Patient diary card for severity of itching (day and night) and sleep disturbance	0–3 point scale patient-assessed itch and sleep loss
Hiratsuka *et al.,* 1996[84]	Physician-assessed inflammation, lichenification, cracking on 15 body areas	0–2 point scale in ascending order of severity
	Patient diary cards for itching and sleep disturbance	0–3 point scale patient-assessed diary cards
Kimata & Igarashi, 1990[194]	Signs: inflammation, lichenification and cracking assessed on four body areas max score 24, 0–8 mild, 9–16 moderate, 17–24 severe (only scores > 9 entered)	0–2 point scale in ascending order of severity
	Symptoms: sleep and itching patient-assessed record card	0–3 scale
Kimata & Hiratsuka, 1994[201]	Physician-assessed signs lichenification, inflammation and cracking on 15 body areas, max. score = 30	0–2 scale
	Patient-assessed symptoms itch and sleep loss on a diary card	0–3 scale
Kjellman & Gustafsson, 1986[209]	Patient diary cards for itch, sleep disturbance and overall severity (redness, vesiculation and crusting, excoriation, lichenification)	0–3 scale
Moore *et al.,* 1998[198]	Physician-assessed erythema, vesiculation, crusting and cracking, scaling, and lichenification in 12 body areas, (Rule of Nines)	0–3 scale (none to severe) max. per area = 15
Pike & Atherton, 1988[212]	Diary charts recording pruritus, sleep disturbance by physician	Body score chart
Thirumoorthy & Greaves, 1978[199]	Patient diary card for itching	*
	Clinical responses of the two sides assessed weekly by clinician and patient	*

* *No scale*

TABLE 14 *Outcome measures: oral SCG – signs and symptoms*

Study	Erythema	Purulence	Excoriation	Dryness	Xerosis	Scaling	Lichenification	Cracking	Fissuring	Exudation	Vesiculation	Pustules/papules	Oozing	Inflammation	Crusts	Infiltration	Induration	Itch	Sleep loss	Physician global severity assesssment	Patient global severity assessment	Area assessment (method used)	Scale named (if modified specify)
Atherton *et al.*, 1982[203]	●		●				●				●				●			●	●	●	●		
Birkeland *et al.*, 1981[208]						●										●		●					
Burks & Sampson, 1988[207*]																		●				RoNAA	
Businco *et al.*, 1986[205†]	●		●				●			●	●				●								
Graham *et al.*, 1984[197]			●	●														●	●				
Kavli & Larsen, 1981[204]	●		●				●											●					
Larsen & Larsen, 1979[206‡]						●	●																
Larsen & Jacobsen, 1980[195]			●	●			●																
Lindskov & Knudsen, 1983[210§]							●											●		●	●		VAS
Ventura *et al.*, 1996[211¶]	●							●		●								●					

Rash distribution and urticaria; † Lumps, redness, weeping, vesiculation and crusting together; ‡ Colour; § Eczema; ¶ Eczema extention; RoNNA, Rule of Nines area assessment

TABLE 15 *Outcome measures: topical SCG – signs and symptoms*

Study	Erythema	Purulence	Excoriation	Dryness	Xerosis	Scaling	Lichenification	Cracking	Fissuring	Exudation/weeping	Vesiculation	Pustules/papules	Oozing	Inflammation	Crusts	Infiltration	Induration	Itch	Sleep loss	Physician global severity assesssment	Patient global severity assessment	Area assessment (method used)	Scale named (if modified specify)
Ariyanayagam *et al.*, 1985[202]	●		●	●			●													●			
Croner *et al.*, 1981[200]																		●	●		●		
Haider, 1977[196]							●	●						●									
Hiratsuka *et al.*, 1996[84]							●	●						●									
Kimata & Igarashi, 1990[194]							●	●						●									
Kimata & Hiratsuka, 1994[210]							●	●						●									
Kjellman & Gustafsson, 1986[209]	●		●				●				●				●								
Moore *et al.*, 1998[198]	●					●	●	●			●				●							RoNAA	
Thirumoorthy & Greaves, 1978[199]																	●						

TABLE 16 *Results of studies of oral treatments*

Study	Main reported results	Authors' conclusions	Quality
Atherton *et al.*, 1982[203]	No difference detected at 4 weeks between the effects of DSCG and placebo	The results do not confirm previous anecdotal reports of effectiveness of SCG in children with atopic eczema	Small and short-term study. Randomisation, blinding and 4-week washout period appear adequate
Birkeland *et al.*, 1981[208]	No significant changes were found between the severe and mild atopic eczema for number of regions involved at the first visit and reduction in disease activity during the trial. Serum IgE in relation to T and B cells shows non-significant differences in the figures in the severe and mild atopic dermatitis for T cells and B cells.	No benefit could be proven for the drug in the clinical investigation or any change in the immunological tests during the trial. There was no demonstrable differences in the applied immunoparameters between mild and severe atopic dermatitis	Method and concealment of randomisation unclear, study described as double-blind. Unclear whether any drop-outs
Burks & Sampson, 1988[207]	SCG (40 mg/kg/day) did not protect against food-induced symptoms in patients with atopic eczema and egg hypersensitivity	Oral SCG is of no benefit in the treatment of children with atopic eczema and food hypersensitivity	Only ten children were studied and eight reacted to food challenge in this crossover study
Businco *et al.*, 1986[205]	Increase in symptom score higher when patients were given DSCG than placebo	SCG seems to have reduced exacerbations of atopic eczema caused by food allergens	Randomisation, blinding and 2-week washout period appear adequate. Small and short-term study. Patients had history of food hypersensitivity
Graham *et al.*, 1984[197]	Mean eczema scores for severity and area not different between groups receiving DSCG and placebo	Tailored diets were of value but SCG did not produce a significant additional effect	Randomisation, blinding and 2-week washout period appear adequate. Small and short-term study. Patients had history of food hypersensitivity
Kavli & Larsen, 1981[204]	A significant reduction in patient-assessed itch was found for chromone carboxylic acid in the placebo, washout, chromone group ($p < 0.05$) after 6 weeks' treatment. Significant differences were found for lichenification, excoriation and redness in the placebo, washout, chromone group for clinically assessed signs ($p = 0.05$). No significant differences were found between chromone followed by placebo groups at 3 weeks treatment	Systemic chromone derivatives relieve certain symptoms in patients with atopic dermatitis. However, statistically significant results in favour of chromone carboxylic acid were obtained only in the group that started on placebo and only after the first 3 weeks of treatment. This may be due in part to the reduced sample at 6 weeks, and possibly also to an increasing awareness during the trial on the part of the patients of antigen avoidance	Method and concealment of randomisation unclear, study described as double-blind. Over half enrolled patients dropped out ($n = 18$) mainly due to increased severity of atopic eczema or ineffective treatment, no ITT analysis carried out
Larsen & Larsen, 1979[206]	No statistically significant differences in the clinician's scores for any parameter	Unable to prove the new chromone drug to be effective in systemic treatment of atopic dermatitis	Method and concealment of randomisation unclear, study described as double-blind. No drop-outs. No results data given. Small sample over a short period of time
Larsen & Jacobsen, 1980[195]	There were no statistically significant differences in the clinical assessments, in the patients' diary cards, or in the use of hydrocortisone cream. Eleven patients preferred the active period, while nine patients preferred the placebo period	This trial could not demonstrate any effect of chromone compound in systemic treatment of atopic eczema. Furthermore, the applied dose resulted in some dyspeptic adverse effects	Method and concealment of randomisation unclear, study described as double-blind. Three drop-outs, no ITT. No results data given. Small sample over a short period of time. Authors conclude: "Our first study [Larsen & Larsen[206]] gave some evidence that FPL 57787 might be effective in the treatment of [atopic eczema]". However, it gave no evidence of benefit. The later study used three times (18 mg t.d.s.) the earlier dose of 6 mg t.d.s.
Lindskov & Knudsen, 1983[210]	No significant differences between the two treatments in the patients' assessments	Unable to confirm the favourable results of DSCG in atopic eczema reported by others	Crossover trial with no washout period. Small study of 14 adults and ten children
Ventura *et al.*, 1996[211]	No difference in eczema score in the DSCG and placebo groups	The usefulness of dietary treatment is confirmed. Orally given DSCG does not seem capable of preventing a secondary sensitisation in patients with cows' milk protein allergy	Parallel group trial. Randomisation and blinding adequate

TABLE 17 *Results of studies using topical SCG*

Study	Main reported results	Authors' conclusions	Quality
Ariyanayagam *et al.,* 1985[202]	Mean eczema severity score reduced significantly at 12 weeks compared with 3 weeks in patients on DSCG but not on placebo. The same effects were seen with daytime itch and night-time itch	Topical SCG as a long-term measure may be useful	Double-blind parallel group with randomisation. Short-term study of 12 weeks with an open label follow-up of 1 year
Croner *et al.,* 1981[200]	No significant group differences found except for less frequent use of steroids	Topical DSCG did not add to the drug's success in bronchial asthma and atopic eczema. Steroid-sparing effect could be worthwhile	Small short-term study. Parallel group randomised double-blind trial
Haider, 1977[196]	Significantly more withdrew for lack of effect from the placebo than the DSCG arms (16/21 vs 4/21)	Safe alternative to topical steroids in the treatment of atopic eczema in children	Small short-term study. Parallel group randomised double-blind trial
Hiratsuka *et al.,* 1996[84]	Equivalent to beclomethasone dipropionate in reducing eczema scores at 2 weeks	Both DSCG and beclomethasone diproprionate produced remarkable eczema improvement	
Kimata & Igarashi, 1990[194]	Itch scores, eczema scores and sleep scores all improved by week 2	Topical cromolyn solution was found to be very effective	Double-blind randomisation appeared adequate
Kimata & Hiratsuka, 1994[201]	Itch scores, eczema scores and sleep scores all improved with DSCG but not with placebo	DSCG adds to the effect of oxatomide	Double-blind randomisation appeared adequate
Kjellman & Gustafsson, 1986[209]	No significant change in itch scores or sleep disturbance reported	Topical DSCG did not relieve the patients' eczema	Double-blind randomisation appeared adequate
Moore *et al.,* 1998[198]	At 1-month crossover period, the group receiving DSCG first has a higher reduction in eczema scores than did those who received placebo first	Topical DSCG has a significant anti-inflammatory effect on moderate-to-severe atopic eczema	Crossover study with satisfactory blinding and randomisation
Pike & Atherton, 1988[212]	No numerical data reported	No statistically significant effect between the active and placebo treatment	Letter
Thirumoorthy & Greaves, 1978[199]	Letter	No significant difference between DSCG and placebo	Eight patients only. Few details given

TABLE 18 *Difference in itch scores produced by DSCG and beclomethasone and comparison with effects seen in a placebo-controlled trial*

Study	Stratum	No. of treatment patients	No. of control Patients	Mean difference	95% CI
Hiratsuka *et al.,* 1996[84]	1	21	21	1.65	1.19 to 2.11 (DSCG in itch scores week 0 to week 2)
Hiratsuka *et al.,* 1996[84]	2	22	22	1.26	0.60 to 1.91 (beclomethasone week 0 to week 2)
Kimata & Igarashi, 1990[194]	3	25	201	0.47	0.47 to 1.53 (difference in itch scores DSCG minus placebo)

Chapter 8

Dietary interventions

Dietary restriction in established atopic eczema

In addition to examining the role of dietary exclusion of possible allergenic foods during pregnancy or lactation with a view to preventing the development of atopic eczema, some RCTs have examined the role of dietary exclusions to improve the severity of **established** atopic eczema. No systematic reviews of dietary manipulation in established atopic eczema could be identified, although some of the published studies have been reviewed by Charman.[334] The eight RCTs examining the role of elimination diets in established atopic eczema are summarised in *Table 19* (Atherton 1980 is the same paper as Atherton 1978). RCTs of dietary exclusion in the prevention of atopic eczema that have also estimated eczema severity in those developing eczema have already been discussed in *Tables 3* and *4*. In the three studies looking at dietary exclusion during pregnancy,[61,66,67] there was no difference in eczema severity between the intervention and control groups. In the studies looking at dietary exclusion during breastfeeding, one reported improvement in eczema severity in the intervention versus control group,[53] while the other[55] did not.

Summary of dietary restriction in established atopic eczema

- None of the interventions and study populations were considered sufficiently similar to each other to warrant statistical pooling.
- Elimination diets are difficult for families and patients to follow, even in the highly motivated environment of a clinical trial.
- Drop-out rates are particularly high for elimination diets and those containing hydrolysate milk substitutes.
- Those RCTs that employ a parallel design with an unblinded normal control diet risk biasing the motivation and ancillary care in favour of the active group.
- Those studies that place all participants on exclusion diets and introduce the suspected offending food versus a control, risk introducing another allergen (e.g. soya) or introducing the suspected allergen (e.g. cows' milk) in an altered and controlled way that does not mimic real life.
- Marked order effects suggest that the crossover study is not the best method of assessing the benefits of dietary exclusion.
- There is little evidence to support an egg- and milk-free diet in unselected atopic eczema patients.
- There is no evidence to support the use of an elemental- or few-foods diet in atopic eczema.
- There is some evidence that the addition of a probiotic such as Lactobacillus may be beneficial for atopic eczema in those already on a cows' milk whey hydrolysate diet, though in the absence of a control group on no special diet it is hard to say if this is a real benefit.
- There is some evidence to support the use of an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs in their blood.
- Methodological concerns such as poor concealment of randomisation allocation, lack of blinding and high drop-out rates without an intention-to-treat analysis suggest that the above studies should be interpreted with great caution.
- Future studies should be longer term, more pragmatic and ensure that randomisation is concealed.
- If participant blinding is not possible, objective outcomes such as photographic records viewed by independent blinded observers should be used.

Apart from elimination diets for the treatment of established atopic eczema, uncontrolled elimination diets followed by double-blind placebo-controlled food challenges with foods suspected to aggravate symptoms have also been tried in atopic eczema.[365–369] Although such blind challenges have sometimes been performed in random sequence, they are not the same as RCTs of food elimination. Instead they try to answer the question: 'Does food X make a particular child's atopic eczema worse?' The precise relationship between such food challenge studies and long-term benefits of exclusion of those suspected foods to atopic eczema sufferers is not clear. Up to 63% of selected children with atopic eczema exhibit one or more reactions (mainly in the skin) to foods in double-blind placebo-controlled challenges,[370] though such reactions are lost after 1–2 years in 26–66% of patients.[371] Blood and skin-prick tests are usually only helpful in predicting clinical response if they

are negative.[372,373] It should also be borne in mind that this high negative predictive value has only been shown in relation to provocation of symptoms after double-blind challenge and not clinical response following food elimination, which are not necessarily the same thing. The relationship between atopic eczema and 'food sensitivity', which is subdivided into food hypersensitivity, food intolerance and allergic adverse reactions to foods (immunologically mediated), is a complex one and readers are referred to a clear evidence-based work by David[374] for further information.

Supplementation with essential fatty acids

Polyunsaturated fatty acids are essential components of all cell membranes. There are two families of such essential fatty acids: *n*-6 (e.g. linoleic and arachadonic acid) and *n*-3 (e.g. eicosapentanoic acid). Some of these substances are precursors of a group of substances called eicosanoids, which may play an important part in the inflammatory and immunological processes of atopic eczema. Alterations in linoleic acid metabolism have been demonstrated in some patients with atopic eczema, suggesting that a defect in the enzymatic conversion of this essential fatty acid by δ-6-desaturase might be responsible for defects in the lipid barrier of the skin, a decreased postnatal maturation of T-lymphocytes, and the decreased production of anti-inflammatory metabolites in the skin. These observations are the rationale for dietary supplementation with essential fatty acids in atopic eczema. Such supplementation includes evening primrose oil, containing 8–10% gamma-linoleic acid (GLA), and more recently borage oil (containing at least 23% GLA). Topical use of evening primrose oil has also been tried. Fish oils are particularly rich in *n*-3 fatty acids, and it has been suggested that these may compete with *n*-6 fatty acids in a way that might reduce the inflammatory components of atopic eczema.

We located five RCTs of oral borage oil supplementation,[246–250] four RCTs of fish oil supplementation,[251–254] four RCTs of topical evening primrose oil,[232–234,241] two of which repeated the same study,[233,234] and ten published RCTs of oral evening primrose oil[235–240,242–245] (including one study published twice[242,245]) for the treatment of atopic eczema, and these are described in *Tables 20–29*, respectively.

Comment

Other and ongoing systematic reviews

A previous meta-analysis of nine placebo-controlled RCTs of evening primrose oil in 1989 conducted by the manufacturers concluded that evening primrose oil had a modest beneficial effect.[375] They included seven small unpublished studies, and these have not been made available within the public domain for others to evaluate their results and quality. They excluded the largest study by Bamford and colleagues[240] in their main analysis as they implied that the investigators had allowed the active and placebo capsules to become mixed up on the basis of a subsequent blood analysis conducted within the company. These allegations have been denied by Bamford (Bamford J, personal written communication, 1996), and it is difficult to see how such a mix up could have occurred given that this was one of the best-quality reported studies with several measures in place to ensure concealment of allocation.

A further meta-analysis of 20 published and unpublished RCTs of evening primrose oil has been conducted by two of the authors of the current report[376] in 1997 for the Department of Health, but permission to publish the data has not been granted.

There is currently an ongoing, more detailed systematic review of oral GLA supplementation being conducted by one of the authors within the Cochrane Skin Group, which hopes to publish its findings later this year. Pooling has therefore not been attempted in this scoping review. It is reasonable to consider pooling borage oil with evening primrose oil studies on the basis that the purported active agent is GLA.

Borage oils

Only one large well-reported RCT has evaluated borage oil in atopic eczema,[249] and that study found no overall benefit or hint of benefit when the two main groups were compared. However, a subgroup analysis (proportion unspecified) of the best complying patients and those with changes in blood tests, suggested that there could be a benefit in this subgroup. The authors were rightly cautious in interpreting these *post hoc* findings, and in the absence of more detailed analyses, it is difficult to say how much of the positive effect was due to taking the capsules in the required dose and how much was due to the blood test changes. It is difficult to generalise from the subgroup data without knowing more about the poor compliance of some patients, as that itself may be a useful outcome measure of the pragmatic usefulness of the intervention. The subgroup analysis does however call for an RCT of people who are able to demonstrate an increase in GLA metabolites in the blood as an entry criterion. The four remaining

RCTs were quite small, with two[246–248] suggesting an improvement, and two[247–250] suggesting none.

Fish oils

The two smaller RCTs of fish oils suggest some possible benefit in atopic eczema, and the magnitude of relative benefit was very large in the Gimenez-Arnau and colleagues study[253] (though baseline data were not given). The largest and best reported independent study by Soyland and colleagues[252] did not show any hint of difference in benefit between fish oils and placebo.

Topical evening primrose oil

The pilot study of 12 patients by Anstey and colleagues[241] suggested a possible benefit of topical evening primrose oil for patient-assessed changes but not physician-assessed benefit. The success of blinding in that study is suspect as topical evening primrose oil is known to produce an odour on contact with the skin,[377] and the placebo cream was different from the composition of the vehicle used with the active agent. The second study, which compared three increasing doses of GLA with placebo[234] did not show any hint of a dose-response effect, but the sample size in each group was very small. The two studies of skin barrier function described by Gehring and colleagues[232] do not provide any evidence of a useful clinical benefit for topical evening primrose oil above vehicle control at the end of the 4-week treatment period, regardless of the formulation.

Oral evening primrose oil

The two largest[240,243] and best-reported studies did not show any evidence of benefit for evening primrose oil in atopic eczema. The remaining moderate-sized (between 50 and 100 patients) studies show conflicting results,[235,237,238,245] ranging from no hint of improvement[235] to a definite modest 10–20% benefit for some outcome measures when compared with placebo. The three small studies all suggest a benefit to evening primrose oil.

Pyridoxine

Pyridoxine (vitamin B_6) is an essential water-soluble vitamin and is a core factor in many of the body's chemical pathways. Based on an earlier double-blind placebo-controlled study published in abstract form only,[378] a larger and fully reported RCT was conducted by Mabin and colleagues[255] of pyridoxine versus placebo in the treatment of atopic eczema in children with moderate-to-severe disease.

Benefits

Forty-one of the 48 children in this parallel-group RCT study were evaluable at 4 weeks. Median skin severity score increased from 92.3 at the beginning of the trial of the pyridoxine group to 109.0 at the end of the 4-week period. In the placebo group, the median skin severity score fell from 125.5 to 77.0 at the end of the treatment period. The difference between the median change in skin scores was 29.2 (95% CIs ranging from a benefit of pyridoxine of 19.5 to a benefit of placebo of +85.0). There was no statistical difference for skin severity score, daytime itch or nocturnal itch score. With regard to parental observation, 16% in both groups felt that overall the skin was better ($p = 0.95$).

Harms

No serious adverse effects were described in the study, though one child developed a non-specific erythematous rash while taking pyridoxine, and another taking placebo was reported to be much more itchy than usual.

Comment

This was a well-reported study with method of randomisation and allocation concealment and blinding clearly described. No intention-to-treat analysis was performed and no adjustment of the different baseline scores was made. Some of the significant improvement of the placebo group could partly be due to a regression to the mean phenomenon. The study did not provide any evidence to support any benefit of pyridoxine in the treatment of atopic eczema despite the earlier favourable report.

Vitamin E and multivitamins

Three very different RCTs[256–258] have evaluated vitamin supplementation in atopic eczema. The first was an RCT reported by Czeizel and Dobo in 1994 of the Hungarian optimal family planning programme study looking at the effect of multivitamin supplementation around the time of conception and afterwards on postnatal development compared with the use of a tablet containing trace elements.[256] The other RCT[257] was conducted to evaluate the possible benefit of supplementation with selenium and vitamin E compared with placebo in adults with atopic eczema. The rationale for this second trial was that reduced concentrations of selenium had been observed in whole blood of patients with atopic dermatitis. The final RCT was a study in Japan of vitamin E in combination with vitamin B_2 compared with each vitamin separately.[258]

Benefits

In the Czeizel study, data were available on 4122 pregnancies that ended in a live birth. Of these, 2090 were randomised to the 'active' multivitamin supplementation, compared with 2032 in the trace element supplementation group. A whole range of postnatal development factors were collected in the study, including a physical examination and study of medical records in 90% of the evaluated infants. At the end of the 17-month period, there were no significant differences in the occurrence of chronic diseases between the two groups, with the exception of atopic dermatitis and wheezy bronchitis. Fifteen out of 2090 receiving multivitamin supplementation had developed atopic eczema (four had a parent with atopic dermatitis) compared with four out of 2032 receiving trace element supplementation (none of these children's parents had atopic disease). The authors suggested that these unexpected findings may be a chance effect.

In the Fairris and colleagues study,[257] 60 adults with atopic eczema were randomised in a 12-week double-blind study to three groups taking either 600 μg of selenium alone, 600 μg of selenium plus 600 IU of vitamin E or a placebo. Using a severity assessment based on several skin signs at several body sites, mean severity score fell from 21.0 to 13.7 in the selenium only group, from 21.8 at baseline to 15.3 in the selenium plus vitamin E group, and from 20.4 to 14.5 in the placebo group. None of these differences were statistically significant. There was, however, a significant increase in concentration of selenium in whole blood of those taking selenium.

In the Hakakawa and Ogino study[258] 59 participants with mild-to-moderate atopic eczema of the dry type were randomised to vitamin E (d-α-tocopherol) 100 mg plus vitamin B_2 (riboflavin butyrate 20 mg), or vitamin E 100 mg or vitamin B_2 alone for 4 weeks. Of the 49 evaluable participants, response as measured by physician-assessed overall usefulness and global rating, was greater in the combination vitamin group than in the single vitamin group.

Harms

The Hungarian study,[256] in a sense, has detected a possible unwanted harm of an increase of allergic diseases in those given multivitamin supplements in early pregnancy. No adverse effects were reported in the studies of selenium and vitamin supplementation.

Comment

Although the Hungarian study is not really a therapeutic trial of an intervention in atopic eczema, it is nevertheless a large RCT that has found a statistical significant increase in atopic eczema and in wheezy bronchitis and asthma in those receiving multivitamin supplementation compared with trace element supplementation. The numbers of patients in these groups are very small and the results therefore may probably be due to chance. Nevertheless, these findings should be examined in other independent randomised birth cohort studies.

The study of selenium and vitamin E,[257] while small, probably excluded moderate-to-large treatment effects. A method of randomisation was described (unusual for such an early study), though no intention-to-treat analysis was performed.

The short Japanese study[258] on the use of combination of vitamin E and B_2 is difficult to interpret in the absence of a placebo-controlled study of either compound. The validity of the study is also threatened by difficulties in blinding and *post hoc* subgroup analysis of dry skin subtypes at different time intervals.

Zinc supplementation

Oral supplements of zinc salts have become popular remedies for a range of unrelated medical disorders. They have been specifically recommended for the treatment of atopic eczema possibly because skin lesions are an important feature of zinc deficiency. One RCT conducted by Ewing and colleagues in 1991[259] evaluated the possible benefit of oral zinc sulphate at a dose of 185.4 mg/day versus placebo in 15 children with atopic eczema aged 1–16 years for a total of 8 weeks.

Benefits

At the end of the 8-week period, the mean combined disease severity score increased from 36.1 at baseline to 48.7 in the zinc group compared with a change from 34.6 at baseline to 39.3 in the placebo group. Erythema score, surface area score and use of steroids, emollients and antihistamines were also almost identical in both groups and none were statistically significantly different.

Harms

No adverse effects were reported in this small RCT.

Comment

Despite the usual reservations on lack of description of the randomisation process and no intention-to-treat analysis, this small RCT illustrates the importance of an unbiased comparison of possible treatment benefits when compared with earlier

enthusiastic claims of benefit. Even though the trial was quite small, the complete lack of treatment benefit along with small standard errors, argues against missing any moderate-to-large treatment effects.

Summary of dietary interventions

Essential fatty acid supplementation

- The largest and best-reported study on the use of borage oil supplementation in atopic eczema did not suggest any overall benefit compared with placebo.
- That study did suggest that a further RCT in those who are able to take high doses consistently and who have demonstrable changes in a blood test might be justified.
- The largest and best-reported study on fish oil supplementation in atopic eczema did not show any benefit above placebo.
- There is no good RCT evidence to support the use of topical evening primrose in atopic eczema, though it has never been put to the test in a large RCT.
- The nine published RCTs that have evaluated the use of oral evening primrose oil have shown conflicting results.
- The two largest and well-reported studies of evening primrose oil do not show any benefit over placebo.
- The RCTs of GLA (evening primrose oil and borage oil) are the subject of an ongoing Cochrane Skin Group systematic review due to report later in 2000.

Pyridoxine

- One well-supported RCT does not support any benefit of pyridoxine in the management of a child with atopic eczema.

Vitamin E and multivitamins

- One large randomised trial of multivitamin supplementation in early pregnancy has suggested an unexpected increase in atopic dermatitis in children born to mothers randomised to multivitamins compared with trace elements. Although this is probably a chance finding, it needs to be looked at specifically in other similar cohort intervention studies.
- One small trial of selenium and vitamin E supplementation in adults with atopic eczema failed to provide any evidence of a beneficial effect on clinical disease activity.
- A Japanese study of short duration found that vitamin E in combination with vitamin B_2 was more effective than either vitamin alone in the treatment of dry eczematous skin. The clinical significance of these results is difficult to interpret in the absence of a placebo.

Zinc supplementation

- One RCT has failed to show any benefit of zinc supplementation in atopic eczema.

TABLE 19 *Studies of elimination diets in the treatment of those with established atopic eczema*

Study	Interventions (co-treatments)	Study population and sample size	Trial design description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Atherton *et al.*, 1978[230] England	Egg and cows' milk exclusion diet (with soya milk substitution) vs control diet with egg and cows' milk (hydrocortisone, emollients and antihistamines)	36 children aged 2–8 years attending a dermatology clinic with clinically typical atopic eczema	Crossover design that examined three 4-week periods; during the first and third periods, patients were placed on an egg and mill elimination diet and randomly allocated to a soy-based preparation or one containing egg and cows' milk	Eczema area and activity using an unpublished composite score, degree of adherence to diet and skin-prick tests	Of 20 children who completed the trial, 13 showed an improvement during the trial diet period, six showed no change and one showed deterioration On control diet period, three showed improvement, 11 no change and six deteriorated Itch was not statistically significant between the two groups	Method of randomisation and concealment unclear Study described as double-blind, though some unblinding of parents cannot be excluded No ITT analysis and high (44%) drop-out rate	Marked order effect i.e. improvements greater at end of first vs second period whatever the diet content Soya milk (which itself can be allergenic in atopic eczema) used as 'control' food
Munkvad *et al.*, 1984[229] Denmark	Elemental diet (amino acids, essential fatty acids, glucose, trace elements, sorbic acid and vitamins) vs a blended diluted diet of foodstuffs consumed by hospital inpatients (emollients, a topical steroid and antihistamines)	33 adults with atopic eczema covering more than 10% of the body, 13 of whom had a history of intolerance to one or more food elements	Parallel group RCT of hospitalised patients on diets for 3 weeks	Various unpublished extent and intensity signs scored between –3 and +3, photographs before and after, patient itch and sleep, and various serum markers of inflammation A 'major activity' score of > 100 was defined as the criterion for a positive response to treatment	Of 25 evaluable patients, five out of 16 improved on the elemental diet compared with four out of nine on the placebo diet (NS) Itch, sleeplessness, antihistamine use and immunological tests were no different between the two groups	Method of randomisation and concealment unclear Unclear if the reported 'double-blinding' was successful in view of the different composition of the two diets. No ITT analysis with a 24% drop-out rate	History of food intolerance in patients not confirmed during study Small study of an intervention that is unpalatable, impractical and requires hospitalisation and dietetic input
Cant *et al.*, 1986[228] England	Exclusion of egg and cows' milk (with soya substitute) in mothers of infants with atopic eczema who were exclusively breastfeeding vs inclusion of egg and milk (topical steroids and emollients)	19 mothers and babies with established atopic eczema	12-week crossover study divided into three 4-week periods; during first two periods, mothers excluded cows' milk, egg and other foods from their diet and were randomised in first or second period for milk substitutes containing cows' milk and egg or soya Normal diet in third period	Combined area/intensity score (unpublished) with a max. score of 60	Of 17 mothers completing the study, the activity scores decreased by 20% in four babies on soya and one on egg and milk No statistically different mean scores between the two groups Marked period effect in that children of mothers on normal diet in third period continued to improve	Method randomisation described Concealment of allocation unclear Study described as double-blind, though almost half mothers correctly identified substitutes ITT analysis was attempted	Well reported, though very small study conducted alongside a before and after study Soya used as control diet

continued

TABLE 19 contd *Studies of elimination diets in the treatment of those with established atopic eczema*

Study	Interventions (co-treatments)	Study population and sample size	Trial design description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Neild *et al.*, 1986[226] England	Egg- and cows' milk-free diet (using soya as substitute) vs normal diet (topical steroids and antihistamines)	53 unselected atopic eczema outpatients aged 1–23 years	Crossover trial with three 6-week periods; during first and third periods, patients were placed on an egg and cows' milk exclusion diet and randomised to either soya or a milk containing egg and cows' milk	Patient reported itch and sleep loss, use of co-treatments, composite score of area and intensity and skin-prick tests	Of 40 evaluable patients, there was little difference for change in score (area, itch co-treatment use) between the treatment periods and none were statistically significant	Method of randomisation and concealment of allocation unclear Study reported as 'double-blind', though test substances might have tasted differently No ITT analysis and high (25%) drop-out rate	High drop-out rate due to diet too difficult to adhere to Unclear if there was a period or carry-over effect CIs suggested that if anything, patients did worse on the exclusion vs normal diet
Mabin *et al.*, 1995[227] England	Children allocated to three groups: i) few foods diet (eliminating all but five to eight foods) plus whey hydrolysate; ii) few foods diet plus casein hydrolysate; or iii) remain on usual diet (antihistamines and topical steroids)	85 children (median age 2.3 years) with atopic eczema which persisted despite conventional treatment and involving more than 12% of body Breast-fed children were excluded	Parallel single-blind RCT with follow-up until 6 weeks	Skin severity score incorporating extent and severity, and parental record of itch, sleep loss and global improvement	Of 46 evaluable patients, 16 (73%) of the 22 controls and 15 (58%) of the 24 who received diet showed a greater than 20% improvement in skin severity score Improvement in skin severity score in controls and daytime itch score in the whey hydrolysate group was statistically significantly in the 12 statistical out-come comparisons made	Method of randomisation clearly described Concealment of allocation unclear Study described as investigator-blind No ITT analysis and very high drop-out rate (46%)	Good description of patient flow and interventions 35 out of 39 drop-outs were in the diet group, illustrating the difficulty of adopting the few foods diet in even a motivated hospital group No evidence to support benefit from diet and some evidence suggesting that control diet was better
Isolauri *et al.*, 1995[231] Finland	Children with atopic eczema allocated to whey hydrolysate vs an amino-acid derived formula containing no peptides	45 children who were not being breast-fed, who had been fed substitute cows' milk for at least 6 months and who showed a positive reaction to a masked challenge with cows' milk	Parallel prospective randomised study drawing patients from an initial study to determine cows' milk allergy Children were followed-up for 8 months	Atopic eczema severity (extent, intensity of signs and symptoms) measured by the SCORAD system Infants' growth was also measured	Weight gain and infant length was statistically less in the whey hydrolysate group Eczema severity decreased from a SCORAD of 17 to 5 in 22 children on whey hydrolysate compared with a baseline of 21 to final score of 4 at 8 months in the amino acid group	Method and concealment of randomisation allocation unclear Randomised part of the study probably not blinded No drop-outs	Highly selected population Study mainly concerned comparison of growth in amino-acid vs hydrolysate formulae Main statistical comparison of change in eczema severity between the two groups not reported in results, though children in amino acid group had higher baseline score

continued

TABLE 19 contd *Studies of elimination diets in the treatment of those with established atopic eczema*

Study	Interventions (co-treatments)	Study population and sample size	Trial design description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Majamaa & Isolauri, 1997[224] Finland	Cows' milk elimination (extensively hydrolysed whey formula) with and without a probiotic (Lactobacillus GG)	27 infants with clinical history suggestive of cows' milk allergy who were confirmed as being sensitive to cows' milk by double-blind placebo-controlled challenge 19% of the children also had gastrointestinal symptoms	Parallel randomised prospective study monitored for 1 month	Atopic eczema severity measured by SCORAD No *a priori* statement of minimum clinically significant benefit	Of 27 evaluable children, the median SCORAD at baseline was 21 and 26 in the whey alone vs whey plus probiotic groups, respectively; these decreased to 19 and 15, respectively, at the end of 1 month	Method and concealment of randomisation allocation unclear No blinding reported No drop-outs	Authors report statistical significance for the change in score from baseline to the end of the study separately for each intervention, but do not test the difference between the two treatments Regression to the mean could have accounted for the greater improvement in the probiotic group
Lever *et al.*, 1998[225] Scotland	Egg exclusion diet for young children as advised by a dietician vs general advice from a dietician only (mild-to-moderate topical steroids and emollients)	62 children all with positive IgE blood antibodies to egg, only seven of which had a history suggestive of egg allergy	Parallel randomised prospective study of 4 weeks' duration	Eczema severity as assessed by extent in % terms and a composite severity score in 16 body sites	Of 55 evaluable children, the area involved by eczema reduced from 19.6% to 10.9% in egg-free group compared with 21.9% to 18.9% in control group ($p = 0.02$) Severity score reduced from 33.9 to 24.0 in the egg-free group compared with 36.7 to 33.5 in the control group ($p = 0.04$)	Method of randomisation unclear Randomisation performed by same dietician who was giving the intervention Parents unblinded; assessor reported as blinded No ITT analysis Co-treatment use not reported	Study suggested that egg-free diet in those with a positive RAST test to egg may be useful Methodological concerns such as lack of randomisation concealment and increased motivation and ancillary care in intervention group could have resulted in bias

RAST, Radio-allergosorbent test

TABLE 20 *Design, patient characteristics and interventions of included studies: borage oils*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawls and drop-outs
Bahmer & Schafer, 1992[246]	Parallel, RCT	12	20–48	4 months	Mean ADASI score in borage and palm oil 1.63 and 1.89, respectively	Borage oil, two capsules containing 500 mg t.d.s.	Palm oil in similar dose	Unclear	Unclear
Borrek *et al.*, 1997[247]	Crossover, RCT	24	3–17	14 weeks	Chronic eczema	Borage oil	Corn seed oil	Antihistamines, corticosteroids	Two
Buslau & Thaci, 1996[248]	RCT	50		12 weeks	Mild to moderate	2 x 1 g borage oil	Placebo 2 x 1 g palm oil	Emollients	18
Henz *et al.*, 1999[249]	Parallel, RCT	160	14–65	24 weeks	Relatively stable and moderate	Borage oil, 500 mg three capsules daily	Miglyol lipid as placebo three capsules daily	Topical diflucortolone-21 valerate	19 placebo drop-outs, 17 borage oil
Valsecchi *et al.*, 1996[250]	Parallel, RCT	31	2–11 15–38	14 weeks	*	Borage oil, 500 mg capsule containing 80 mg GLA + linoleic acid + small amounts of palmintic acid, oleic and stearic acids	Placebo (liquid paraffin)	Unlimited emollient	One placebo, two borage oil

* *No data given*
ADASI,jAtopic Dermatitis Area Severity Index

TABLE 21 *Design, patient characteristics and interventions of included studies: fish oils*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawls and drop-outs
Bjornboe *et al.*, 1987[251]	Parallel, RCT	31	16–56	12 weeks	Unclear	Max-Epa fish oil (*n*-3) ten capsules daily	Olive oil	Topical steroids	Eight
Gimenez-Arnau *et al.*, 1997[253]	Parallel	48	Mean age 24.2	12 weeks	Chronic and severe	Eicosapentaenoic acid + docosahexaenoic acid (fish oil) vs linoleic acid (vegetable oil)	Placebo (oleic acid)	No other treatment permitted	*
Soyland *et al.*, 1994[252]	Parallel, RCT	145	18–64	4 months	Moderate to severe	Six capsules daily fish oil	Corn oil as placebo	Antihistamines, hydrocortisone, emollients	*

* *No data given*

TABLE 22 *Design, patient characteristics and interventions of included studies: evening primrose oil – topicals*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawls and drop-outs
Anstey *et al.*, 1990[241]	RCT, within person right/left arm parallel	12	4–46	14 days	Typical mild to moderate	Evening primrose oil cream in a water in oil emulsion	E45 cream™	'Usual topical treatments outside test areas'	One
Ferreira *et al.*, 1998[234]	Parallel, RCT	23	3–15	4 months	In remission	Emollients containing 10% GLA vs borage oil (24% GLA) vs rose hip oil (35–40% GLA)	Atoderm™ emollient without essential fatty acids	None	Two
Gehring *et al.*, 1999[232]	Two within-person right/left forearm parallel studies	20 in each study	19–42	4 weeks	Atopy score of 10 or over	Study 1: Evening primrose in an amphiphilic oil in water emulsion Study 2: Evening primrose oil in a water-in-oil emulsion	Study 1: Vehicle was 20% miglyol Study 2: Vehicle was liquid paraffin	None mentioned	One

E45 cream™, Crooke, UK
Atoderm™, not available in the UK

TABLE 23 *Design, patient characteristics and interventions of included studies: evening primrose oil – orals*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawls and drop-outs
Bamford *et al.*, 1985[240]	Crossover, RCT	154	2–16 16–66	3 months	Active and using a topical steroid	< 15 years 2–4 capsules evening primrose oil b.d. > 15 years 6–8 capsules evening primrose oil b.d.	500 mg liquid paraffin and 10 IU of vitamin E	Emollients, topical steroids, oral antihistamines	31 drop-outs: 14 evening primrose oil, 17 placebo
Berth-Jones & Grahan-Brown, 1993[243]	Parallel, RCT	133	7–12 13–60	16 weeks	*	Epogam™ 500 mg (containing GLA) vs Efamol™ 107 mg (contains fish oil)	Placebo (olive oil)	Topical steroids, emollients, antihistamines	21 drop-outs
Biagi *et al.*, 1994[237]	Parallel, RCT	51	2.2–8.5	8 weeks	*	High-dose evening primrose oil 0.5 g/kg/day Low-dose evening primrose oil 50% mix 0.5 g/kg/day + placebo capsules	Placebo olive oil = 10 mg vitamin E	Weak topical steroids, emollients	Three drop-outs

continued

TABLE 23 contd *Design, patient characteristics and interventions of included studies: evening primrose oil – orals*

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawls and drop-outs
Bordoni *et al.*, 1987[239]	Parallel, RCT	24	2–4	4 weeks	*	Efamol, 0.5 g/day	Olive oil placebo	Weak steroids, emollients	Not mentioned
Hederos & Berg, 1996[235]	Parallel	60	1–16	16 weeks	Need regular topical steroids	Epogam, 500 mg evening primrose oil, 40 mg gamma-linolenic acid, 10 mg Vitamin E	Placebo 500 mg sunflower + 10 mg vitamin E	Usual treatment allowed, steroid/antihistamines	Two from evening primrose oil group
Humphreys *et al.*, 1994[238]	Parallel	58	Adults	16 weeks	Moderately severe	Evening primrose oil 500 mg + vitamin E 10 mg 12 x daily	Liquid paraffin 300 mg with 10 mg vitamin E	Topical steroids	Six: four placebo and two active
Lovell *et al.*, 1981[244]	Crossover	32	1.5–13 14–32	3 weeks each	Atopic eczema for at least 6 months	Efamol, (500 mg evening primrose oil + 45 mg gamma-linolenic acid) Adults – four capsules b.d., Children – two capsules b.d.	Liquid paraffin	Mild topical steroids	Not mentioned
Schalin-Karrila *et al.*, 1987[236]	Parallel, RCT	25	19–31	12 weeks	Moderate to severe	Evening primrose oil (360 mg linoleic acid, 50 mg oleic acid, 45 mg gamma-linolenic acid) four capsules b.d.	Placebo 500 g liquid paraffin	Emollient, oral antihistamines, mild topical steroids	One evening primrose oil; not mentioned in placebo group
Wright & Burton, 1982[242]	Crossover	99	0.8–11 15–58	12 weeks	Moderate to severe	Efamol (360 mg linoleic acid, 45 mg gamma-linolenic acid divided into three different doses for adults and two different doses for children)	Placebo 500 mg liquid paraffin	Mild topical steroids, emollients, oral antihistamines	16 adults, three children

Efamol™, Scotin, UK
Epogam™, Searle, UK

TABLE 24 *Outcome measures signs and symptoms: borage oil*

Study	Erythema	Purulence	Excoriation	Dryness	Xerosis	Scaling	Lichenification	Cracking	Fissuring	Exudation	Vesiculation	Pustules/papules	Oozing/weeping	Oedema	Inflammation	Crusts	Infiltration	Induration	Patient itch	Doctor itch	Sleep loss	Physician global severity assesssment	Patient global severity assessment	Area assessment (method used)	Scale named (if modified specify)
Bahmer & Schafer, 1992[246]																									
Borrek *et al.*, 1997[247]	●		●			●	●				●	●		●		●				●	●			Multiple area	Costa
Buslau & Thaci, 1996[248]	●					●	●						●						●						
Henz *et al.*, 1999[249]	●		●			●	●				●	●		●		●				●	●			Multiple area	Costa
Valsecchi *et al.*, 1996[250]	●		●			●	●				●	●								●				●	

Note:
Additional outcomes: Henz et al.,[249] *also pigmentation/depigmentation and amount of topical steroid; Borrek* et al.,[247] *also pigmentation; Buslau & Thaci*[248] *also inflammation*

TABLE 25 *Outcome measures signs and symptoms: fish oils*

Study	Erythema	Purulence	Excoriation	Dryness	Xerosis	Scaling	Lichenification	Cracking	Fissuring	Exudation	Vesiculation	Pustules/papules	Oozing/weeping	Oedema	Inflammation	Crusts	Infiltration	Induration	Patient itch	Doctor itch	Sleep loss	Physician global severity assesssment	Patient global severity assessment	Area assessment (method used)	Scale named (if modified specify)
Bjornboe *et al.*, 1987[251]	●		●			●	●						●						●					●	
Gimenez-Arnau *et al.*, 1998[253]																				●				RoNAA	Ra jka
Soyland *et al.*, 1994[252]	●			●		●	●											●	●	●					

Note:
Additional outcomes: Bjornboe et al.,[251] *also visibility and severity; Soyland* et al.,[252] *also effect on daily living; Gimenez-Arnau* et al.,[253] *also disease extension and course of eczema*

TABLE 26 *Outcome measures signs and symptoms: evening primrose oil*

Study	Erythema	Purulence	Excoriation	Dryness	Xerosis	Scaling	Lichenification	Cracking	Fissuring	Exudation	Vesiculation	Pustules/papules	Oozing/weeping	Oedema	Inflammation	Crusts	Infiltration	Induration	Patient itch	Doctor itch	Sleep loss	Physician global severity assesssment	Patient global severity assessment	Area assessment (method used)	Scale named (if modified specify)
Topicals																									
Anstey *et al.*, 1990[241]	●			●		●	●										●		●			●	●		
Ferreira *et al.*, 1998[234]					●															●					
Gehring *et al.*, 1999[232*]																									
Orals																									
Bamford *et al.*, 1985[240]	●		●			●	●						●						●					●	
Berth-Jones & Graham-Brown, 1993[243]	●		●	●		●	●	●			●			●		●				●	●		●	RoNAA	Leicester/ Costa
Biagi *et al.*, 1994[237]	●		●			●	●				●	●		●		●									
Bordoni *et al.*, 1987[239]	●		●			●	●				●			●		●				●	●				
Hederos & Berg, 1996[235]	●		●	●		●	●									●				●	●	●			
Humphreys *et al.*, 1994	●					●	●													●		●	●		
Lovell *et al.*, 1981[244]	No data available																								
Schalin-Karrila *et al.*, 1987[236]				●											●					●		●		●	
Wright & Burton, 1982[242]	●					●														●		●	●		

Note:
Additional outcomes: Bamford et al.,[240] *also physician-assessed visibility and severity, patient-assessed flakiness, visibility, severity, effect on daily living, discomfort with appearance, appetite and stress; Berth-Jones & Graham-Brown,*[243] *also pigmentation; Biagi* et al.,[237] *also evidence of infection, pigmentation and extent; Bordoni* et al.,[239] *also pigmentation; Hederos & Berg,*[235] *also fidget; Humphreys* et al.,[238] *also surface damage*

[*]*The Gehring* et al., *1999*[232] *study only evaluated objective laboratory measures of skin barrier function including transepidermal water loss, skin hydration and irritation after sodium lauryl sulphate provocation*

TABLE 27 *Results: borage oils*

Study	Main reported results	Authors' conclusions	Quality/comment
Bahmer & Schafer, 1992[246]	Using within-patient change in ADASI score, five out of seven patients treated with borage oil showed a favourable effect compared with one out of five treated with palm oil	Positive effect of borage oil in atopic eczema warrants a larger study	Pilot study awaiting full translation. Novel use of time-series data to analyse within-patient changes in ADASI score
Borrek *et al.*, 1997[247]	After 10–14 weeks of treatment there was no improvement of the eczema under active compared with placebo. Both groups showed improvement while taking placebo. This result could be seen in the objective investigations (Costa score, three times per treatment period) as well as in the daily patients documentation. The patients whose eczema has improved under borage oil (n = 10) had no special characteristics, so that authors could not identify any responder-type	There was no improvement of the eczema under borage oil group compared with placebo	Small study, which showed no difference between active drug and placebo. Awaiting translation for methodological quality
Buslau & Thaci, 1996[248]	Of the 32 evaluable patients, 14 out of 18 patients (78%) in the borage oil group compared with six out of 14 (43%) patients in the palm oil group showed a significant improvement in ADASI score compared with baseline	Borage oil showed good effects on the course of mild-to-moderate atopic eczema	Awaiting full translation. No ITT analysis carried out and large drop-outs. Unclear what a 'significant improvement' meant to patients in terms of magnitude of response
Henz *et al.*, 1999[249]	The reduction in Costa score points was similar in the placebo- and borage oil-treated groups, though improvement of individual symptoms over placebo was observed for erythema, vesiculation, crusting, excoriation, lichenification, and insomnia, but not for pruritus (no data given). No statistically significant differences were noted between the two treatment groups regarding the primary efficacy criterion 'corticosteroid dosage until response' (p = 0.8949). Significant benefit shown in a subgroup of 'good compliers'	This study shows no overall efficacy of gamma-linolenic acid-containing borage oil in atopic eczema, with steroid use being the primary response parameter, though it suggests that a subgroup of patients may benefit from this well-tolerated treatment	Method and concealment of randomisation not stated, study described as double-blind, success of blinding not recorded. No ITT analysis. Authors state that all previous evening primrose oil studies look at 8–10% gamma-linolenic acid, whereas borage oil looked at 23% gamma-linolenic acid concentration. Significant effect shown in subgroup (*post hoc*) of best compliers and whose blood changed. No overall difference in main comparison
Valsecchi *et al.*, 1996[250]	There was no statistically significant difference (p = 0.165) between the mean reduction from baseline clinical score of the placebo (48.4) and the GLA group (70.8). Mean baseline score was higher in the GLA group at 281.0 compared with 251.3 in placebo	Dietary supplements of GLA resulted in a significant improvement in the clinical conditions of atopic eczema compared with baseline; however, a simultaneous improvement of the clinical status, compared withy baseline, was observed with placebo, and there was no significant difference between the two treatments	Method and concealment of randomisation not stated, blinding not stated, no ITT. Published as a letter only. No difference between the two groups, but study under-powered to detect modest benefits

TABLE 28 *Results: fish oils*

Study	Main reported results	Authors' conclusions	Quality/comment
Bjornboe *et al.*, 1987[251]	The total patient's symptom score showed significantly greater improvement in the experimental group compared with control group; mean change 11.3 and 1.3, respectively, baseline scores not given (p < 0.02). The physician-assessed scores showed no statistically significant difference between the groups	Results favoured the experimental group with regard to scale itch and overall subjective severity compared with the controls	Method and concealment of randomisation unclear, study described as double-blind. Eight withdrawals and drop-outs, no ITT analysis carried out. Discrepancy of outcomes between patients and physicians. Multiple outcomes
Gimenez-Arnau *et al.*, 1998[253]	Only 6-week results presented for all three groups due to high drop-out rate in vegetable oil and placebo groups. This showed a 75% reduction in median Rajka scores in the fish oil group compared with 5.3 in the placebo and 8.8 in the vegetable oil groups (p < 0.001). Baseline scores not given	Linoleic acid is useful to treat atopic eczema	Method and concealment of randomisation unclear, study described as double-blind. Very scant methods and results data. No mention of withdrawals or drop-outs
Soyland *et al.*, 1994[252]	The mean clinical score for the six parameters evaluated the physicians showed an improvement from 4.4 to 3.1 (30%, p < 0.001) in the fish oil group, and from 4.2 to 3.2 (24%, p < 0.001) in the corn oil group. No significant differences between the two groups for any outcome	There was a progressive significant improvement of the clinical condition in both groups, compared with baseline scores. However, there was no significant difference between the two groups, which causes the possibility of a placebo effect	Method and concealment of randomisation unclear, study described as double-blind. Twenty-four withdrawals/drop-outs, no ITT analysis carried out. Large study with no hint of any difference of response between the two groups

TABLE 29 *Results: evening primrose oil*

Study	Main reported results	Authors' conclusions	Quality/comment
Topicals			
Anstey *et al.*, 1990[241]	Analysis of results revealed a significant difference between the two groups in the mean absolute change in patient scores over the 14-day period (p = 0.006) and also in percentage change over 14 days (p = 0.021). In both cases the change was positive, indicating improvement in eczema and that evening primrose oil was the better cream. There were no significant differences for change in doctor's assessment	Topical evening primrose oil has potential as treatment for atopic eczema and warrants further clinical studies	Method and concealment of randomisation unclear, study described as double-blind. Marked discrepancy between patient and doctor assessment may suggest unblinding. One drop-out, no ITT analysis carried out. A very small sample over a very short time of only 2 weeks, but acknowledged as a pilot study
Ferreira *et al.*, 1998[234]	Clinical assessment of xerosis and pruritus revealed improvement in all four groups, slightly more pronounced in the three GLA groups. None of the changes statistically significant	GLA-containing emollients can be a useful improvement in the management of atopic eczema patients	Method of concealment of randomisation unclear, no mention of blinding. Two drop-outs/withdrawals, no ITT analysis carried out. To be included, eczema had to be in remission, those who had eczema flare became failures. No hint of a dose/benefit between the different concentrations of evening primrose oil
Gehring *et al.*, 1999[232]	In study 1, which compared oil-in-water evening primrose oil emulsion to vehicle, barrier function assessed in various ways improved in both groups equally. In study 2, which compared a water-in-oil evening primrose oil emulsion to a different vehicle, the authors claimed that there was evidence of a stabilising effect of the active preparation above vehicle, yet the graphs for graphs for skin hydration and transepidermal water loss and irritation potential do not suggest any clinical or statistically differences at the end of the 4-week study	That the choice of vehicle is an important factor in the efficacy of evening primrose oil	Method and concealment of randomisation not described. No ITT analysis. Described as double-blind. This study described two different studies. In study 1, an evening primrose oil-in-water emulsion was compared with vehicle in a right/left forearm comparison in 20 participants, and in study 2, an evening primrose oil water-in-oil emulsion was compared against a different vehicle in 20 different participants. The authors then make inferences about one emulsion compared against the other without any direct data to support this. The authors' conclusions are not supported by their data. The study shows the general improvement of barrier function that occurs with oil applied to the skin, but provides no evidence of efficacy of evening primrose oil above vehicle
Orals			
Bamford *et al.*, 1985[240]	No significant effect on erythema, scale, excoriation, lichenification, or overall severity in 123 patients with atopic eczema of average severity while they took oral doses of evening primrose oil (2 or 4 g in children, 6 or 8 g in adults). Actual data shown graphically in four figures	Evening primrose oil had no significant effect on the lesions of patients with a diagnosis of atopic eczema and lesions of average severity	Method and concealment of randomisation unclear, study described as double-blind. Thirty-one drop-outs, no ITT analysis carried out. Study very clearly written up, good information on how many patients were approached and how compliance was checked. Later correspondence by company accused authors of mixing up tablets
Berth-Jones & Graham-Brown, 1993[243]	At 16 weeks, the mean (SEM; no. patients) improvements in Leicester scores were 8.48 (2.85; 33) for patients on Epogam, 2.54 (2.89; 35) for patients on Efamol marine, and 7.15 (2.88; 34) for those on placebo. On neither active regimen was mean improvement significantly different from placebo at 16 weeks (p = 0.74 for Epogam, 0.26 for Efamol marine)	Our study, which avoided the methodological and analytical problems of previous studies, found no effect of essential fatty acid supplementation in atopic eczema	Method and concealment of randomisation unclear. Study described as double-blind. No ITT (21 drop-outs). Well-reported study otherwise. No improvement in evening primrose oil or Efamol marine singly or combined, similar in children and adults
Biagi *et al.*, 1994[237]	There was a trend towards improvement in the low-dose group, which approached significance (p = 0.077) and a significant improvement in the high-dose group compared with placebo (p = 0.046) for overall physician-rated severity. There were no significant changes for the symptoms of itch and for the extent of disease in the evening primrose oil group compared with placebo	The overall severity of atopic eczema improved significantly on a high dose of evening primrose oil compared with placebo, independent of whether the children had manifestations of IgE-mediated allergy	Randomisation and concealment not stated, blinding not elaborated/tested for. No ITT analysis, three drop-outs. Benefit only in higher-dose group and for one out of three main outcome measures regardless of whether children were atopic or not

continued

TABLE 29 contd *Results: evening primrose oil*

Study	Main reported results	Authors' conclusions	Quality/comment
Bordoni *et al.*, 1987[239]	After 4 weeks, the symptoms of patients treated with evening primrose oil significantly improved ($p < 0.01$), in placebo-treated children the clinical status remained largely unchanged. No summary data of magnitude of benefit given, but can be visualised in figure	Evening primrose oil substantially improved the clinical symptoms of atopic eczema in two-thirds of the treated children after 4 weeks of therapy	Method and concealment of randomisation unclear, 'doctor unaware of which patients receiving which treatment' suggests single-blind study. Drop-outs not mentioned, presume ITT analysis. Evening primrose oil suggested benefit, very short-term study. High-dose capsules for children
Hederos & Berg, 1996[235]	Both groups of patients were substantially improved with respect to baseline but no significant differences between Epogam and placebo groups were observed. The mean % improvement from baseline for patient global assessment was 10.0 and 7.1% for Epogam and placebo, respectively. The corresponding % improvement for physician-assessed global improvements were 11.0 and 13.8% for evening primrose oil and placebo, respectively	Study demonstrated significant improvements in atopic eczema during the 16 weeks' treatment, but no significant difference was found between active and placebo treatment in a group of children who need regular treatment with topical steroids	Method and concealment of randomisation unclear. Study described as double-blind. Well described study. No size differences between two groups. ITT analysis carried out, two withdrew in evening primrose oil group
Humphreys *et al.*, 1994[238]	Twenty-three out of 27 patients taking active treatment showed an improvement in their clinical score for erythema by the end of the treatment period compared with 11 out of 23 in the placebo group. The results for surface damage were very similar, 12 out of 23 in the placebo group showing an improvement in clinical score, compared with 23 out of 27 in the GLA group. No benefit for lichenification	Adjunctive treatment with gamolenic acid in evening primrose oil should be considered in patients with chronic atopic eczema	Method and concealment of randomisation unclear, blinding unclear. No ITT analysis carried out, (six drop-outs) good description of drop-outs though. Statistics well described. Well-described study but three groups a little confusing. Baseline severity very different in GLA group than placebo but this was adjusted in analysis
Lovell *et al.*, 1981[244]	Doctor assessment baseline 6.26 (±0.24) reduced to 5.27 (±0.38) after evening primrose oil and 5.64 (±0.38) after placebo. Patient assessment baseline 5.96 (±0.16) reduced to 5.02 (±0.37) after evening primrose oil and 5.54 (±0.38) after placebo	Patients receiving Efamol showed a modest but significant improvement on both the doctor's and their own assessment	Method and concealment of randomisation unclear, study described as double-blind. Clinical significance of a change in score from 5.96 to 5.02 not clear. Possibly not done correct statistical test on differences between scores
Schalin-Karrila *et al.*, 1987[236]	In the evening primrose oil group, a statistically significant improvement was observed in the overall severity and grade of inflammation ($p < 0.001$) from baseline and a significant reduction in the surface area involved as well as in dryness and itch compared with baseline ($p < 0.01$). Patients in the placebo group showed a significant reduction in inflammation compared with baseline ($p < 0.05$). Unclear if there was a comparison of change in clinical scores between the two groups	Thus in every clinical parameter the degree of improvement was significantly greater in the evening primrose oil group than in the placebo group	Random method and concealment method not mentioned, success of blinding not recorded, yet possible that placebo group could have bowel problems given they had 4 g of liquid paraffin daily. No ITT analysis (one from evening primrose oil, not mentioned in placebo group). The evening primrose oil group started off more severe. Authors concluded that evening primrose oil superior for global severity, inflammation, dryness, itch
Wright & Burton, 1982[242]	In the low-dose groups itch was the only symptom that responded better to evening primrose oil than placebo. In the high-dose groups the patient assessments showed that the evening primrose oil was significantly superior to the placebo with regard to itch ($p < 0.003$), scaling ($p < 0.002$), and general impression of severity ($p < 0.01$). The doctor assessments also showed a beneficial effect of the active treatment on the overall severity of the condition ($p < 0.002$). The other symptom scores showed the same trend but failed to reach statistical significance	Various doses of oral evening primrose oil in 99 patients with atopic eczema showed that the preparation produced a significant clinical improvement when taken in high dosage	Random method and concealment method not mentioned, success of blinding not recorded. No ITT analysis, 16 adults and three children dropped out. Only itch improved in low-dose groups whereas most improved in high-dose groups. Multiple significance tests. Published separately twice

Chapter 9

Non-pharmacological treatments

House dust mite reduction

There is strong circumstantial evidence that house dust mite antigens are an important precipitating factor for atopic eczema.[267] The presence of immune sensitisation and allergic reactivity to house dust mite in the majority of atopic eczema patients, the fact that cutaneous patch tests with house dust mite extract produces an eczematous reaction in which allergen-specific helper T-lymphocytes are found, the improvement of atopic eczema when sufferers are removed to low house dust mite environments, and the exacerbation of existing atopic eczema areas following direct application of house dust mite extract,[379] all argue for a possible role of house dust mite allergen in atopic eczema. There are many methods for attempting to reduce house dust mite levels in the home including the use of mattress and pillow covers that are impervious to house dust mites, frequent vacuum cleaning (with or without high performance filtration), and use of acaricidal sprays. It has been argued that measures such as sprays (e.g. benzyl benzoate or permethrin) which only kill mites[380] are not effective as a sole treatment because the allergenic faeces and dead mites are still present.[267]

In chapter 13 (*Treatments with no RCTs*), it is pointed out that no RCTs on house dust reduction as the sole therapy for prevention of atopic eczema could be identified. A total of five RCTs evaluating the role of house dust mite reduction in the treatment of **established** atopic eczema were identified.[260–263,267] Two further studies of changing housing environments by Sanda and colleagues[381] and Fukaya and colleagues[382] were excluded as the intervention groups were not randomised. Another two studies described as prospective randomised studies[383,384] were excluded as they did not involve any randomised therapeutic intervention comparisons.

Benefits

The first small RCT by Colloff and colleagues[262] evaluated the daily use of natamycin (a spray used to kill house dust mites) versus matched placebo spray with and without vacuum cleaning in a parallel group study for 4 months in 20 young adults with atopic eczema. They demonstrated that it was the vacuum cleaning and not the natamycin spray that had a significant impact on reducing house dust mite numbers. There was no significant clinical improvement in those who had been allocated to natamycin versus placebo. The mean symptom score (maximum score 288) in the natamycin and vacuum group changed from 55.2 at baseline to 38.6 at 4 months compared with 45.2 to 35.8 in the group with no natamycin and no daily vacuuming.

A second small, but important RCT was conducted by Tan and colleagues[263] in 1996 with duplicated publication in 1998 and again in 1999. Tan and colleagues randomised 60 patients (30 adults and 30 children) for a total of 6 months to an intensive dust mite eradication regimen comprising Gore-Tex® (Intervent, UK) bedding covers, benzyl-tannate spray to kill mites and denature their allergens, and a high filtration vacuum cleaner, or to a control group of plain cotton bedcovers, placebo spray and a standard upright vacuum cleaner with a poor filtration performance. One trained nurse applied the bedcovers and spray each week, and participants were encouraged to vacuum bedrooms daily. They showed a dramatic and very similar reduction in concentration of house dust mite major allergen (*Der p1*) in bedroom carpets in both the active and placebo treatment groups at the end of 6 months. Disease activity, as recorded in terms of surface area involvement and a composite severity score (maximum score 108) measured at one point at the end of the 6 months, reduced by a small amount in both groups, but more so in the active group. The mean reduction in scores for the active and placebo groups were 12.6 and 4.2 units, respectively. Those in the active treatment group were more severe to begin with, and so an analysis of covariance was conducted to allow for baseline scores and initial house dust mite antigen levels. This showed a mean difference of 4.2 in change of score (95% CI 1.7 to 6.7 units; $p = 0.008$) between the two treatments. Further analysis also suggested that it was changes in the mattress and carpet dust in the bedroom that mediated much of the treatment effect. Subgroup analysis suggested that only children had a clinically and statistically significant benefit, and that there was no correlation between clinical improvement and positive skin prick tests at the study outset.

Another small study in Japan by Endo and colleagues[261] evaluated the potential benefit

of intensive vacuum cleaning in the rooms of 30 children with atopic eczema for a total of 12 months. Both groups were visited every 3 weeks by a team of mite specialists who either cleaned room floors, mattresses and quilts very thoroughly and encouraged parents to clean in the same way in-between visits, versus a less intensive clean (vacuum suction power reduced to 50%) with similar cleaning in-between visits. Parents were thus unblinded to the intervention. A statistically significant decrease in mite numbers in favour of the intensive cleaning group was only noted for the room floors. Clinical scores, as evaluated by a physician blind to treatment allocation, were significantly improved in the active group compared with baseline but not in the control group. Clinical scores were given in graphical form only and the appropriate statistical test of mean difference between the two treatments was not reported.

Another unblinded RCT by Nishioka and colleagues[260] evaluated the benefit of encasing quilts and mattresses in microfine fibres versus simple cleaning measures alone in 57 Japanese infants with atopic eczema who were not allergic to house dust mite as determined by blood tests at the study outset. After 1 year, they found that 31% of children in the encasement group compared with 63% in the control group had serological evidence of house dust mite sensitivity ($p < 0.02$). The authors did not report any outcomes on atopic eczema disease activity in that paper. Correspondence with the authors suggests that there were no differences between the two groups at the end of the study for the clinical outcomes, though there was a reduction in topical corticosteroid requirement in the intervention group.

Harms

None of the studies reported any adverse events of the anti-house dust mite treatments. This does not necessarily imply that none occurred. The imposition of daily vacuuming for a long period has a cost in terms of time for parents and sufferers, as does the purchase of a high filtration vacuum cleaner, impermeable mattress covers and mite sprays.

Comment

It is a pity that so few studies on house dust mite avoidance have been performed on atopic eczema. Those that have been done tend to be small and difficult to generalise in the absence of more pragmatic studies. In none of the studies was the method of randomisation and concealment reported, and no intention-to-treat analyses were performed (though drop-outs were quite low). The validity of blinding in the Tan study in unclear due to the use of very different vacuum cleaners. It is also unclear which method of reducing house dust mites is the most efficient as studies have tended to use several measures at once. Data from the Tan and colleagues[263] study suggest that just vacuuming with an ordinary household cleaner achieves similar and massive reductions of house dust mite antigen levels in bedroom carpets to those achieved by the more expensive high filtration vacuum cleaners that are advertised in patient support group magazines. The Tan and colleagues study suggests a definite benefit for a range of intensive measures to reduce house dust mite levels around the home, but the clinical relevance of the small changes in scores observed is difficult to determine in the absence of patients' evaluations or outcome measures that capture the chronicity of disease over the entire 6-month period. The Endo and colleagues[261] study suggested some clinical benefit with frequent intensive vacuum cleaning, but this could not be related to reduction in house dust mite numbers. On the basis of the Tan study, the Endo study could be criticised for comparing two active treatments, and that a comparison of frequent vacuuming versus 'normal cleaning' would have been better given the fact that any form of active intervention for intensive or high-filtration vacuuming is difficult to blind.

Both Tan and Endo are to be commended for conducting such long-term studies. Further such studies in other populations, separating the different interventions for reducing house dust mite, are needed. It is important that such trials are as pragmatic as possible to determine which groups respond best, which interventions are the most cost-effective and whether the laborious interventions are sustainable in less-motivated people.

House dust mite hyposensitisation

Hyposensitisation refers to the technique of trying to induce an immunological and clinical tolerance to allergens that might be playing a role in allergic disease by repeated and progressive exposure to increasing amounts of allergen, as is performed for example, in hay fever desensitisation. Three RCTs that evaluated the role of desensitising atopic eczema patients to potential causative allergens were located.[264–266] Another study[385] was excluded as it was unclear whether participants were randomised.

Benefit

The first small study by Glover and Atherton[264] evaluated the use of a tyrosine-adsorbed extract of

house dust mite in 26 children with atopic eczema who were house dust mite positive on skin-prick testing. In the first part of the study, children were randomly allocated to weekly active or placebo injections for 8 months. Clinical scores improved dramatically in both groups, but there were no obvious differences between the groups. In the second part of the study, the 13 children who had been allocated active treatment in the first part of the study were offered a further 6-month period of monthly injections. The seven who accepted were then randomly allocated to receive active treatment or placebo. Redness and skin thickening scores (but not surface damage) deteriorated more in the control group and these differences were statistically significant.

Another study by Galli and colleagues[265] looked at the possible benefit of a mixture of house dust mite allergens given in an oral suspension three times weekly in children with atopic eczema who were sensitised to house dust mite. Three groups were compared, one non-randomised group of children with concurrent asthma and or rhinitis (n = 26), and two groups with exclusive atopic eczema who were randomised to oral hyposensitisation (n = 16) or no specific treatment other than 'conventional therapy' and measures to reduce house dust mite (n = 18). Comparison of change in clinical scores between the two randomised groups did not reveal a statistically significant or clinically relevant improvement in the active group.

A further study by Wen and colleagues[266] was conducted in Shanghai with allergenic extracts of house dust mite manufactured at that university. In that study, 56 patients with atopic eczema (mean age 24.8 years) were randomly allocated to weekly injections of local allergenic extract (18 patients), a partially purified extract (20 patients) and normal saline placebo (18 patients) for 1 year. Clinical scores (unspecified) were reduced in all three groups and possibly more so in the two active groups, though no statistical tests were performed. The data was presented in graphical form only.

Harms

Apart from local discomfort at injection sites (similar in each group), no adverse effects were reported in either small study. Caution is needed based on the rare but potentially life-threatening hazard of an anaphylactic reaction when desensitisation has been done with bee sting or hay fever allergy. Wen and colleagues state in their paper that allergenic extracts of house dust mite have been used for 20 years for treating and diagnosing mite allergy in China and that there have been no recorded deaths due to anaphylaxis. Weekly injections for children are also painful and require attendance at a healthcare facility.

Comment

It is possible that the lack of statistical significance in the Glover study was due to lack of power or a large placebo effect due to the injections. Improved treatment concordance and ancillary care could also explain the impressive improvements in those having placebo injections. Similarly, the lack of obvious benefit in the Galli study could be due to inadequate numbers, other concurrent treatments such as reduction in house dust mite measures, or that the oral allergen hyposensitisation therapy was inactive via the gut route. It is difficult to make any further judgement on the Wen paper due to the scant methodological details provided.

Avoidance of enzyme-enriched detergents

Detergent enzymes may cause skin irritation and occasionally hypersensitivity reactions leading some physicians to advise atopic eczema patients to avoid the use of such detergents in favour of alternative 'non-biological' detergents.[386] The authors located one RCT that tested the hypothesis that enzyme-containing detergents are more likely to aggravate atopic eczema than a non-biological detergent.[268]

Benefits

After a 1-month washout using their normal detergent, 26 adults with mild-to-moderate atopic eczema (mean age 25 years) were randomised in a double-blind crossover study to receive either a trial detergent containing enzyme concentrations reflecting the highest quantity in commercial enzyme-enriched detergents or a visually identical detergent without enzymes as control, for a 1-month period followed by a further month with the opposite detergent. Topical steroids were permitted during the study and weighed. In the 25 patients completing the trial, there was no hint of difference between the active detergent and the control in terms of SCORAD score (29 on active, 29 on control, with 95% CIs for the mean difference extending from –4 to +5 on a scale of 108), usage of topical steroid (44 g/month in active versus 43 g/month on control), patient-reported itch (1.3 versus 1.3), or patient-reported eczema activity (1.4 versus 1.4).

Harms

None of the patients had contact dermatitis to enzymes when patch tested at the end of the study,

and there was no evidence of specific blood IgE against any of the enzymes.

Comment

Although this study was small, the virtual absence of any differences between the enzyme and non-enzyme detergents and the corresponding narrow CIs provide convincing evidence of a lack of harmful effect. The study was not sponsored by industry.

Benefit from specialised clothing

Intolerance to wool is frequently reported in atopic eczema patients and has been used as a minor criterion for diagnosing this condition. We found three RCTs[269–271] evaluating clothing material in atopic eczema, two of which, by Diepgen and colleagues in 1990 and 1995,[269,270] evaluated the irritative capacity of poncho-like shirts made of four different materials (cotton versus other synthetics of different fibre structure). The other RCT by Seymour and colleagues[271] evaluated the clinical effects of different types of nappies on the skin of normal infants and infants with atopic eczema in a 26-week trial.

Benefits

In the Diepgen 1990 study,[269] 55 patients with atopic eczema were compared with 31 control patients without atopic eczema and randomised to one of four poncho-like shirts of varying fibre roughness. The intensity of itching or discomfort due to repeated wearing of these shirts was evaluated by means of a points system, whereby 10 equals a maximum comfort and 1 equals maximum discomfort. At the end of the study, those wearing cotton reported a comfort score of 8.4 compared with 7.3, 3.6 and 3.3 for the other textile shirts in increasing order of weight and fibre roughness (estimated from graph). The difference between the cotton and other fibres was significant only for the latter two groups.

The 1995 study by Diepgen and colleagues[270] (published in a German textile journal) evaluated seven different garments on 20 atopic eczema patients with mild-to-moderate disease (average age 25.3 years) with and without a 'sweat test' designed to lower the itch threshold. The garments included cotton, and polyester garments made with different fibre roughness, yarn roughness and fabric weaves. The study was a randomised crossover study (Diepgen T, personal oral communication, January 2000), with each garment worn under standardised conditions on 4 consecutive days. Comfort, as assessed on a visual analogue scale, was statistically significantly higher for warp-knits compared with jersey knits, but no different for cotton and polyester of fine fibre construction (assessed by scanning electron microscopy). Garment comfort in all groups was reduced after sweating.

In the Seymour study,[271] cloth nappies were compared with cellulose core nappies versus cellulose core nappies containing absorbent gelling material in 85 babies aged less than 20 months of age who had atopic eczema and who were recruited by an advertising campaign. Average grade of eczema on the body as well as degree of nappy rash was scored by an independent dermatologist. At the end of the 26-week period, there was no clinical or statistical difference between the different nappy types for overall grade of atopic eczema. Nappy rash, however, was significantly less in the group using cellulose nappies with absorbent gelling material, compared with the others at 26 weeks and throughout the trial ($p < 0.05$).

Harms

No adverse effects are reported in these small studies, though specialised cotton clothing for atopic eczema sufferers is more expensive than other synthetic fibres.

No specific adverse effects were reported in the trial of different nappies, though nappy rash itself (the main efficacy outcome of this study) could be considered an adverse effect, which is desirable to prevent.

Comment

The studies by Diepgen and colleagues in 1990 and 1995 tested the hypothesis that cotton clothing is best for atopic eczema sufferers. The success of blinding in both trials is under question in view of the different roughness of the various shirt fibres. Magnitude of effects were not stated in the Diepgen 1995 paper, and it is possible that the study could have missed small differences between cotton and polyester fabrics comfort. The purported need for specialised clothing can result in considerable increased economic burden to eczema families and to the State. The two RCTs both suggest that there is nothing special about cotton for atopic eczema sufferers apart from smooth fibres. Other synthetic fibres can be constructed with similar smooth fibres using yarns and fabric construction that is just as comfortable for atopic eczema sufferers. It would be wise to repeat such studies in the UK and elsewhere before implementing policy decisions, and public knowledge of the availability and cost of cotton alternatives would be an advantage to eczema sufferers.

It was good also to locate an RCT evaluating different nappy types in atopic eczema. It was unclear in this study if the group with atopic eczema simply wearing a cloth nappy were randomised in the same way as the other two groups and whether statistical comparisons were made to the control population who were not part of the same randomised group. The study, nevertheless, suggests that nappy rash is less severe in atopic infants who wear nappies with gel absorbent material, though there appears to be no benefit for the general eczema control elsewhere. There was no evidence to support any benefit of conventional disposable nappies over cloth nappies, though the study may have lacked power to demonstrate small differences.

Salt baths

Salt has been used for centuries in the treatments of skin diseases, particularly psoriasis, popularised by holidays at the Dead Sea where the combination of high salinity and ultraviolet light may benefit patients. Some physicians recommend regular salt baths as a measure for controlling atopic eczema, presumably based on anecdotal reports of patients' eczema clearing after bathing in the sea while on holidays. Salt could help atopic eczema because of its cleansing properties (saline is a weak antiseptic agent) or by drawing fluid out of oedematous acute eczematous skin. Despite its advocates, we could find no RCTs comparing the use of salt baths versus ordinary baths. One RCT (published in German) of 40 patients with psoriasis and atopic eczema evaluating synthetic Dead Sea salt baths plus phototherapy against 3% salt baths was excluded as results for the eight atopic eczema patients were not given separately.[387] We did locate one Japanese RCT comparing deep-sea salt versus physiological saline, which will be reported further here.[272]

Benefits

One-hundred patients with mild-to-severe atopic eczema aged 15 years and over were randomised to either deep-sea water or physiological saline. Both waters were sterilised and heated to 65 degrees centigrade then sprayed onto the body before home bathing and washed away after 10 minutes. Treatment was daily for 1 week. Doctor's global evaluation and several other skin signs reduced by only a small amount (~15%) in each group after 1 week, and there were no clinical or statistical differences in the change in scores between each group.

Harms

No adverse effects were reported in this study. There were five drop-outs for reasons not related to the treatment.

Comment

Quality of reporting was good in the Adachi study, but they compared two types of salt that could have been equally active. We agree with the author's conclusions that possibly a longer contact with sea water is necessary. The study duration was also very short (1 week). The uptake of an intervention that consists of spraying each other with a concentrated salt solution is also likely to be limited in the UK and possibly quite costly to patients. It is a pity that a simple RCT comparing salt baths versus ordinary baths has not been done. Even an RCT comparing the effect of regular versus irregular bathing would be informative given the different strongly held views of frequency of bathing recommendations in children with atopic eczema. One recent non-randomised study[388] from Japan has compared the benefit of sea water therapy at a beach with and without dolphins to encourage children with severe atopic eczema to enjoy the sea water. This needs to be tested further in an RCT.

Nurse education

The effective topical treatment of a child with atopic eczema is dependent upon good management by the parents. Good parental concordance can be achieved by regular follow-up visits and good patient–physician relationships, and also by active training and information given in an educational session by a nurse or other appropriate carer. One RCT[273] has evaluated the possible additional benefit of a single session provided by a nurse in educating parents of children with atopic eczema versus conventional dermatological care.

Benefits

Fifty consecutive patients aged 4 months to 6 years 2 months, with atopic eczema of varying severity were randomised to either conventional treatment by a dermatologist or the same treatment plus a single session by a nurse ('a nurse lesson'), which included general information about atopic eczema and environmental control, information and demonstration of topical treatment and also a discussion of realistic expectations. The study lasted for 3 months and was unblinded. At the end of the 3-month evaluation period, mean eczema score (maximum score 96) had fallen from 26.4 at baseline to 7.1 in the group given standard dermatological care plus education compared with 21.3 at baseline to 10.8 for conventional care alone ($p < 0.05$). This comparison was not adjusted for baseline scores, which were different. Each score also showed a statistically significant reduction in favour of the education group compared with the

standard dermatological care, and hydrocortisone consumption was significantly greater in the intervention group.

Harms
No adverse effects were reported in this study. Those patients in the intervention group had to attend one additional session with the nurse.

Comment
This RCT suggests a modest benefit from a single nurse education session following standard dermatological care. The authors are to be applauded for randomising the treatment groups, though the lack of blinding and failure to perform an intention-to-treat analysis limits the study quality. The study nevertheless suggests a modest benefit to a single session of nurse education, though the component of the 'package' of the nurse education that conferred the most benefit is unclear. It is possible for instance that most of the benefit could be due to increased and appropriate use of hydrocortisone, which tends to be underused in the community because of inappropriate fear of adverse effects. Further RCTs in other countries that use a similar educational package and blinded outcome measures are needed.

Bioresonance

Bioresonance therapy, also called biophysical information therapy (BIT) has become popular as an alternative medical treatment for a variety of allergic diseases in Europe. Bioenergy is defined as the bioelectric magnetic field which is unique to materials, and that bioelectric waves produced by people can have diagnostic and therapeutic purposes. The proponents of this theory claim that the main purpose of BIT is to give a strong impulse to spontaneous healing energies of the body for self-regulation. The ultrafine electromagnetic waves of the patient's body, as well as their disturbances and presence of allergens, are purported to be transmitted for diagnostic and therapy using brass wire electrodes analysed by a 'bioresonance apparatus'. This electronic instrument allegedly distinguishes between pathological and normal healthy waves from a patient. Pathological waves can be reversed electronically ('corrected to healthy ones') by the separator, and transmitted back to the patient for a therapeutic effect. The use of such BIT is frequently accompanied by claims of complete cure for allergies. One RCT conducted in Switzerland has evaluated the efficacy of bioresonance in children with atopic eczema.[274]

Benefits
Thirty-six children with atopic dermatitis admitted as inpatients to a high-altitude specialist treatment centre for atopic eczema in Davo, Switzerland were randomised according to sex, age and severity of disease to receive sham (placebo) or active treatment with the bioresonance apparatus. The bioresonance was conducted exactly as described in the specific literature and by a qualified BIT therapist for at least 4 weeks. Blinding was obtained by a specially designed switchbox operated by an engineer who kept its randomisation code outside the clinic in a sealed envelope. Patients were allowed their normal treatment with creams, emollients and dietary restrictions as required throughout the study. For the short-term outcome (at least 4 weeks), total disease severity score in the active group had fallen from 39.8 to 27.3 at the end of the study period compared with a fall from 35.3 to 26.6 at the end of the sham treatment ($p = 0.23$). No difference was observed for the sleep score, though pruritus score was slightly improved in the actively treated group ($p = 0.12$). There were no clinically or statistically significant differences between the two treatment groups in a number of immunological markers in the blood and long-term outcomes measured 8 months after the treatment.

Harms
No adverse effects were described in the study, though the therapy can attract a considerable financial cost outside of health services.

Comment
This study was very carefully reported and authors were meticulous in giving the bioresonance a 'fair test' by following the intervention as meticulously as possibly. The study was blinded, and randomisation and concealment of allocation were well described, though an intention-to-treat analysis was not performed (4 out of 36 children dropped out). The results do not show any evidence to support benefit of bioresonance therapy. Although the study was relatively small, the study was powered to exclude a 35% benefit of relevant treatment benefit of bioresonance therapy in the sensitive COSTA scoring method. Therefore, although small benefits cannot be excluded by the study, the study failed to show evidence of any moderate or large treatment effects of this mode of treatment. It may be argued that the treatment was tried in a situation where marked treatment benefits were already occurring as a result of inpatient stay at high altitude (with very low house dust mite levels), and ideally a similar RCT could be performed in a more usual outpatient setting.

Psychological approaches

Psychological approaches to the management of atopic eczema may be quite diverse ranging from specific cognitive approaches to behavioural approaches such as habit reversal. Psychological and emotional factors have always been considered important in atopic eczema, though it is unclear to what extent such factors are a result of the eczema rather than the other way round. It has been postulated that much of the scratching (which can be pleasurable) in atopic eczema becomes a habit, and that such habit is detrimental, as scratching damages the skin and leads to further eczema forming in the so-called scratch–itch–scratch cycle. Habit-reversal is a modified behavioural technique, which teaches patients to recognise the habit, identify situations that provoke the habit, and then to progressively train them to develop a 'competing response practice' such as simply touching, squeezing or tapping the itching area, or to develop other ways of moving their hands away from the itching area.[389] The technique has been described in two RCTs[106,276] conducted by the same team from Sweden, and compared with topical cortiscosteroids. A further RCT has evaluated the potential benefit of three psychological approaches versus dermatological education in the prevention of relapse in atopic eczema.[275] Another RCT[390] of psychiatry support for patients with eczema was excluded as close inspection revealed that the patients had eczematous dermatoses of diverse types and only one case of atopic eczema was present in that study.

Benefit

In the Melin and colleagues study,[276] 17 patients with atopic eczema aged 19–41 years were randomised into two groups. One group was treated with hydrocortisone cream alone and the other group was treated with the cream plus two sessions of habit-reversal treatment during the first week of the treatment period of 28 days. The study was unblinded. At the end of the assessment period, there was a 67% mean reduction in global eczema score in the habit-reversal plus hydrocortisone cream group compared with 37% score reduction in the hydrocortisone only group ($p < 0.05$). Total score of self-assessed annoyance was also markedly reduced in the active versus comparator groups. Mean percentage reduction of scratching episodes per day was 79% in the habit-reversal and hydrocortisone group compared with 49% in the hydrocortisone only group ($p < 0.01$). In the later study conducted by the same team,[106] 45 patients (mean age 24.8 years) were randomised in a parallel fashion to four groups for a period of 5 weeks:

- application of hydrocortisone cream for the entire 5-week period
- application of betamethasone valerate (a strong topical steroid) for 3 weeks followed by hydrocortisone for the remaining 2 weeks
- application of hydrocortisone plus habit-reversal for the 5-week period
- application of betamethasone plus habit-reversal for the first 3 weeks followed by hydrocortisone plus habit-reversal for the remaining 2 weeks.

The study was unblinded. Results are reported more fully in the section on topical corticosteroids (see chapter 4 and appendix 3). The authors reported significant differences between the behaviour therapy groups and those taking steroids alone for total skin status. Scratching was reduced by 65% in the hydrocortisone only group, 74% in the betnovate followed by hydrocortisone group, 88% in the hydrocortisone plus habit-reversal group, and 90% in the betnovate and hydrocortisone and habit-reversal groups (statistics not presented).

The study by Ehlers and colleagues in 1995[275] evaluated the use of an autogenic training as a form of relaxation therapy (ATP) versus a cognitive-behavioural treatment (BT), versus a standard dermatological educational programme (DE) versus combined DE and BT (DEBT). One hundred and thirteen patients attending an outpatient clinic in Germany were randomised to these four groups and were also compared with an additional standard medical treatment group who were not part of the random assignment. Investigators were blinded as to the group allocation. The intervention was for 3 months and patients were followed-up for 1 year in order to evaluate disease relapse. At the end of 1 year, mean skin severity lesion score dropped from 29.5 to 28.8 in the DE group, 33.7 to 19.8 in the ATP group, 31.0 to 20.7 in the BT group, and 35.4 to 25.8 in the DEBT group. There were no significant differences in mean severity of itching between the four randomised groups. DEBT led to significantly larger improvement in global skin severity than DE alone and this was also accompanied by significant reductions in topical steroid use.

Harms

In the Ehlers study, the behavioural approaches required 12 weekly group sessions of 1.5 to 2 hours each with a group size of between five and seven patients. No adverse events were reported in any of the trials, though some of the drop-outs could possibly be related to the fact that extra visits were needed for the behavioural technique.

Comment

The Ehlers study[275] was clearly reported and included an assessment of patient expectation of treatment benefit. No intention-to-treat analysis was performed, but drop-outs were low (nine out of 113 at 3 months). Over 14 outcome measures were reported in the study, which introduces the possibility of multiple hypothesis testing. The authors also performed statistical tests in comparison to a non-randomised control group, which may not be justified. Nevertheless, the magnitude of improvement for those receiving behavioural techniques in addition to their standard dermatological care (which included topical corticosteroids) was moderately large, and carried more weight than the Melin and Noren studies because assessments were made by an investigator blinded to the treatment allocation. The combination of habit-reversal plus judicious use of topical corticosteroids seems an attractive one and evidence from two RCTs supports its use. Both RCTs were unblinded, and conducted in the hands of enthusiasts. The generalisability of these findings to other populations should be determined in further RCTs, using objective assessment methods that are clinically meaningful, and conducted by investigators blinded to group allocation. The magnitude of the benefits in these unblinded studies were considerable, particularly when these were above that which could be expected with topical corticosteroids.

Ultraviolet light

A proportion of atopic eczema sufferers have fewer flare-ups and decreased skin lesions during summer. This observation, along with the benefit of ultraviolet light in psoriasis led to the introduction of different forms of ultraviolet light for the treatment of atopic eczema.[391]

Ultraviolet radiation (UVR) makes up a fraction of the electromagnetic spectrum, which can be further subdivided into:

- UVC – the rays that do not pass through the earth's atmosphere
- UVB – the rays responsible for nearly all biological effects following sunlight exposure including tanning, burning and skin cancer, and
- UVA – those rays closest to the visible spectrum that pass through glass, and are the least harmful to the skin.[392]

Hence, treatment is with either UVA or UVB or a combination of both. Another form of UVA exists called PUVA (psoralen plus UVA) or psoralen photochemotherapy. Psoralen is a photoactive drug taken by mouth or mixed in a bath, which is given with UVA radiation to enhance its effectiveness. PUVA has proven efficacious in psoriasis and is currently used in the treatment of eczema.[393]

The mechanisms by which ultraviolet light affects atopic eczema are not completely understood. However UVB is immunosuppressive because it blocks the function of antigen-presenting Langerhans cells and alters the production of cytokines by keratinocytes. There is also evidence that UVA is able to alter both Langerhans cell and eosinophil functions in patients with atopic eczema.[394]

We located six RCTs[278–283] published in six papers evaluating the use of ultraviolet light in atopic eczema, and these are summarised in *Table 30*. The only two RCTs of PUVA that might have included atopic eczema patients had to be excluded as it was either not clear if those with 'chronic hand eczema' were atopic[393] or because data on the subset of atopic eczema patients were not given separately.[395] Statistical pooling of summary measures was not possible due to the differences in the type of ultraviolet light in each study and the lack of common outcomes at the same endpoints.

Comment

Generally the studies were quite small and poorly reported. Blinding was likely to have become unmasked in placebo-controlled trials due to the obvious tanning on one half of the body, along with mild burning and marked treatment effects. Although the right/left body comparison design had its limitations in terms of blinding, the lack of effect on placebo-treated body halves argues against a systemic effect of ultraviolet light treatment. Treatment effects were generally large and of rapid onset (i.e. within 1–2 weeks). Future studies should consider using a simple parallel group design and they should be of longer duration in order to capture duration of remissions.

Harms

Treatment with ultraviolet light usually ties patients to twice- or thrice-weekly visits to hospitals. Mild degrees of skin redness and burning are also common short-term adverse effects. Occasionally more severe burning may occur. There is no direct information on the long-term risk of skin cancer in atopic eczema patients undergoing ultraviolet light treatment. Although data on cohorts of psoriasis patients undergoing PUVA suggest that cancer risk only increases after around 250 treatment sessions, extrapolating from these studies to another

inflammatory disease with a generally younger patient population raises some concerns. This is particularly so for melanoma skin cancer where it is thought that most risk is acquired from ultraviolet light in the first 20 years of life. Specific cohort studies of different modalities of ultraviolet light treatment of atopic eczema treatment are recommended.

Summary of non-pharmacological treatments

House dust mites

- Considering that the circumstantial evidence for implicating house dust mites in atopic eczema is so strong, it is surprising that only three RCTs have examined the usefulness of house dust mite reduction.
- There is some evidence that reduction of house dust mite allergen around the home can result in a benefit to atopic eczema sufferers.
- The clinical relevance of such benefit and whether it is sustainable is unknown.
- The most clinically useful and easiest method of reducing house dust mite allergen around the home in atopic eczema is not known.
- There is little evidence to support the use of high-filtration vacuum cleaners above ordinary ones.
- There is no evidence to support the sole use of sprays, which only kill house dust mites.
- More studies on house dust mite eradication are needed, which separate the different interventions.
- Such studies should be larger and more pragmatic than those already done and should include a cost-effectiveness analysis.
- The role of hyposensitisation therapy in atopic dermatitis has not been adequately tested.

Enzyme detergents

- Although parents of children with atopic eczema in the UK commonly avoid enzyme-containing detergents in the belief that alternative agents are 'kinder' to the skin, one Danish RCT did not find any evidence to support such a notion.

Cotton clothing

- Two RCTs suggest that specially woven smooth synthetic garments are just as comfortable as cotton to people with atopic eczema.
- Another RCT suggests that disposable nappies containing an absorbent gelling material result in less nappy rash than conventional disposable nappies or cloth nappies, though no benefit for atopic eczema in general was demonstrated.

Salt baths

- A Japanese RCT of 1-week duration has not found any difference between deep-sea water and physiological saline sprays before bathing.
- RCTs comparing salt versus ordinary baths and regular versus infrequent baths in people with atopic eczema are needed.

Bioresonance

- There is no RCT evidence to support the use of bioresonance treatment in atopic eczema.

Psychological approaches

- The results of three RCTs suggest that psychological interventions such as behaviour-therapy habit-reversal techniques are a useful adjunct to dermatological treatment in atopic eczema. Generalising from these RCTs to other centres with less enthusiastic and appropriately trained staff requires further evaluation.

Nurse education

- One small unblinded RCT has suggested a modest benefit from supplementing a dermatological consultation with a single session with a dermatological nurse to provide more background information and to demonstrate the use of topical treatments.

Ultraviolet light

- There is some RCT evidence to support the use of UVB (broad and narrow band) versus placebo in atopic eczema.
- There is some RCT evidence to support the use of high dose UVA in preference to UVB/UVA in atopic eczema.
- There is some RCT evidence to support the use of narrow band UVB (TLO1) in preference to ordinary UVA in atopic eczema.
- There is some RCT evidence to indicate a benefit of high-dose UVA in the treatment of acute eczema flares, with efficacy slightly superior to topical steroids.
- Missing evidence includes a comparison of high-dose UVA versus narrow band UVB, PUVA versus placebo, PUVA versus UVB or topical steroids, and any form of ultraviolet light versus other systemic immuno-modulatory treatments.
- Future studies should be long term (i.e. 6 months or more), in order to note the duration of remissions and the effects of ultraviolet light on disease chronicity.
- Long-term multicentre surveillance studies are needed in large cohorts of patients in order to estimate subsequent skin cancer risk.

TABLE 30 *RCTs of ultraviolet light in atopic eczema*

Study	Interventions (co-treatments)	Study population and sample size	Trial design description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Jekler & Larko, 1988[280] Study 1	UVB three times per week (20–153 mJ/cm^2 up to 63–816 mJ/cm^2) vs placebo (visible light) three times per week (emollients and hydrocortisone)	17 patients over the age of 15 years, most of whom had skin type III (tans easily, seldom burns	Prospective, RCT left/right parallel study of 8 weeks' duration	Patients assessed for pruritus, lichenification, scaling, xerosis, vesiculation, excoriations, erythema Variables assessed on a scale of 0–3, plus a global assessment	Improvement from baseline of 1.5 (mean) to 0.7 for UVB and 1.4 for placebo for overall clinical response ($p < 0.001$). Thus the total score was significantly lower for the UVB treated side	Described as randomised but method unclear. Blinding unlikely due to mild burning on UVB-treated side No ITT analysis	Unclear if randomisation referred to side of active/placebo treatment or whether to type of minimal erythemal dose Large magnitude of treatment effect for all parameters Large (11/17) drop-outs due to 'intercurrent disease' and lack of time for treatments
Jeckler & Larko, 1988[280] Study 2	UVB three times per week given at 80% of minimal dose required to produce redness (MED) vs UVB at 40% of MED (emollients and hydrocortisone)	25 patients with mean age of 25.9 years, most with skin type III	Randomised right/left side parallel study for 8 weeks	Same as for study 1 above	Clearing or considerable improvement in 15/25 on high-dose UVB vs 16/25 with low-dose (NS)	Methods very scanty Randomisation unclear; probably unblinded No ITT analysis	Further details of study found in Jeckler 1992 thesis. This study of high- vs low-dose UVB suggested very little difference between the two, but power of study is very limited
Jekler & Larko, 1991[281]	UVA (average 8.1 mW/cm^2) vs UVB (0.85 mW/cm^2) three times per week (emollients and hydrocortisone)	33 patients with mean age of 23.3 years Mean disease duration of 19.6 years Most with skin type III	Prospective, randomised left/right parallel study of 8 weeks' duration	Patients assessed for pruritus, lichenification, scaling, xerosis, vesiculation, excoriations, erythema and an overall evaluation on a score of 0–3 (none to severe) Healing evaluated on a scale of 3 to –1 (3 = healed, –1 = worse)	Improvement from mean baseline of 10.3 (range 6–18) for clinical signs (total score) decreased to 5.5 for UVA and 6.4 for UVB Pruritus scored separately with baseline of 2.2 improving to 1.1 after UVA and 1.3 after UVB	Described as single-blind and randomised but methods unclear Differential tan on UVA side of the body likely to have unblinded study 12 withdrawals and drop-outs, no description given, and no ITT analysis	Both treatments induced large improvements compared with baseline, with some small statistically significant change in favour of UVA Most patients preferred UVA
Jekler, 1992[282]	Mixed UVA (74%) and UVB (26%) vs UVB three times per week	30 patients with mean age of 24.8 years and mean disease duration of 20.5 years	Prospective, randomised left/right parallel study of 8 weeks' duration	Patients assessed for pruritus, lichenification, scaling, xerosis, vesiculation, excoriations, erythema and an overall evaluation on a score of 0–3 (none to severe) healing evaluated on a scale of 3 to –1 (3 = healed, –1 = worse)	A decrease from baseline score of 10.8 to 5.2 for UVAB and 6.1 for UVB ($p = 0.002$ for difference in scores between treatments) 21/24 patients reported mild burning with UVB, which was sever in six patients compared with three episodes of mild burning with UVA/B (none severe)	Described as randomised but method unclear No blinding No withdrawals or drop-outs	This thesis also presents the two studies reported in Jeckler 1988 in more detail; a further three small left/right comparison studies are also described comparing UVA vs UVB and low-dose UVB vs UVA/B, and UVA vs UVA/B, but it is unclear if these were RCTs

continued

TABLE 30 contd *RCTs of ultraviolet light in atopic eczema*

Study	Interventions (co-treatments)	Study population and sample size	Trial design description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Krutmann *et al.*, 1992[283]	High-dose UVA1 (0–130 J/cm^2 o.d.) vs UVA–UVB therapy (up to 30 mj/cm^2 UVB and 7.5 j/cm^2 UVA daily (emollients)	25 young adults with atopic eczema and definite atopy	Prospective, randomised, parallel study of 15 days' duration	Costa scoring system: erythema, oedema, vesicles, exudation, crusts, excoriations, scales, lichenification, pruritus, loss of sleep on a 7-point scale (0 = no lesion, 6 = extremely severe)	A decrease from baseline of 53 (overall score) to 14 after UVA1 ($p < 0.001$ against comparator change) Comparative data for UVA-UVB not given but shown in graphical form only; UVA–UVB 52 at baseline changed to 38 (estimated from graph)	Described as 'randomly selected patients' but method unclear Author contact 'treatments randomly allocated' No blinding No drop-outs or withdrawals	Unclear if patients randomised but confirmed by authors Large treatment effects – all in favour of high-dose UVA1 over UVA/B
Krutmann *et al.*, 1998[278]	High-dose UVA1 130 J/cm^2 o.d. vs o.d. fluocortolone 0.5% cream or ointment vs UVA–UVB minimal erythema dose-dependent o.d.	53 patients acute severe exacerbation of atopic eczema	Prospective, randomised, parallel study of 10 days' duration	Costa scoring system: erythema, oedema, vesicles, exudation, crusts, excoriations, scales, lichenification, pruritus, loss of sleep on a 7-point scale (0 = no lesion, 6 = extremely severe)	Improvement over baseline for total clinical score: high-dose UVA1 baseline of 56 reduced to 26, fluocortolone baseline of 60 reduced to 35 and UVA-UVB baseline of 60 reduced to 42 (all after 10 days' treatment); $p < 0.0001$ Mean reduction in total disease activity was 9.7 for 21 evaluable patients on narrow-band UVB, 4.8 on UVA and 0.4 on placebo, the change significant at the 5% level for narrow-band UVB vs placebo only	'A randomisation sequence generated by random numbers' No blinding No withdrawals or drop-outs	Very short duration Results had to be estimated from graphs Useful to have a comparison with topical steroids Study suggests superiority of high-dose UVA over a topical steroid
Reynolds *et al.*, 1999[279]	Narrow-band UVB (up to max of 1.2 J/cm^2) vs UVA (up to max of 15 J/cm^2) or placebo (visible light) all twice weekly (mild-to-moderate topical steroids plus emollients)	73 adult patients with moderate-to-severe atopic eczema	Prospective, randomised, double-blind parallel study of 12 weeks' duration	Five clinical features at six separate body sites plus itch and sleep loss (VAS), and extent of disease recorded by one observer	The proportion of patients reporting reduction in itch over 24 treatments was 90% ($p = 0.02$) for narrow-band UVB, 63% for UVA and 53% for placebo ($p = 0.02$ compared with placebo) Changes for sleep loss failed to reach statistical significance	Study described as randomised (in balanced blocks), controlled, and double-blind No ITT analysis	Published in abstract form only at time of report Only 47 out of 73 patients completed study Study possibly partly unblinded due to lack of pigmentary changes on one side and burning in others

continued

TABLE 30 contd *RCTs of ultraviolet light in atopic eczema*

Study	Interventions (co-treatments)	Study population and sample size	Trial design description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Der-Petrossian *et al.*, 2000[277]	Narrow-band UVB vs bath PUVA 1 mg/l as 8-MOP three times per week	12 patients with severe/chronic atopic dermatitis with a mean age of 27 years ± SD of 11.3 years	Prospective, randomised, single-blind half side comparison of 6 weeks' duration	Patient-rated itch and sleep loss (VAS 0–10 cm) as part of SCORAD, doctor-rated global severity, doctor-rated global changes of modified SCORAD for eight signs and symptoms	Baseline scores of 100% SCORAD for bath-PUVA and UVB reduced by 65.7% for bath-PUVA-treated side and 64.1% for UVB-treated side ($p = 0.48$)	Study described as randomised, and investigator blinded No ITT analysis carried out; two withdrawals, one due to exacerbation of atopic dermatitis, an another due to a differential response in terms of less erythema reactions to the bath-PUVA side	A small study that took care to ensure that both treatments were given in equal doses Big falls in SCORAD scores for both treatments with little difference between the two

MED, minimal erythema dose

Chapter 10

Systemic immunomodulatory agents

Allergen–antibody complexes of house dust mite

Anti-house dust mite antibodies are very common in atopic eczema patients and may play a part in the disease process. Previous studies in the field of asthma have suggested that injection of complexes of house dust mite allergen (*Der p 1*) with antibodies may result in clinical improvement. We found one RCT[285] that evaluated the role of house dust mite allergen–antibody complex injections versus placebo in the treatment of atopic eczema. The study was covertly duplicated the following year in the *Journal of the American Academy of Dermatology*, and both papers were used to generate the summary as each contained additional details. The later publication documented 24 patients who were randomised compared with 23 in the original report. The missing patient is documented in the secondary report as he no longer satisfied the entrance criteria at the time of the first injection. Twenty-four adults with severe atopic eczema, all of whom had evidence of sensitisation to house dust mite were entered into a placebo-controlled study of injections of house dust mite allergen–antibody complexes 4 months after an initial washout period of 6 weeks. The study was followed by a more prolonged open period.

Benefits

Of the 23 evaluable patients at 4 months, there was a statistically significant improvement in disease intensity index in those receiving active injections. Disease intensity was measured on a complex scale, which multiplied extent versus six physical signs. This reduced from 1000 to 612 in the active and from 1000 to 859 in the placebo group. Percentage mean reduction in itching was not so large, reducing from 3.3 to 2.2 in the active group and from 3.3 to 2.6 in the placebo group.

Harms

Three patients in the active group developed a delayed-type inflammatory action at the injection site and itching increased within 24 hours after injection in four patients on active and on two patients receiving placebo therapy.

Comment

Method of randomisation and concealment of allocation was unclear in this study, though blinding was probably successful. The 'beneficial' treatment effects are difficult to interpret given the use of an invalidated exploded scale and absence of a patient's perspective. The modest benefit demonstrated in this study needs to be replicated elsewhere before the intervention can be recommended as a treatment option.

Cyclosporin

Cyclosporin is a polypeptide of fungal origin. It is a potent inhibitor of T-lymphocyte-dependent immune responses and interleukin 2 production.[396] Primarily, cyclosporin was introduced as an immunosuppressive agent to prevent graft rejection after tissue transplantation. In dermatology, cyclosporin is used for the treatment of immune-mediated skin diseases such as cutaneous graft-versus-host reaction, immunoglobulous diseases, psoriasis and atopic dermatitis.[391]

Cyclosporin is usually restricted to short-term use in severe refractory atopic dermatitis in adults and children.[397] It requires careful monitoring due to its potential adverse effects, notably kidney toxicity and hypertension.[398] Although cyclosporin has a low degree of penetration through the skin, topical applications have been suggested for reducing the potentially serious adverse effects associated with oral cyclosporin.[297]

Cyclosporin can be administered orally in doses of between 2.5 mg/kg and 5 mg/kg body weight[34] or topically in an ointment or gel containing cyclosporin microcrystalline 10%.[294]

Statistical methods

Rate differences were estimated for categorical variables and differences in means for continuous variables. The Mantel–Haenszel type method of Greenland and Robins[399] was used to estimate the pooled rate difference for all strata under the assumption of a fixed-effects model. A CI for the pooled risk difference was calculated using the Greenland–Robins variance formula.[399] The Q ('combinability') statistic is given with its associated probability on k (number of strata) minus one degree of freedom. This has low power as a strict test of homogeneity. There are no comprehensive

rules on when to use random effects and when to use fixed effects models; debate continues in the statistical community.[400] However, when this was significant at the 0.05 level, a random effects analysis was applied.[401] The pooled mean effect estimate was calculated using weights calculated as the inverse of the variance for each study.

In the trials, estimates of error were not reported in a consistent manner. When standard errors were reported for both the treatment and control arms, both were used in the calculations. When only the pooled estimate was given, the variances for the treatment and control arms were assumed to be the same. When quantitative values were reported in graphical form only, these were read electronically from the scanned images and the responses and their associated variances were estimated by linear interpolation as described by Poolsup and colleagues.[402]

Results

Of the twelve eligible reports of RCTs (*Tables 31–36*), two dealt with topical cyclosporin[294,297] and ten with oral cyclosporin.[286–293,295,296]

Topical application

The two reports[294,297] on the use of topical cyclosporin gave conflicting results. While in a study of 20 patients, De Prost and colleagues[297] reported positive results based on assessments of pruritus, erythema, oozing, crusts, xerosis and lichenification, De Rie and colleagues[294] reported no benefit in a study of seven patients with atopic eczema. Both studies used an intrasubject design with randomised applications to comparable lesions. Neither provided any justification for sample size chosen. On the basis of the available evidence, the efficacy of cyclosporin in atopic eczema has yet to be rigorously evaluated.

Oral therapy

Of the ten reports of RCTs of oral cyclosporin therapy, those by Zonneveld and colleagues[288] and Zurbriggen and colleagues[289] were comparisons of dose schedule and formulations, respectively, and therefore provided little evidence on the value of cyclosporin. One of the trials[291] adopted a randomised parallel group design with 23 patients receiving cyclosporin and 23 placebo. The study showed that both disease severity and area involvement were reduced by cyclosporin treatment (5 mg/kg/day) by week 6. At the end of the 6-week trial, 15 of 19 of the patients on cyclosporin compared with six of 19 patients on placebo reported at least a moderate improvement. The estimated rate difference was 39% (95% CI 10 to 62). One small study by Harper and colleagues[286] of continuous versus intermittent cyclosporin A in children, suggested that more consistent control is achieved with continuous therapy when given over a 1-year period. This longer-term study did not demonstrate any clinically significant change in kidney function (serum creatinine) and blood pressure in either group.

Three of the remaining six reports were of the same trial[293,295,298] with most of the outcome data reported in the Sowden and colleagues report.[295] None of the studies compared cyclosporin with an active agent, with all three remaining RCTs being comparisons of cyclosporin with placebo.[290,292,295] Those studies gave some poolable data because of similarities in study design and the use of a consistent visual metric analogue scale for scoring itch (*Table 36*). However, because of the crossover design used in all three trials, only the first phase of each study was used so that our estimates were not confounded by carry-over effects. *Table 37* shows the estimated mean difference in itch scores for the cyclosporin group compared with the placebo group for each of the three studies as well as the pooled estimate at the end of the first period.

Irrespective of whether a fixed- or random-effects model was used, the pooled estimate showed that cyclosporin was effective in relieving eczematous itch compared with placebo as shown in *Figures 4* (fixed effects) and *5* (random effects).

Generally positive results were reported for sleep loss, area involvement, reduction in steroid use and erythema.

The small study remaining by Miranda and colleagues[287] compared oral cyclosporin A with oral transfer factor for 6 months and found no statistical differences in a range of outcomes between the two. No intention-to-treat analysis was performed. Three patients in the cyclosporin A group reported excess hair growth (hypertrichosis).

Comment

There is little doubt that cyclosporin is effective for the treatment of atopic eczema when compared with placebo but that continued use is necessary for the prevention of relapse, which is rapid once therapy is discontinued. Clinical scores return close to baseline values within 8 weeks.[292] Adverse effects of the drug, notably on the liver and kidneys, suggest that long-term treatment is not justifiable. Even in short-term trials, cases of hypertension and elevations of serum bilirubin and creatinine have been reported.[291] Reducing dose schedules or prolongation of treatment-free intervals have yielded unconvincing results with obvious poorer control of the disease and modest decrease in drug

TABLE 31 *Design, patient characteristics and interventions of included studies: cyclosporin*

Study	Design	No. of patients	Age (years)	Duration	Severity	Oral cyclosporin dosage	Comparator	Co-treatments	Withdrawals and drop-outs
Orals									
Allen, 1991[298*]	Crossover, double-blind, randomised	33	17–56	16 weeks	Severe	5 mg/kg/day	Placebo	Topical steroids	Four crossed over prematurely (p-c) Six did not complete second phase (c-p)
Munro *et al.*, 1994[292]	Crossover, double-blind, randomised	24	19–48	8 weeks	Chronic	5 mg/kg/day	Placebo	Topical steroids	Five
Salek *et al.*, 1993[293*]	Crossover, double-blind, randomised	33	17–56	16 weeks	Severe	5 mg/kg/day	Placebo	Topical steroids	Four crossed over prematurely (p-c) Six did not complete second phase (c-p)
Sowden *et al.*, 1991[295*]	Crossover, double-blind, randomised	33	17–56	16 weeks	Severe	5 mg/kg/day	Placebo	Topical steroids	Four crossed over prematurely (p-c) Six did not complete second phase (c-p)
van Joost *et al.*, 1994[291]	Parallel, double-blind, randomised	46	17–68	6 weeks	*	5 mg/kg/day	Placebo	Hydroxyzine 10 or 25 mg, emollients	18 due to lack of response from trial medication
Wahlgren *et al.*, 1990[296]	Crossover, double-blind, randomised	10	22–42	10 days	Stable,moderate or severe	5 mg/kg/day	Placebo	1% hydrocortisone, emollients	None
Zonneveld *et al.*, 1996[288]	Parallel, open, randomised, dose-finding study	78	18–70	8 weeks	Severe, long standing	5–3 mg/kg/day	3–5 mg/kg/day	Antihistamines, emollients, antibiotics, steroids	48: lack of efficacy, adverse effects, non-compliance
Zurbriggen *et al.*, 1999[289]	Crossover, double-blind, randomised	14	20–64	8 weeks	Severe	4–4.5 mg/kg Sandimmun™	4–4.5 mg/kg Neoral™	Monitored steroids and emollients	One: protocol violation
Cordero Miranda, 1999[287] (Spanish, translated)	Parallel study	23	3–40	6 months	Not stated	4 mg/kg	Oral transfer factor in escalating dose (units not specified)	1% hydrocortisone	Three in treatment group, two in transfer factor group
Harper *et al.*, 2000[286]	Parallel, unblinded, randomised	43	2–16	12 months	Severe	Max. of 5 mg/kg/day continuously	Max. of 5 mg/kg/day given as intermittent 3-month course	Topical steroids of any potency	Three excluded after baseline due to abnormal assessments A further eleven dropped out during the study
Topicals									
de Prost *et al.*, 1989[297]	Left/right comparison, double-blind, randomised	20	2–29	2 weeks	Stable	10% topical gel	Placebo	*	One to adverse effects
De Rie *et al.*, 1991[294]	Left/right comparison, double-blind, randomised	8	3–55	3 weeks	*	10% topical gel	Placebo	*	*

*Sandimmum™, Neoral™, Novartis, UK; * Same study of 33 patients*

TABLE 32 *Outcome measures: oral cyclosporin*

Study	Outcome measure	Scale
Allen, 1991[298*]	Erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and lichenification at six body sites	0–3 scale
	Extent of disease	Rule of Nines
	Patient-assessed sleep and itch	0–100 mm VAS
Salek *et al.*, 1993[293*]	Disease activity: erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and lichenification at six defined body sites	0–3 scale
	Disease extent: Rule of Nines	Max. score 108
	Patient-assessed itch and sleep loss	1–100 mm VAS
	Patient-assessed health-related quality of life	UKSIP, EDI
Sowden *et al.*, 1991[295*]	Clinician-assessed disease activity of erythema, purulence, excoriation or crusting, dryness or scaling, cracking or fissuring, and lichenification at six defined body sites	0–3 scale
	Clinician-assessed extent of disease	Rule of Nines
	Patient-assessed itch and sleep loss	0–100 mm
	Patient and doctor global assessments	Five-point scale
Munro *et al.*, 1994[292]	Composite scale for erythema, excoriation, lichenification using Rule of Nines	0–3
	Itch and sleep loss	10 cm VAS
van Joost *et al.*, 1994[291]	Physician-assessed severity in six regions for erythema, infiltration, vesicles and papules, dryness and scaling, cracking and fissuring, excoriation and crusting	0–3 scale
	Lichenification scored separately	0–3 scale
	Physician-assessed extent of disease	Rule of Nines
	Physician-assessed itching and sleep loss	0–3 scale
	Patient-assessed global assessment	Four-point scale
Wahlgren *et al.*, 1990[296]	Patient-assessed itch	Symtrack
	Patient-assessed itch	100 mm VAS
	Physician-assessed severity at 20 areas (no details)	0–3 grading
Zonneveld *et al.*, 1996[288]	Area assessment	Rule of Nines
	Severity assessment of six body regions for erythema, lichenification, vesicles/papules, dryness/scaling, cracking/fissuring, excoriation	0–3
	Patient-assessed itch and sleep loss	0–3 scale
	Patient and physician global assessment	0–3 scale
Zurbriggen *et al.*, 1999[289]	Area assessment	Rule of Nines
	Severity assessed at six sites for (no more detail given)	0–10 scale
	Itch and sleep loss. Note: reference given for details (see Sowden paper)	
Cordero Miranda, 1999[287]	Physician-assessed erythema, 'eczema', lichenification, itch, oedema	0–3
	Global physician's assessment every 15 days	Five categories (cure, excellent, moderate, no change, worse)
Harper *et al.*, 2000[286]	Patient-rated itch, irritability, sleep loss and global severity	100 mm VAS
	Doctor-rated global severity	Five-point scale
	SASSAD score	
	Doctor-rated extent using Rule of Nines	
	Renal function and blood pressure	

UKSIP, UK Sickness Impact Profile; EDI, Eczema Disability Index; SASSAD, Six Area, Six Sign, Atopic Dermatitis

TABLE 33 *Outcome measures: topical cyclosporin*

Study	Outcome measure	Scale
de Prost *et al.*, 1989[297]	Observer-assessed pruritus, erythema, vesicles and oozing, crusts, xerosis and lichenification	0–3
	Global evaluation	Five grades (cure–deterioration)
De Rie *et al.*, 1991[294]	ADSI: pruritus, erythema, exudation, excoriations, lichenification.	0–15

exposure. As recommended by Zaki and colleagues,[397] cyclosporin should be reserved for the short-term treatment of refractory disease, and even then its superiority over oral steroid therapy, a substantially cheaper alternative, is as yet untested.

Levamisole

Levamisole hydrochloride is a drug widely used in veterinary medicine for treating helminthic parasites. The drug was found to have wide immune-enhancing properties particularly on stimulating white blood cells. Because patients with atopic eczema have some evidence of decreased cell-mediated immune responses and recurrent secondary infections, it seemed reasonable to consider a possible benefit of levamisole in cases of atopic eczema. One small RCT of levamisole in atopic eczema has been published.[299] Another double-blind placebo-controlled study of 15 children in Spain[403] was published in the same year, though it was unclear if randomisation had been used in that study. The Alomar study[403] showed no evidence of any benefit of levamisole. The White and Hanifin study[299] will be described in more detail.

Benefits

Thirty-six patients aged 13–64 years with atopic eczema were randomised to levamisole hydrochloride or placebo according to body weight with topical triamcinolone as co-treatment. Of 26 evaluable patients at the end of the 6-month trial, there were no clinical or statistically significant differences in patients' objective improvement, frequency of infections, physician prediction of active treatment, clinical scores, or immunological markers such as IgE changes. In the active groups, six of 11 patients noticed improvement compared with six of 15 in the placebo group. Mean percentage improvement in a composite sign score (not defined) was 44% in the levamisole group and 16% in the placebo group.

Harms

One patient developed urticaria and another developed nausea and vomiting while taking levamisole.

Comments

The quality of this study was surprisingly good for such an early publication with a clear description of the blinding process and testing for success of blinding. Despite the lack of intention-to-treat analysis and very small sample size, there is not a hint of any benefit of levamisole in this study or in the Alomar study. The placebo benefit in the studies was quite remarkable in that they were greater than those on active treatment. The authors conclude that the study emphasises the need for randomised double-blind comparisons for new drugs such as levamisole in view of the previous claimed excellent results from uncontrolled studies. Although the study was under-powered to miss small treatment effects, it is unlikely that levamisole has any long-term moderate-to-large treatment benefit in atopic eczema.

Platelet-activating factor antagonist

Platelet-activating factor (PAF) is a powerful mediator of certain inflammatory reactions and has been implicated in inducing itch and contact urticaria. Thus, it seemed reasonable to try a PAF antagonist in atopic dermatitis, a disease characterised by itching and various inflammatory processes. One RCT[300] compared a solution of PAF antagonist with vehicle (placebo) in a study of 44 patients who applied one solution or the other on opposite sides of symmetrical lesions of atopic eczema for a period of 28 days. Patients were mainly young adults and were recruited from five centres in Europe.

Benefits

Based on an intention-to-treat population analysis, 57% of those on the experimental PAF antagonist 'responded' (response not defined by authors) compared with 61% on placebo at the end of the treatment period. Based on the evaluable population of 36 patients, 18 of the experimental group showed marked improvement or total clearing on the site treated with the solution compared with 17 of the 36 for the site treated with placebo. Other parameters of atopic dermatitis severity showed similar lack of difference apart from a transient statistically significant benefit for itching at Day 14 but not on Day 28.

TABLE 34 *Outcome measures: oral cyclosporin versus placebo – signs and symptoms*

Study	Erythema	Purulence	Excoriation	Dryness	Xerosis	Scaling	Lichenification	Cracking	Fissuring	Exudation	Vesiculation	Pustules/papules	Oozing	Inflammation	Crusts	Infiltration	Induration	Itch	Sleep loss	Physician global severity assesssment	Patient global severity assessment	Area assessment (method used)	Scale named (if modified specify)
Allen, 1991[298*]	●	●	●	●		●	●	●	●						●			●	●			RoNAA	
Salek *et al.*, 1993[293*]	●	●	●	●		●	●	●	●						●			●	●			RoNAA	
Sowden *et al.*, 1991[295*]	●	●	●	●		●	●	●	●						●			●	●	●	●	RoNAA	
Munro *et al.*, 1994[292]	●		●				●											●	●			RoNAA	
van Joost *et al.*, 1994[291]	●		●	●		●	●	●	●		●	●			●	●		●	●		●	RoNAA	
Wahlgren *et al.*, 1990[296]																		●					
Zonneveld *et al.*, 1996[288]	●		●	●		●	●	●	●		●	●						●	●			RoNAA	
Zurbriggen *et al.*, 1999[289]																		●	●			RoNAA	
**Same study of 33 patients*																							

TABLE 35 *Outcome measures: topical cyclosporin – signs and symptoms*

Study	Erythema	Purulence	Excoriation	Dryness	Xerosis	Scaling	Lichenification	Cracking	Fissuring	Exudation	Vesiculation	Pustules/papules	Oozing	Inflammation	Crusts	Infiltration	Induration	Itch	Sleep loss	Physician global severity assesssment	Patient global severity assessment	Area assessment (method used)	Scale named (if modified specify)
de Prost *et al.*, 1989[297]	●				●		●				●		●		●			●		●			
De Rie *et al.*, 1991[294]	●		●				●			●								●					ADSI

TABLE 36 *Itch data reported in or derived from the cyclosporin trials*

Study	Cyclosporin group		Placebo group	
	No. of patients	Mean difference in itch scores (SD)	No. of patients	Mean difference in itch scores (SD)
Munro *et al.*, 1994[292]	12	35.9 (22.9)	12	16 (20.1)
Sowden *et al.*, 1991[295]	17	27.7 (17)	16	36 (17)
Wahlgren *et al.*, 1990[296]	10	7 (10.8)	10	–1 (12.7)

TABLE 37 *Estimates of mean difference in itch scores for cyclosporin*

Study	Stratum	No. of treatment patients	No. of control patients	Mean difference	Approximate 95% CI
Munro *et al.*, 1994[292]	1	12	12	19.9	2.66 to 37.14
Sowden *et al.*, 1991[295]	2	17	16	24.1	12.49 to 35.70
Wahlgren *et al.*, 1990[296]	3	10	10	8.0	–2.33 to 18.33
Pooled estimate of weighted mean difference (WMD) in itch score = 15.92				*Approximate 95% CI = 8.87 to 22.96*	
Chi-square (for WMD) = 19.62 (df = 1); p < 0.0001				*Q ('combinability' for WMD) = 4.37 (df = 2); p = 0.1125*	
DerSimonian–Laird pooled WMD = 16.70				*Approximate 95% CI = 5.87 to 27.54*	
DerSimonian–Laird Chi-square = 9.13 (df = 1); p = *0.0025*					

Harms

Fourteen out of 15 patients complained of skin dryness and burning immediately after application of the treatment. Data were not presented separately for the active versus vehicle treatment. There was one case of possible contact dermatitis related to the trial medication and another who developed severe erythema.

Comment

There appears to be no benefit from the PAF antagonist in this small study, although it lacks the power to exclude a potentially useful benefit. Randomisation, concealment of allocation, and blinding was poorly described, though an intention-to-treat analysis was performed.

Interferon-gamma

One of the immunological abnormalities characteristic of atopic eczema is reduction in a chemical messenger called interferon-gamma. Recombinant interferon-gamma inhibits IgE synthesis by human peripheral blood lymphocytes *in vitro*. Since atopic eczema is characterised by excessive production of IgE in response to ingested and airborne allergens, a potential therapeutic role for a substance such as interferon-gamma, which helps to switch off IgE synthesis, has been postulated and demonstrated in an open study.[404] Two RCTs of interferon-gamma in atopic eczema were located.[302,303] An earlier abstract[405] quoted in Renz and colleagues (1992)[301] referred to an RCT of 14 atopic eczema patients treated by gamma-interferon or saline. It was unclear if these patients were also participants in the larger study reported in 1993,[302] and the lack of methodological detail precluded further discussion of this study.

Benefits

In a 12-week multicentre study of 83 patients with severe atopic eczema aged between 2 and 65 years, daily subcutaneous injections of recombinant interferon-gamma at a dose of 50 $\mu g/m^2$ was compared with placebo injections with topical corticosteroids continued as co-treatment. All patients were instructed to take oral acitaminophen (an analgesic) before and after injections to protect against headaches and aching limbs associated with interferon therapy. Those randomised to active treatment were significantly older than those on placebo. At the end of the assessment period, 45% of 40 patients on active treatment compared with 21% of 43 on placebo were reported as having greater than 50% global improvement ($p = 0.016$) as judged by a physician who was blinded to treatment allocation. Corresponding figures for the proportion of patients with more than 50% patient/parent-reported global improvement was 53% and 21% for active versus placebo treatment, respectively ($p = 0.002$). Other physical signs, such as redness and scratch marks, were statistically significantly reduced by about 30% in the active group, and a similar magnitude of improvement was seen for induration, itching, dryness and lichenification, though these were not statistically significant. Response was greatest in

FIGURE 4 *Difference in itch scores (fixed effects)*

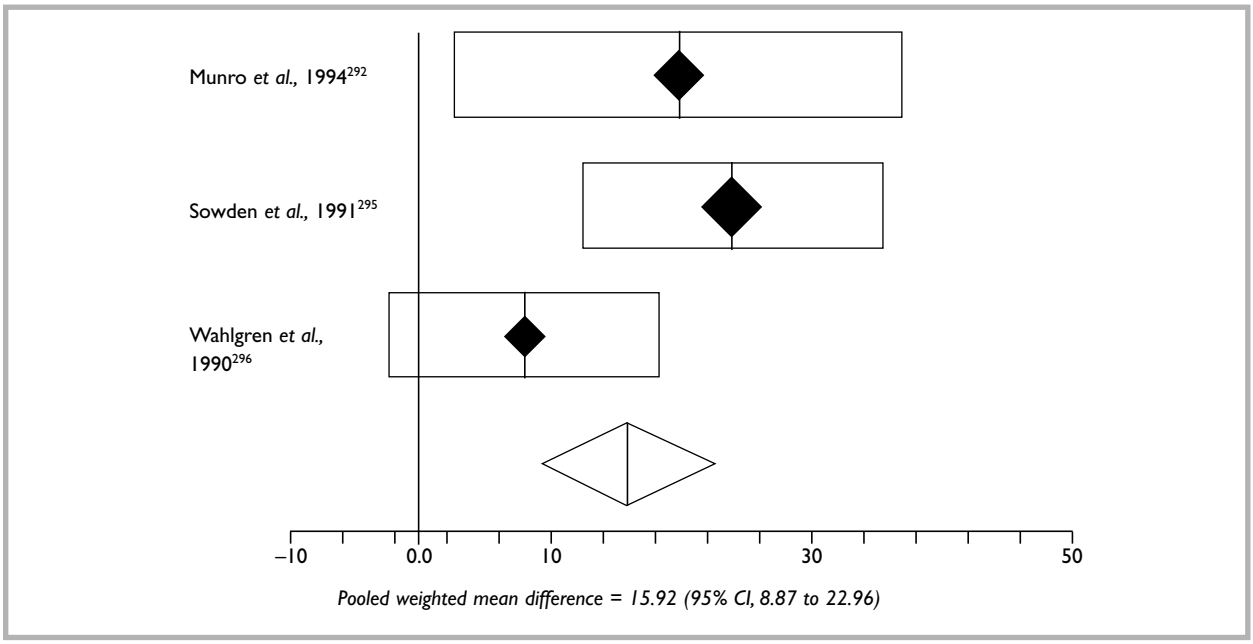
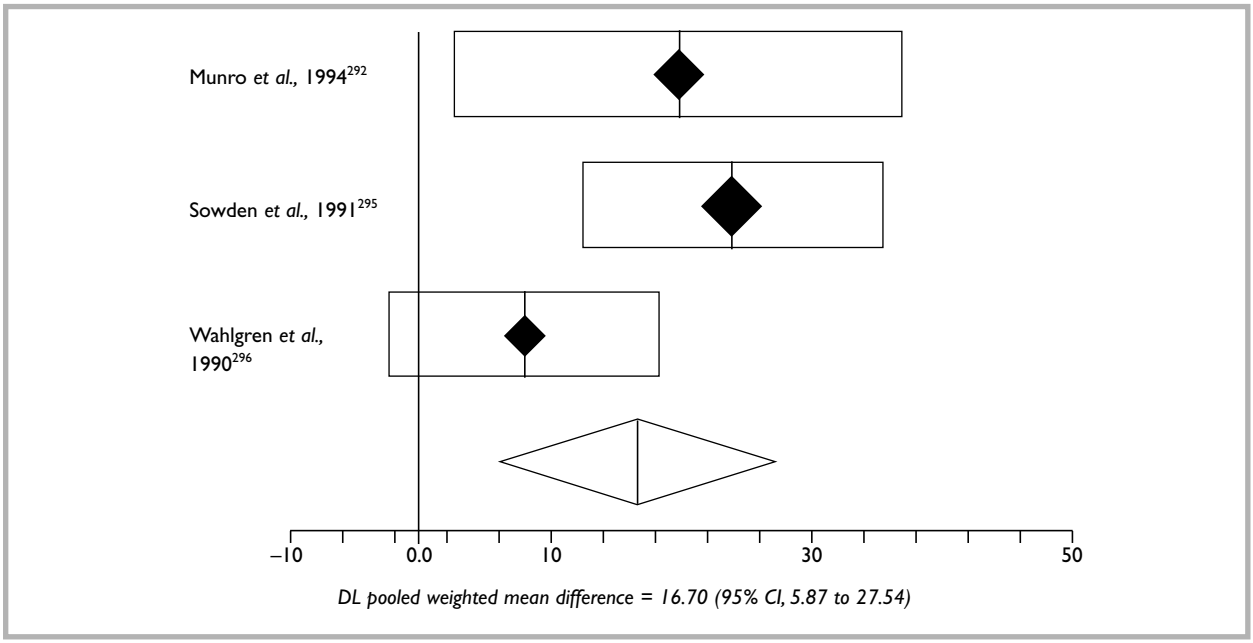


FIGURE 5 *Difference in itch scores (random effects)*



younger patients. Serum IgE levels did not fall significantly. Another more recent study by Jang and colleagues[303] has compared high- versus low-dose interferon gamma (1.5 versus 0.5 million units/m^2) versus placebo given subcutaneously three times week to patients with recalcitrant atopic dermatitis aged 18–42 years for 12 weeks. At the end of the evaluation period, clinical improvement measured by means of a composite of different physical signs and surface area, was markedly better in the two interferon gamma groups compared with placebo ($p < 0.05$), but not between the two interferon-gamma dose groups, except perhaps with a more rapid benefit in the first 6 weeks in the higher dose group. A host of other immunological markers were assessed.

Harms

Despite taking analgesia, 60% of those on active treatment in the Hanifin and colleagues study experienced headache, 32% muscle ache and 39% chills compared with 28%, 12% and 5%, respectively, for those on placebo. A fall in white cell count occurred in five patients on interferon-

gamma which normalised with continued treatment. Seven patients on active treatment had mild elevations of liver transaminase levels that did not affect therapy. Three out of the 41 patients treated with intereferon-gamma in the Jang and colleagues study discontinued therapy: two due to disease flare and one due to abnormal liver function tests. Despite taking acetaminophen as required for flu-like symptoms, 54% of those taking interferon-gamma experienced adverse effects including fever and muscle aches. Rates of adverse events in the placebo group were not described.

Comment

Quality of reporting was pleasantly high in the Hanifin study with a clear description of generation of randomisation sequence and an intention-to-treat analysis. Description of placebo and concealment of allocation was unclear, and blinding was likely to have been unmasked due to the marked therapeutic response and interferon-related adverse effects in those on active treatment. Quality of reporting was less satisfactory in the Jang and colleagues study. The methods of randomisation and concealment were not described. The fact that the three groups were of very different sizes (20 and 21 in low- and high-dose interferon versus only ten in the placebo group) suggests that some method other than simple randomisation was used. Blinding was not mentioned in the report, and an intention-to-treat analysis was not carried out.

There seems little doubt that interferon-gamma was markedly effective in these two studies of severely affected individuals, but at a cost in terms of adverse events. The inconvenience and cost of daily injections is a limiting factor in a chronic disease that can last many years.

Thymic extracts and their synthetic derivatives

Impaired T-lymphocyte cell function and sustained serum IgE levels have been described consistently in atopic eczema. This, along with observation that patients with primary T-cell immunodeficiency, such as Wiskott–Aldrich syndrome, have elevated IgE and lesions identical to atopic eczema, has prompted researchers to explore the therapeutic value of agents that promote the differentiation and function of mature lymphocytes. Initial work on calf thymic extracts given as an elixir or injection (thymomodulin and thymostimulin) was superseded by synthetic pentapeptides (thymopentin) given by injection. Thymomodulin is calf thymus acid lysate given orally in syrup form. Thymostimulin is a mixture of heat-stable polypeptides extracted from calf thymus and given by injection. Thymopentin is a synthetic pentapeptide corresponding to some of the amino acid sequences of human thymopoetin, the hormone responsible for promoting differentiation and function of mature lymphocytes.

Benefits

Thymomodulin

Two RCTs of thymomodulin in atopic eczema were identified from the same research group[304,305] but could not be combined as each dealt with quite different patient groups and interventions.
The Fiocchi and colleagues study[304] compared thymomodulin syrup at a dose of 3 mg/kg/day with placebo in 12 children with atopic eczema followed-up for 6 months. They showed improvement in several clinical signs in the intervention group (e.g. extent decreased by 12.3 versus 24.0 in the thymomodulin and placebo groups, respectively, measured on a scale with a maximum of 60 points), and also in a number of blood immunological indices. The Cavagni and colleagues study[305] compared thymomodulin syrup at a dose of 120 mg/day versus placebo in a group of 19 children with food allergy who were also placed on restriction diets. At the end of 90 days, significant improvements were noted in only one of four clinical signs (excoriations). Those on thymomodulin appeared to react less to re-challenge with foods that were considered allergic.

Thymostimulin

Two studies have evaluated thymostimulin in atopic eczema, one in adults[306] and one in a mixture of adolescents and adults.[307] The Staughton and colleagues study[306] has only been published in abstract form and reports that reduction in disease severity (actual values not given and results not statistically significant) was noted in an unspecified number of adults randomly allocated to thymostimulin 1.5 mg/kg twice weekly versus placebo in a crossover study. The Harper and colleagues study[307] randomly allocated 29 young adults to thymopentin 1.5 mg/kg twice weekly for 10 weeks versus placebo injections. Co-treatment with topical steroids, emollients and antihistamines was allowed. Of the 26 evaluable patients, the median percentage score (measured on a multiparameter scale) in the placebo group was 99% of baseline compared with 80% in the thymostimulin group ($p = 0.008$), though there was no statistically significant differences for patient-assessed itch and sleep loss. Longer-term follow-up for 12 months showed a loss of the differences between the two groups within 4 weeks.

Thymopentin

Four RCTs were identified. The patient populations and interventions were not sufficiently similar to permit pooling of efficacy data. The first study by Kang and colleagues[311] in 1983 was a small study of 18 participants (mean age 33 years) who were randomised to three times weekly injections of thymopentin (50 mg) or placebo for 6 weeks. Mean improvement in a compound score (maximum 18) was 2.38 and 0.82 in the active and placebo groups, respectively ($p < 0.05$), with five out of eight participants in the active group and two out of ten in the placebo group reporting 'good' improvement ($p < 0.05$). The second much larger study by Leung and colleagues[310] in 1990 randomised 100 young adults with moderate-to-severe atopic eczema in parallel fashion to either daily subcutaneous thymopentin (50 mg) or placebo injections for 6 weeks. They found that improvement in itch was observed in 66% of thymopentin-treated versus 40% of placebo-treated patients ($p = 0.02$), and also statistically significant differences for global severity scores and eczema extent in favour of those on active treatment. Baseline scores and co-treatment usage was very similar in the two groups. The third study by Stiller and colleagues[308] in 1994 randomised 39 adults with severe atopic eczema to three times weekly thymopentin (50 mg) or placebo for 12 weeks. They reported a statistically significant improvement in total severity score (maximum 3) from 2.19 to 1.68 in the active group versus 2.18 to 2.02 in the placebo group ($p = 0.029$). Overall patient-assessed improvement (on a scale of 1 to 5 where 1 = excellent, 2 = good, 3 = fair, 4 = poor and 5 = very poor) was also statistically significantly greater in the active group (from 3.11 initially to 2.78 at week 12) compared with the placebo group (from 3.00 initially to 2.92 at week 12).

The fourth study by Hsieh and colleagues[309] was an unusual one, which was mainly interested in elucidating disease mechanisms. Instead of evaluating the effectiveness of thymopentin, they looked at the effect of withdrawal as surrogate evidence of efficacy. Thus they treated 16 children with three times weekly injections of thymopentin (50 mg) for 6 weeks and then randomised them to continue with either thymopentin or saline injections for a further 6 weeks. The data suggest an impressive decline in total severity score (maximum 15, with higher scores signifying worse disease) from 6.0 at 6 weeks to 12.8 at 12 weeks compared with 5.8 to 4.0 in those who continued on active injections ($p < 0.001$; values estimated from graph as data not given). All eight patients in the thymopentin group finished the 12-week trial, whereas three out of eight of those later randomised to placebo dropped out because of a flare-up of disease.

Harms

No information on harms was given in the Fiocchi, Cavagni, Staughton, Kang or Hsieh studies. One patient in the Harper trial was withdrawn due to possible thymopentin-induced diffuse alopecia areata. Drop-outs in the placebo and active arms of the Harper trial were very high after 12 months (about 70% in each arm). Fourteen of 48 patients (29%) and ten of 52 patients (19%) in the thymopentin and placebo groups, respectively, reported adverse effects in the Leung study, with no particular differences between the two groups apart from three patients in the active group developing local swelling at injection sites lasting up to 30 minutes. Fifteen out of eighteen patients on thymopentin compared with sixteen out of seventeen on placebo experienced adverse events in the Stiller study, which were not specified any further apart from possibly more cutaneous infections in the placebo group.

Comment

The quality of reporting of studies in this category was generally poor, with none (except the Leung study) explicitly describing randomisation procedure, concealment, success of blinding and none performing an intention-to-treat analysis. Study participants were generally well described. The Fiocchi and colleagues study failed to perform the appropriate statistical test (i.e. they only compared before and after scores for eczema severity instead of the difference between thymomodulin and placebo). The Kang and colleagues study erroneously used statistical tests for paired data when the data were unpaired, and they also put great emphasis on enhanced treatment response in patients under the age of 34 years – a *post hoc* finding. Success of blinding was also controversial, for example, in the Kang and colleagues study because physicians were able to guess the correct treatment in 72% of patients. Studies were generally very small, introducing the risk of discarding a potentially useful treatment because the studies were under-powered from the outset. The largest study (Leung *et al.*) was well described and demonstrated a potentially clinically useful effect of thymopentin in the 6-week trial period. Although the Stiller study also showed a statistically significant benefit, the clinical relevance of the small changes in complex scores is unclear. It is also apparent that the Stiller study was part of a much larger multicentre study whereupon the authors freely admit to a policy of conducting a

separate statistical analysis for each centre. However, the number of other centres is never stated, and we have been unable to locate the published data from the other studies. There are therefore strong grounds to suspect publication bias.

Despite these quality limitations, some of the studies do suggest some benefit of thymic extracts/synthetic derivatives in severe atopic eczema, and it is unclear why this mode of treatment was abandoned around 10 years ago. This could be due to cost or the fact that three times weekly injections are not a practical treatment of a chronic skin disease such as atopic eczema, particularly in children.

Immunoglobulin

One small RCT published in French was identified and translated.[312] Based on earlier observations that systemic immunoglobulin may be helpful for nasal and eye allergy, this study evaluated intramuscular injections of immunoglobulin (Allerglobulin™, not available in the UK) versus albumin in a course of ten injections over 3 months. In total, 47 adults and children over the age of 2 years were studied (mean age 15.5 years; age range 2–37 years). Eczema extent and a range of intensity items such as erythema, oedema, itching, and lichenification were recorded, as well as a global evaluation. The authors reported that 72.8% of the 22 patients receiving immunoglobulin had a global amelioration of their disease compared with only 36% of the 25 patients in the control group. Results for all of the intensity items were not fully reported, though it was commented that itching, degree of lichenification, and topography of lesions were all significantly (statistically) improved.

Harms

Adverse effects were not discussed in this paper.

Comment

Positive results are difficult to assess due to their multiplicity and unclear clinical relevance. Randomisation, concealment of allocation, and blinding was poorly described, and it was unclear whether an intention-to-treat analysis was performed. Nevertheless, the positive results of this small preliminary study deserve further work.

Transfer factor

Transfer factor is an extract from white blood cells that is thought to play a key role in cellular immunity. As cellular immunity has been claimed to be impaired in atopic dermatitis, transfer factor has been tried in this condition. One small RCT[313] was identified and translated from Spanish. This study compared intramuscular injections of transfer factor with placebo injections in 24 adult outpatients with atopic dermatitis using a parallel group design for a total duration of 8 weeks. The main outcomes of interest to the authors were immunological markers in the blood such as immunolglobulin levels and T-lymphocyte subset counts. Global clinical improvement according to a physician is also recorded. At the end of 8 weeks, six out of 12 patients (50%) in the transfer factor group were reported to have experienced 'major' improvement compared with four out of 12 (33%) in the placebo group (not statistically significant). The 95% CI around the 17% difference between the two treatments ranged from –22% (i.e. a 22% difference in favour of placebo), to a +55% in favour of transfer factor. Various statistically significant differences in immunological parameters were noted at the end of the study.

Harms

No adverse effects were reported in this small study. No drop-outs were reported. Intramuscular injections are painful.

Comment

This was a small study lacking power to pick up even moderate clinical benefits, though it is acknowledged that clinical response was not the primary aim of the paper. The method of randomisation was clearly described, and the study was described as double-blind. The method of conceal-ment of allocation was unclear. Numbers were exactly the same in each group (n = 12), which in the absence of blocking, raises concerns as to whether simple randomisation was implemented.

Summary of systemic immunomodulatory agents

Allergen–antibody complexes

- One small RCT has suggested benefit for allergen–antibody complex of house dust mite in the treatment of atopic eczema.

Cyclosporin A

- There is no evidence to support the efficacy of topical cyclosporin A in atopic eczema.
- Oral cyclosporin A is effective in atopic eczema but the long-term adverse effects on kidneys and blood pressure are a serious concern, particularly when treating a young population.

- The value of a short holiday period of symptom relief in a chronic condition such as atopic eczema is questionable.
- The cost-effectiveness of cyclosporin or oral steroids versus azathioprine needs to be tested.

Levamisole
- There is little evidence to support any benefit in the use of levamisole in atopic eczema.

PAF
- There is no evidence to support a useful treatment benefit of PAF antagonist based on the results of a small right/left comparison study in 36 patients.

Interferon-gamma
- Daily interferon-gamma injections are an effective treatment for severe atopic eczema but at the cost of frequent flu-like symptoms despite taking analgesia.

Thymic extracts
- There is some evidence of benefit of thymic extracts/synthetic derivatives in severe atopic eczema, and it is unclear why this mode of treatment has been abandoned.
- Cost and the need for weekly injections are limiting factors for long-term treatment with thymopentin, particularly in children.

Systemic immunoglobulin
- One small study of intramuscular immunoglobulin versus albumin suggests marked benefit in children and adults with atopic dermatitis. This study needs to be replicated.

Transfer factor
- One Cuban RCT of intramuscular transfer factor did not find any evidence of any clinical benefit, though the study was too small to pick up even moderately large clinical benefits.

Systemic immunomodulatory agents
- At present, there appear to be no effective and convenient systemic immunodulatory treatments with a good long-term safety record available for the treatment of severe atopic eczema.

Chapter 11

Complementary therapies

We define complementary therapies as a group of therapeutic and diagnostic disciplines that exist largely outside the institutions where conventional healthcare is taught and provided.[406]

Chinese herbal medicine

Chinese herbal medicine forms part of a system that includes oral and/or topical Chinese herbs, acupuncture, diet and exercise for both treatment and prophylaxis of disease. Medicinal plants of various kinds can be taken orally usually in combination with others as a decoction by boiling them in water, and drinking the 'tea' produced, or as external applications directly to the skin. Prescriptions are individually determined based upon an overall assessment of the patient including pulse, appearance of tongue, and disease features, hence, standardised formulae are not generally prepared. Mode of action points towards anti-inflammatory and immunosuppressive properties by down-regulating local T cell-mediated reactions.[407]

Benefits

We located one systematic review[408] reporting two randomised trials of atopic eczema,[314,315] one on adults and one on children, which the authors did not feel were appropriate to pool. Adverse effects such as slight abdominal distension and headaches were highlighted in that review. The authors conclude: "At present it is unclear whether Chinese herbal treatments of eczema do more good than harm."

In addition to these two trials we have identified a further two,[316,317] which evaluated oral Chinese herbal decoction compromising *Ledebouriella seseloides*, *Potentilla chinensis*, *Clematis armandii*, *Rehmannia glutinosa*, *Paenia lactiflora*, *Lophatherum gracile*, *Dictamnus dasycarpus*, *Tribulus terrestris*, *Glycyrrhiza glabra*, *Schizonepeta tenuifolia*, except Sheehan[315] who used *Anebia clematidis* instead of *Clematis armandii*. All four RCTs are reported below.

The efficacy study of children by Sheehan and Atherton[315] evaluated Chinese herbs (as above) in a decoction versus placebo comprising a mixture of 'inert' plant materials, once daily, in 47 children with atopic eczema over an 8-week period. Skin was assessed using a score of 0–3 for erythema, surface damage (the net effect of papulation, vesiculation, scaling, excoriation and lichenification) plus percentage area affected (maximum score 180) and patient preference. Median percentage changes of the clinical scores from baseline were 51% for Chinese herbs compared with 6.1% for placebo for erythema, and 63.1% and 6.2% change for surface damage in the herbs versus placebo groups, respectively. A 1-year follow-up study of the children concludes that Chinese herbal medicine, in the medium term, proved helpful for approximately half the children who originally took part in the RCT.[409]

The adult study by Sheehan and colleagues[314] evaluated Chinese herbs (as above) in a decoction versus 'inert plants' placebo, once daily, in 40 adult patients with atopic dermatitis. Skin was assessed using a score of 0–3 for erythema, surface damage (the net effect of papulation, vesiculation, scaling, excoriation and lichenification) plus percentage area affected. Maximum score was 180 and patients' subjective comments included itch, sleep loss and preference. Geometric mean total body score for erythema at the end of Chinese herbs treatment was 12.6 and at end of placebo phase was 113 (baseline scores not given). The geometric mean for surface damage at the end of Chinese herbs treatment was 11.3 compared with 111 at the end of placebo phase (baseline values not given).

The study by Latchman and colleagues[317] evaluated the same combination of Chinese herbs as above (finely ground) versus the same Chinese herbs in a new palatable form of freeze-dried granules in 18 patients with atopic eczema over an 8-week period. Skin was assessed using a score of 0–3 for erythema, surface damage. There was a significant reduction in erythema and surface damage compared with baseline ($p < 0.001$). The groups showed no difference in clinical outcome between formulations.

The study by Fung and colleagues[316] evaluated the same combination of Chinese herbs above versus 'inert plants' placebo in 40 patients with atopic eczema over an 8-week period. Scores based on the severity and extent of erythema, surface damage, lichenification and scaling were recorded. There was a general trend of clinical improvement for both Chinese herbs and placebo. There was no

statistically significant treatment effect over placebo for all four clinical parameters, except for lichenification at week 4.

Harms

Unpalatability of the herbs in both active and placebo groups was a common adverse effect causing ten drop-outs in Sheehan and Atherton[315] study and eight drop-outs in the Sheehan and colleagues[314] study. Other adverse effects included abdominal distension, headaches, transient dizziness, gastrointestinal upsets, one lichenoid eruption and one facial herpes. There is a concern with Chinese herbs of potential hepatotoxicity; however, all the studies, except Latchman and colleagues carried out pre and post-treatment liver function tests with no abnormalities detected.

Comments

All studies were randomised but method and concealment of allocation were not described. All were described as double-blind, except Latchman and colleagues[317] where no blinding was mentioned. No intention-to-treat analysis was carried out. It is questionable whether the placebo plants are truly inert in the treatment of eczema. The children study by Sheehan and Atherton[315] reports large effects from Chinese herbal medicine highlighting a promising treatment of atopic eczema. This has not been replicated in the other studies, though they are all quite similar. Clearly more RCTs with larger sample sizes over a longer period of time are needed.

Massage therapy

It is possible that massage therapy might be beneficial in atopic eczema as a stress-reducing and enjoyable interaction between parent and child, by increasing peripheral circulation (which may be defective in atopic eczema) or by increasing compliance with topical treatments. One small RCT of massage therapy in young children has been identified.[321]

Benefits

Twenty children with atopic eczema (mean age 3.8 years) were randomised to continue with standard therapy with topical corticosteroids, emollients and antihistamines or standard therapy plus a course of daily 20-minute massage following video demonstration for a period of 1 month. Parents in the massage group reported greater degrees of improvement in anxiety scores, tactile defensiveness, and a coping index when compared with the control group. Certain eczema activity signs (e.g. scaling and excoriation) improved statistically from baseline in the active group compared with only scaling in the control group, though the appropriate statistical comparison of differences between the two groups was not done.

Harms

No adverse effects were reported in this study. The cost of instruction by a therapist and video for one session was estimated at $30.

Comment

This small pilot study showed that parents and their children who were allocated to massage therapy in addition to their standard care were less anxious and more able to cope. Even though much of these effects could have been partly due to the unblinded nature of the study, increased coping with a chronic disease is a desirable goal. It appears that the technique of massage can be taught cheaply and quickly. It is unclear whether the technique has any specific benefit on overall atopic eczema activity, and more trials in other countries are needed.

Hypnotherapy/biofeedback

Hypnotherapy and biofeedback used to develop relaxation techniques with or without mental imagery may be beneficial in the management of atopic eczema to distract from the symptoms associated with the itch–scratch–itch cycle.[320] One RCT has been located that addresses the use of these techniques in atopic eczema.[320]

Benefits

Forty-four children with atopic eczema were randomised to either hypnotherapy, biofeedback or discussion only, for a period of 20 weeks after being stabilised on topical and oral treatment in a 2-week run-in period. This study attempted to measure changes in the objective symptoms of erythema, surface damage and lichenification, which resulted from attempts to reduce children's subjective experience of itching (and subsequent scratching) using:

- relaxation that focused specifically on reducing itching (hypnotherapy)
- relaxation that did not involve any direct imagery *per se* (biofeedback)
- an 'attention placebo' group who were encouraged to discuss the eczema without any mention of symptom control.

The children in the hypnotherapy and biofeedback groups showed a significant reduction from baseline in the severity of surface damage and lichenification compared with the control group.

There was no difference between the two relaxation techniques. Erythema was not changed by the interventions.

Harms
No adverse effects were reported in this study.

Comments
This study shows that relaxation techniques, with or without direct imagery, may be of some benefit in the management of atopic eczema. The girls in the hypnotherapy group showed greater improvement than the girls in other groups and showed greater improvement than the boys in the hypnotherapy group. Lack of blinding threatens the validity of the study. The authors state that all the parents and children in the study were aware that the aim of the study was to help them with their symptoms further threatening the validity of the study. In particular the 'attention placebo' was designed to avoid mentioning symptom control. There were 13 drop-outs but no explanation was given for reasons. No intention-to-treat analysis was carried out, hence, it is not clear what effect the high number of drop-outs had on the results.

Homeopathy and aromatherapy

We located one study protocol[318] in German with an English abstract assessing the efficacy of classical homeopathic treatment in 60 patients with atopic dermatitis. The patients were randomised to receive a homeopathic treatment or a placebo for a period of 8 months. The homeopathic doctor was free to change remedies, dosages or potencies if required by the reaction or a new case-picture of the patient presented according to classical homeopathy principles and guidelines.

We located one abstract[319] of a preliminary study on the effect of aromatherapy on childhood atopic eczema. Sixteen children were treated with either counselling and massage with essential oils by both the therapist and the mother or the same treatment without essential oils. Parent-assessed day-time irritation score, night-time disturbance scores and general improvement scores were assessed for a period of 8 weeks. The results showed a statistically significant improvement of the eczema in the two groups of children following therapy, but there was no significant improvement shown between the experimental and control groups. Correspondence with the author confirms the study was randomised. The full report will be available shortly.

Summary of complementary therapies

Chinese herbs
- Two studies of Chinese herbal treatment conducted in children and adults by the same research team found significant benefits compared with placebo.
- Two further RCTs conducted by independent groups failed to demonstrate any clear clinical benefit.
- Further larger and long-term RCTs of Chinese herbal treatment seem worthwhile.

Hypnotherapy/biofeedback
- One unblinded study of hypnotherapy and biofeedback suggests a benefit in terms of surface damage and lichenification but not erythema.

Aromatherapy
- One small study of massage with and without essential oils plus counselling has suggested benefits of counselling and tactile contact but no benefit from addition of essential oils.

Massage therapy
- One small study of massage therapy in addition to standard care in children has suggested benefit in terms of reduced anxiety and better coping skills.

Chapter 12

Other interventions

Nitrazepan

Nitrazepan is a widely used benzodiazepine drug for night-time sedation. As itching at night can be a major problem for patients with atopic eczema, the benefit of nitrazepam in atopic eczema has been evaluated by an RCT conducted by Ebata and colleagues.[322]

Benefits

Ten adult outpatients with atopic eczema were entered into a double-blind placebo-controlled cross-over trial of three successive nights whereby they were given either 5 mg of nitrazepan or a placebo, with a washout interval of 4 days. An infrared video camera to identify bouts of scratching lasting more than 5 seconds was used to calculate the percentage of total scratch time in each group as an index of nocturnal scratching. Total scratch time was very similar between the two groups, occurring in 6.5% of the time for those taking nitrazepan compared with 5.4% of the time with placebo. Frequency of bouts of scratching was slightly less in the nitrazepan group, but the mean duration of scratching bouts was longer in the nitrazepan group compared with placebo (both comparisons statistically significant at the 5% level). Degree of itching and the condition of atopic dermatitis did not change during the 2 weeks of the study.

Harms

Although no adverse effects were mentioned in the results section, the authors comment that none of the patients experienced any rebound insomnia or residual sedative effect following the nitrazepan tablet.

Comment

This very small study lacks power to exclude moderate-to-small treatment benefits of nitrazepan, though there was no indication of any benefit in the patients studied. The most interesting thing about the study was the novel method use to assess nocturnal itch, though it remains to be seen whether this objective measure is a good predictor of general eczema improvement as measured by validated scales or patient-evaluated measures.

Ranitidine

The histamine type 2 receptor antagonist, ranitidine, modifies the immune system, possibly by its inhibition of histamine activity. Based on the observations that a few atopic patients treated with ranitidine for gastric ulcer have improved, Veien and colleagues[323] conducted an RCT of ranitidine treatment for hand eczema in patients with atopic eczema versus placebo.

Benefits

Forty-seven adults with a clear description of hand eczema and atopic eczema elsewhere (allergic contact eczema excluded) were randomly allocated to oral ranitidine, 300 mg twice daily or placebo tablets of identical appearance for a total of 4 months. A potent topical steroid cream (beta-methasone valerate) and lubricating ointment to be used on the hands only was permitted throughout the trial. Thirty-eight of the 47 patients completed the 4-month trial, and intention-to-treat analysis was conducted. The total in a composite position-assessed sign score was reduced from a mean of 10.17 to 4.91 in the group receiving ranitidine and a topical steroid compared with a reduction from a mean of 10.58 to 7.46 in the group receiving placebo in the topical steroid ($p = 0.07$). Most of this reduction was due to significant reduction in area involvement. Seventeen out of the 23 patients treated with ranitidine reported clearing or marked alleviation compared with eight out of the 24 patients in the placebo group ($p = 0.02$).

Harms

No adverse effects from either ranitidine or placebo were reported in this study.

Comment

Although most trials of 'hand eczema' had to be excluded from this report because the nature of the eczema was unspecified, this study provides a clear description to indicate that those included probably had atopic eczema as the sole cause for their hand dermatitis. Although the method of randomisation, concealment and degree of success of blinding is unclear, the intention-to-treat analysis was helpful. The proportion of patients cleared or markedly alleviated (a combined physician/patient score) and other composite scoring methods suggest a modest benefit of ranitidine in this subgroup of adult atopic eczema patients. It is important to replicate the results of this single RCT.

Theophylline

The β-adrenergenic theory of atopy implies a general defect of β-receptors in atopic eczema patients leading to low levels of cAMP within cells. In order to test the importance of the β-adrenergenic theory in atopic eczema, Ruzicka[324] conducted a small RCT crossover study of the phosphodiesterese inhibitor theophylline (which increases cAMP levels) versus placebo in adults with atopic eczema.

Benefits

Fourteen adults were included in the study, 12 of whom were evaluable at the end of 2 weeks. They took either 300 mg of a theophylline/ethylenediamine preparation or identical placebo tablets daily in addition to antihistamines. At the end of the 2-week period, the mean number of antihistamine tablets used by the patients was 1.65 and 1.78 in the theophylline and placebo periods, respectively. Mean symptom score was 1.82 in the theophylline and 1.68 in the placebo period, and sleep disturbance was 5.0 out of 14 nights in the theophylline group compared with 4.4 out of 14 in the placebo groups. No other differences were statistically significant.

Harms

No adverse effects were mentioned in this study, but theophylline is a drug with a narrow therapeutic range which can result in cardiac toxicity.

Comment

Methodological details of this short report are scanty. Although there was no obvious difference between the two groups, the study was very small and of very short duration. It is difficult to exclude any possible benefit of theophylline on the basis of this study.

Salbutamol

Based on previous animal studies, which demonstrated that the β_2-adrenoceptor agonist salbutamol can reduce inflammation, Archer and MacDonald[325] conducted an RCT of salbutamol ointment (1% base in white soft paraffin, twice daily) plus a placebo oral tablet with oral salbutamol (a slow-release spandet 8 mg twice daily plus white soft paraffin placebo ointment twice daily) versus a placebo spandet and white soft paraffin only in a 2-week crossover study in 20 adults with atopic eczema.

Benefits

Itching, number of affected zones, skin thickening, vesiculation, epidermal change and redness were recorded as outcomes and none of these showed any clinically useful or statistically significant changes. Reduction in the score for redness was highlighted by the authors as being statistically significant in favour of the ointment and tablet salbutamol when compared with placebo, though baseline scores were very different. Baseline redness score for patients on salbutamol ointment was 22 at the beginning and this decreased by 9.5 at Day 14 (maximum possible score 60). Baseline median score for oral salbutamol was 29 with a median decrease of 10.5 compared with a baseline score of 14 for the placebo and median decrease of 8.5.

Harms

There were five withdrawals with three due to adverse effects. Tremor was reported by five patients taking oral salbutamol and in one patient using the salbutamol ointment. Some degree of systemic absorption of salbutamol ointment was demonstrated in two patients.

Comment

The method of randomisation, concealment of allocation, and investigator blinding in this study was not described. No intention-to-treat analysis was performed. Although the statistically significant improvement in redness in those taking salbutamol has been highlighted, this was not declared as a main outcome measure out of the six outcome measures beforehand, and could probably be explained by regression to the mean given the higher baseline scores for those taking salbutamol. Although no clinically useful benefits of salbutamol ointment were demonstrated in this study, it is probably too small to exclude even large treatment effects.

Papaverine

Papaverine is a naturally occurring compound found in opium but lacking in the narcotic activity. It is a potent inhibitor of the enzyme phosphodiesterase and it is this property that provides a possible beneficial action for atopic eczema. Atopic eczema is characterised by elevated phosphodiesterase levels in mononuclear cells. Papaverine has been advocated for many years for the treatment of atopic eczema, and based on a previous open study, Berth-Jones and Graham-Brown[326] conducted a crossover RCT of oral papaverine versus placebo in atopic eczema. Another RCT was published a year after by Shupack and colleagues[327] of a similar small placebo-controlled crossover trial of oral papaverine hydrochloride in the treatment of atopic eczema.

Benefits

In the Berth-Jones and Graham-Brown study, 50 patients with a mean age of 25.6 years were

randomised to receive either papaverine hydrochloride 100 mg four times daily or 60 mg four times daily for children under 12 years, or matching placebo each for 4 weeks. All patients had moderate-to-severe atopic eczema and were allowed to continue with emollients, a bath oil and a topical steroid preparation throughout the trial. Outcome measures included itching assessed on a visual analogue scale by patients, clinical scoring of extent and severity and rate of usage of topical steroid preparation. Of the 45 evaluable patients, mean itch score in the last 7 days of each treatment period was 58.6 in the active phase compared with 55.7 in the placebo phase (maximum score 140). Clinical score (maximum of 720) in the active phase was 178 and 176 in the placebo phase. Baseline scores were not presented in the papers. Topical steroid usage was very similar between the two groups.

In the Shupack and colleagues study, 30 patients aged 18 and above were randomised into a crossover study of papaverine hydrochloride in doses of 150–300 mg three times daily compared with placebo as an adjunctive treatment to emollients and topical steroids. Of the 20 (out of 30) patients who completed both phases of the crossover, no statistically significant advantage over placebo for any of the parameters of itching, physician's and patient's global evaluation were reported. Apart from non-significant *p*-values, the actual data for these changes were not presented in the paper.

Harms

No serious adverse effects were reported in the Berth-Jones study and symptoms such as tiredness were similar in both groups. In the Shupack study, however, three of the study patients on active treatment developed abnormal liver function tests, which were not due to infectious hepatitis. Nausea occurred in 46% of patients on papaverine compared with 27% on placebo, though this difference was not statistically significant.

Comment

The method of randomisation in both of these studies was unclear as was concealment of allocation of randomisation. Drop-out rates were modest in both studies and no intention-to-treat analysis was performed. Although both studies were small, the Berth-Jones study in particular provides additional data to inform the reader on the possibility of missing clinically useful benefits. Based on their results, the power of their study to detect the 25% improvement in the itch score was over 85% and the power of the study to detect a 25% improvement in the clinical score was between 75% and 80%. Although the authors clearly started the trial with an enthusiasm for papaverine based on a previous open study, the study has demonstrated the need to use methods such as RCTs to reduce the possible bias associated with the reporting of such open studies. The abnormal liver function tests in the Schupack study are also a cause for concern.

Suplatast tosilate

It has been suggested that a rebound phenomenon occurs in people with atopic eczema who have been treated for prolonged periods with strong topical corticosteroids. We found one small RCT[328] that evaluated the role of an anti-allergic medication called suplatast tosilate (which down-regulates production of IgE and related cytokines) versus bufexamace ointment to prevent rebound from topical steroids in atopic eczema.

Benefits

Thirty-two patients who had been treated with strong steroid ointment for several years were randomised to either bufexamace ointment (a non-steroidal anti-inflammatory ointment) or bufexamace ointment and oral suplatast tosilate (400 mg/day). In the control group, 15 patients experienced the rebound phenomenon after 2 weeks compared with only two of 17 patients in the active group (rebound was undefined). Several cytokines increased in the control group but not in the active group.

Harms

No adverse effects were reported in this small study.

Comment

The issue of rebound from regular use of topical steroids is a serious and important one as it is possible that the regular use of corticosteroids increases the chronicity of disease while benefiting the short-term control of flare-ups. This small study was unblinded (the control group did not have an oral placebo) and the 'rebound' was completely undefined and therefore highly prone to investigator bias. The study should be followed by a randomised, controlled double-blind trial over a long period with clinical outcomes and a vehicle-only comparison group.

Summary of other interventions

Nitrazepam

- One small RCT failed to show any benefit of nitrazepam at night for night-time scratching as detected by infrared camera.

Ranitidine
- One RCT has suggested a modest benefit of oral ranitidine treatment above placebo for hand eczema in patients with atopic eczema. These results need to be replicated elsewhere.

Theophylline
- One RCT of 12 patients has compared oral theophylline versus placebo for 2 weeks in atopic eczema and not found any treatment benefits.

Salbutamol
- There is no RCT evidence to support the use of topical or oral salbutamol in atopic eczema.

Papaverine
- Two small RCTs do not suggest that oral papaverine has a clinically important benefit in the short-term treatment of atopic eczema.

Suplatast tosilate
- One small unblinded study suggests a possible benefit of suplatast tosilate in preventing the steroid 'rebound phenomenon', but is difficult to interpret in the absence of a vehicle-only group.

Chapter 13

Discussion

Treatments with no RCT evidence

As pointed out in chapter 1, a systematic review that is driven only by published RCT data can only answer questions that have been asked by such trials. Many other treatments, combinations of treatments, and management approaches are used for people with atopic eczema throughout the world. Some, such as climatotherapy are probably very rarely used if at all in the UK, whereas others such as wet-wrap bandages and oral azathioprine are used by a large number of UK dermatologists.[36] Questions need to be asked about these therapeutic options in order to identify possible research gaps. Therapies that had not been identified by our team were canvassed from colleagues and professional networks as described in chapter 2, and the results are shown in *Table 38*.

Division between RCTs and no RCTs is arbitrary

Table 38 probably only identifies some of the questions that can be asked of therapies that are currently used in atopic eczema. Some treatments (e.g. type IV phosphodiesterase inhibitors) are relatively new and experimental, and clinical trials will hopefully be conducted (or are currently in progress) in the near future. It should also be remembered that just because treatments for which some RCT evidence was found, mentioned in the previous chapters, this does not mean that the questions regarding each of those interventions have been answered. Thus in the section on emollients, there are at least ten important unanswered questions remaining. Similarly, just because there is one RCT evaluating deep-sea water versus physiological salt water does not mean that the evidence for salt water baths has been 'sorted', as no RCTs have been located that answer the more urgent question of whether salt baths have any benefit above ordinary baths.
The division between treatments for which no RCTs could be found and those for which some RCTs were found is therefore somewhat arbitrary. *Table 38* should be viewed as an **indication** of some aspects of therapies that were not discussed in the commentaries in the results chapters, rather than as a comprehensive blueprint of unanswered questions for future primary and secondary research.

TABLE 38 *Therapeutic interventions currently in practice for which no RCTs could be found*

Pharmacological	Complementary treatments	Miscellaneous
• Antimetabolites such as methotrexate	• Acupuncture	• Antibacterial clothing
• Cytotoxic immunosuppressants e.g. Mycophenolate mofetil	• Calendula cream	• Climatotherapy (high-altitude low-allergen environments)
• Leukotrine receptor antagonists e.g. Montelukast*	• Spa treatment	• Different ways of using conventional treatments e.g. short bursts of strong topical steroids vs longer-term weaker preparations*
• Oral azathioprine*		• Exercise
• Oral prednisolone*		• Extracorporeal photopheresis
• Thalidomide		• Hospital admission
• Type IV phosphodiesterase inhibitors		• Occlusive dressings e.g. Duoderm™/ Granuflex™
		• Organisation of care, e.g. special eczema clinics, community liaison nurses, nurse follow-up clinics, joint primary/secondary care chronic disease clinics
		• Stress management
		• Water softening devices
		• Ways of improving adequate dosage/concordance, e.g. use of the fingertip unit
		• Impregated bandages, e.g. Ichthopaste™ or Quinabands™
		• Wet-wrap bandages

**Ongoing trials have been identified for these agents DuoDERM™, Granuflex™, ConvaTec, UK; Ichthopaste™, Smith & Nephew Health, UK; Quinabands™, SSL, UK*

Difficult sites and combinations of treatments

In addition to the interventions mentioned in *Table 38*, consideration also has to be made of treatment of atopic eczema at specific difficult body sites such as the scalp or backs of hands, as there may be specific issues such as formulation, penetration, cosmetic acceptability and adverse effects related to such sites. It has also been pointed out that future studies should consider evaluating entire management approaches that mimic real practice. Thus, combinations of treatments such as emollients, topical steroids and education should be evaluated together rather than in isolation (Meredith B, personal oral communication, 1999).

Prevention

It is also important to always consider prevention of atopic eczema in the widest sense by means of intrauterine or early life environmental manipulation.[16] Although the links between the environment and atopic eczema are still in the early stages of research,[5] energy needs to be directed at prevention as well as treatment of established cases with pharmaceutical agents that at best only control symptoms.

Diagnostic tests

Although diagnostic tests are not regarded strictly as 'treatments', certain tests such as patch tests also need to be evaluated as an aspect of the management of atopic eczema. This is because discovering a superimposed contact allergy (e.g. to lanolin, a steroid or a preservative in a cream) could significantly improve the disease, which had all been put down to constitutional factors. Ideally the benefit of such testing, which has considerable time and health costs if applied to all atopic eczema sufferers, needs to be put to the test by means of RCTs. This will reduce selection bias and will also permit evaluation of clinical outcomes as opposed to just positive patch test results, the clinical significance of which is not always clear in atopic eczema patients. Likewise, the popular request for 'allergy tests' among families of children with atopic eczema in the belief that their child's atopic eczema is caused by one specific allergy, needs to be put to the test in an RCT with long-term clinical measures rather than blood or skin tests as outcomes. This applies to the lucrative high-street industry of performing 'allergy tests' on vulnerable atopic eczema sufferers in addition to the more conventional tests performed in hospitals.[410]

Horizon scanning

It is likely that the next 5 years will witness an increase in the number of topical pharmaceutical agents for treatment of atopic eczema. Thus treatments such as tacrolimus and ascomycin derivatives are already well down the road to development and evaluation, and others such as cytokines and phosphodiestarase inhibitors are following. Two recent review articles have considered future developments.[26,391]

Validity and robustness of results

Sensitivity analyses in the traditional sense of exploring the effects of removing certain studies with particular characteristics within a meta-analysis is very limited within this report due to the little pooling that was possible. Further consideration of the validity of the results of this report is worth a brief mention in this section.

Missed studies

It is acknowledged that a predominantly electronic bibliographic database search will miss certain RCTs that have been misclassified on those databases, articles from journals not listed on those databases and unpublished studies. In terms of a reference standard for published studies, we compared the results of handsearching the entire contents of *Clinical and Experimental Dermatology* for atopic eczema trials and those with our electronic searching. None of the five controlled trials had been missed by our searching methods. Two were included as RCTs, two excluded as non-RCTs and a further study was excluded as it evaluated experimentally induced reactions in atopic eczema patients. Our yield of RCTs of antihistamines in atopic eczema (31 reduced to 21 after evaluating the hard copies) was very similar to the yield identified by a more intensive independent search by members of the Cochrane Skin Group (Diepgen P, personal oral communication, 2000). We found eight more RCTs for antihistamines than a recently published 'systematic review' of antihistamines in atopic eczema.[362]

Given the fact that at least 200 specialist dermatology journals have been identified (Delamere F, personal oral communication, 2000), many of which are not registered with MEDLINE, it is likely that some RCTs of atopic eczema have been missed, particularly in non-English and less-well-read journals.

The authors also suspect that there is a large body of unpublished data held by pharmaceutical companies for various reasons. Clinicians who have lacked the time or motivation to publish their results also hold such unpublished data. It is likely that more 'negative' studies fall into these categories. Estimating the magnitude of this hidden part of the iceberg of evidence is difficult without additional research. In the field of evaluating evening primrose oil for instance, two of the authors of the current report were commissioned by the Department of Health in 1997 to conduct a meta-analysis of all trials. Sadly, permission to publish this report has never been granted, but it did contain the results of nine additional small unpublished studies held on file by the company. Despite writing to the company for any unpublished data for this report, no data have been forthcoming to date (*Tables 39* and *40*). The extent of holding unpublished data on file by pharmaceutical companies is difficult to assess, but it is likely to continue to some degree if the UK drug licensing process (which is privy to all such data) maintains its current code of keeping such data out of the public domain.[411] Some large drug companies such as Glaxo Wellcome and Schering Healthcare have recently signed-up to

TABLE 39 *Responses from pharmaceutical companies of requests for unpublished or missed RCTs*

Company	Response?	Result
Glaxo Wellcome	Yes	All in public domain
Janssen-Cilag	No	
UCB Pharma	No	
Hoescht Marion	Yes	No RCTs
Schering-Plough	Yes	No new, all in public domain
Wyeth	No	
Stafford-Miller	Yes	No RCTs
Novartis	Yes	No new RCTs
Merck Sharp	No	
Pfizer	Yes	No research in this area
Sinclair	Yes	No RCTs
Fisons	No	
Searle	Yes	Compiling data

TABLE 40 *Responses from pharmaceutical companies of requests for unpublished or missed RCTs*

Company	Response?	Result
Leo	Yes	Six RCTs
		Summary of FU9202DK unpublished trial excluded because unspecific hand eczema, Ramsay 96 already included, excluded Poyner 1996 unclear whether had atopic eczema, and Hill 1998 hand eczema, one, two included: Wilkinson 1985 and Thaci 1999
Galderma	No	
Bioglan	Yes	Two RCTs
		Berberian 1999 and Drake 1994 already included both trials on file
		No unpublished papers available
Yamanouchi	No	
Crookes	Yes	No RCTs but a very useful file sent containing research on E45 emollient published and unpublished data
Seton	No	
Scholl	No	
Kestrel	No	
Quinoderm	No	
Bristol Myers	Yes	No unpublished RCTs carried out
Steifel	No	
Dermal	Yes/No	No unpublished RCTs
Schering Healthcare	Yes	None on file
Typharm	No	
Phyto pharmaceuticals	Yes	
Squibb	No	

a policy of making all unpublished RCT data available to Cochrane reviewers. This is a welcome development. There is a case to be made for it to be compulsory that all clinical data relating to trials on patients within the NHS to be made available as part of ethical approval of any study.

Author bias

As stated in chapter 2, blinding of authors/institution was unrealistic as certain key words would have immediately identified the study to one of the reviewers who is very familiar with the field. Although bias in the way certain drugs or interventions are described is bound to happen in any subjective narrative report, the authors have striven to minimise such effects by adopting a standard approach and by explicitly separating the reported data from their own comments.

External validity

Only one[127] out of 283 studies contained a clear indication (such as the words general practice, community or primary care in the title, abstract or methods) that the study was carried out in a primary care setting. Given that most cases of atopic eczema are treated in the UK, the generalisability of the results of the studies conducted in a hospital setting summarised in this report may be limited. The magnitude of benefit from say, a topical corticosteroid, may be reduced substantially in milder disease in the community as there is less potential to improve from a higher baseline severity score. Other issues such as patient preference, and different concordance rates in primary care may further limit the generalisability of studies conducted in well-motivated patients in hospital. It is for these reasons that future pragmatic trials should be considered in primary care.

The need for updating

Inevitably, RCTs are continually being performed in atopic eczema, and there will be a time when research stands still in order to summarise the totality of evidence. Based on our own search updates, we estimate that around one new RCT on atopic eczema is published each month. In addition, we are aware of at least ten ongoing RCTs in atopic eczema including interventions such as topical corticosteroids, Montelukast and tacrolimus through informed contacts, the Cochrane Skin Group and the National Research Register. Those making treatment guidelines or recommendations based on the results of this report are therefore advised to update their conclusions with further searches. Those topic areas that will be taken forward as Cochrane Reviews will be updated automatically as part of the Cochrane Collaboration process.

Chapter 14

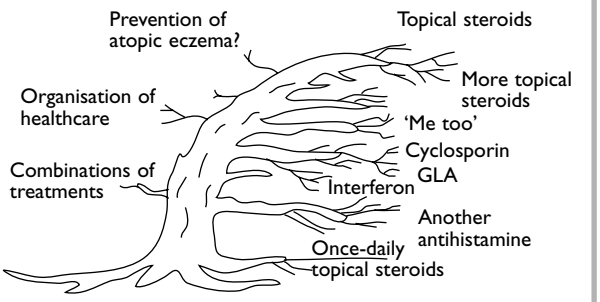
Summary and conclusions

Research included in the review

Coverage and clinical relevance

To the best of our knowledge, this is the first ever comprehensive glimpse of all RCTs of atopic eczema conducted to date. The quality and quantity of 272 included RCTs covering treatments for atopic eczema is highly variable, and the clinical relevance is often difficult to understand because of complex quantitative outcome measures. It is clear that most RCTs have been about issues that are important to the Pharmaceutical Industry, often competing for a niche in a 'me too' market. This is understandable, but as chapter 13 pointed out, there is a major discrepancy between what answers these studies provide and what physicians and their patients often ask. As *Figure 6* suggests, issues such as prevention of atopic eczema, manipulation of trigger factors and organisation of care are mere twigs in the tree of atopic eczema RCTs at present.

FIGURE 6 *The tree of RCTs of atopic eczema over the past 40 years has been a lopsided one*



Much investment has gone into evaluating different topical corticosteroids, yet we still know little about the best way to use them. Little is known about other simple cheap alternatives such as topical coal tar, use of bandages and salt water baths. Many newly developed and potentially toxic drugs such as cyclosporin A have been thoroughly studied (12 RCTs), yet there is a complete absence of RCTs on some alternatives such as azathioprine and oral steroids. Such a discrepancy can give rise to the illusion that one is useful and the other is not in the current climate of evidence-based medicine, whereas the correct conclusion is that there is insufficient evidence to decide between them at present. The lack of informative RCTs for the most widely used treatments for atopic eczema (i.e. emollients and bath additives) is striking. This is particularly so when a recent detailed economic study in Nottingham suggested that the emollient and bath oils accounted for 81% of total NHS prescribing costs for children with atopic eczema in the community.[412]

In addition to the 'pull' of the Pharmaceutical Industry's agenda, lack of public investment into researching the treatment of atopic eczema has been another factor leading to the unbalanced coverage of the tree of RCTs in atopic eczema. We did not identify one RCT of atopic eczema supported by the UK Medical Research Council in our search. Clinical trials are expensive and time consuming to run, and it is a credit to some working in the NHS that they have managed to carry out well-designed large independent RCTs in their own time.[243] It is also possible that some of the obvious gaps in researching atopic eczema treatment have not been addressed simply because researchers working in relative isolation have not asked the right questions, or because the more practical questions concerning comparison of several commonly used treatments are too difficult or are perceived as less interesting to researchers than testing a 'new' drug.

Despite the authors' familiarity with the subject area, some genuine surprises occurred as a result of the review, such as the finding of two RCTs that suggest cotton clothing is no better than soft synthetic fibres, identifying a well-conducted RCT on bioresonance that did not show any benefit, and finding out that there is no good RCT evidence to support the use of topical antibiotic/corticosteroid combinations. On the positive side, there were some RCTs indicating a potentially useful benefit of psychological and various non-pharmacological approaches. It was also interesting to locate five RCTs that suggested there was little, if any, advantage in using topical corticosteroids twice as opposed to once daily as this might have clear benefits to patients in terms of convenience of fewer adverse effects, as well as offering potentially very large cost savings to the NHS if adopted on a national scale.

What about non-RCT data?

While it is perfectly appropriate to use non-RCT data to answer questions on natural history and adverse effects, the authors have stuck to their policy of only considering the RCT as the study design that is able to minimise bias the most. Throughout the report there are examples of RCTs (levamisole[299] in chapter 10 and papaverine[327] in chapter 12) not demonstrating any benefit to an intervention despite earlier enthusiastic results from non-RCT studies. The RCT design does not guarantee freedom from bias of course, and threats to the validity of individual studies have been commented upon throughout the report.

Quality of reporting

Quality of reporting was generally very poor in most of the studies. Our primary quality criteria of a clear description of generation of the randomisation sequence, concealment of allocation of randomisation, adequate description of blinding and an intention-to-treat analysis were hardly ever fulfilled. These features have been shown to lead to biased estimates of treatment effects.[46] Some studies just reported *p*-values and no data. Others have performed multiple significance tests on six or more different physical signs at different time intervals and highlighted those that are positive without declaring any *a priori* main outcome measures. This is akin to throwing a dart and drawing a dartboard around it.[413] Other common problems were lack of CIs, failure to take different baseline scores into account, and testing changes between baseline for two drugs separately as opposed to comparing the change in scores between treatments.[414]

Many studies, particularly earlier ones, were clearly under-powered. This is not necessarily a problem providing they have been interpreted correctly with CIs to present a range of plausible treatment effect, but this was seldom the case.[415] More worryingly was the fact that several authors misinterpreted lack of evidence of treatment benefit in small studies as being equivalent to evidence of no effect. Duplicate publication was also rife, as indicated by the list shown in appendix 4.

The situation has probably improved over the past 10 years, particularly with the major dermatology journals. Thus, studies such as that conducted by Boguniewicz and colleagues[159] are a pleasure to read as there is a clear description and flow chart of what has happened to all those who were originally entered into the study. These changes probably reflect a change in standards of clinical trial reporting in larger journals. The recent adoption of the CONSORT statement (designed to improve clinical trial reporting) by journals such as the *Archives of Dermatology, Journal of the American Academy of Dermatology* and the *British Journal of Dermatology* is a welcome step forward.[416]

Study design issues

Five points are worthy of further consideration in terms of study design for atopic eczema studies and these are discussed below.

Studies need to be longer

Perhaps the most important point is to encourage longer duration of future RCTs of atopic eczema. For most people, atopic eczema is a chronic intermittent disease, and studies that evaluate numbers of relapses and duration of symptom-free periods are required in addition to studies that measure short-term reduction in clinical signs.

Awareness of a large placebo/vehicle effect

As some studies have demonstrated,[299] the placebo or vehicle effect in atopic eczema can itself account for around 30% improvement. This needs to be taken into account when conducting sample size estimates for RCTs.

Profusion of outcome measures of uncertain clinical significance

Given such a range of outcome measures and complex scales with different symptom and sign weightings in atopic eczema, there is plenty of scope for introduction of bias when assessing a new drug by selecting a scale that is likely to enhance the specific feature which the drug is designed to improve (e.g. erythema or itch). Many of the 'named' scales have not been tested adequately.[417] In many studies, the word 'validated' when referring to a scale simply meant that it had been used before. There are almost as many un-named scales as there are trials, and these may introduce a major bias towards enhancement of treatment response.[418] There has been a tendency to concentrate on the physical signs of atopic eczema in such scales to the exclusion of patient data on the basis that the former is 'objective' and the latter is 'subjective'. Yet the variability of the 'objective' measures is often more than patient's symptoms, and their repeatability between physicians is often poor.[31] The clinical significance of a difference in a quantitative score of 13.4 between two treatments is also difficult for physicians to relate to patients.[337] Greater consideration should therefore be given to including patient-derived outcome measures alongside the physician-based scales, and use of scales should be restricted to a few well-tested ones unless there are good reasons to do otherwise.

Future studies need to make it very clear whether the arm of treatment is to control symptoms, improve quality of life for patient and family, or to clear the entire rash (which may be unrealistic at present).

Crossover designs

Although the efficiency in terms of reduced numbers for a crossover design is attractive for trials of agents in atopic eczema, the fluctuating nature of the disease makes it less suitable for this type of approach. Data from the second half of a crossover study may have to be discarded in the presence of a period or carry-over effect, though this has rarely been tested for in the trials. Left/right body or limb comparisons are also popular but introduce problems with blinding and systemic absorption. Simple parallel group RCTs that are pragmatic in nature are most justifiable.

Separate atopic eczema patients from others

As can be seen from appendix 2, there is a large wastage of RCT evidence for many interventions that have included people with atopic eczema, as they have been lumped in with other inflammatory dermatoses such as psoriasis or lichen simplex, and their results not separated. Discarding such evidence might appear a little harsh. Although some might feel comfortable in generalising from studies evaluating all forms of eczema to atopic eczema, the RCT evidence discussed in the section on topical corticosteroids suggests that different inflammatory diseases respond differently to the same treatment. Atopic eczema patients therefore need to be separated from patients with other inflammatory dermatoses, or at least their results should be presented separately.

Future research priorities

Primary research

With such glaring gaps in our current knowledge about the effectiveness of treatments for atopic eczema, it is difficult to know where to start in recommending research priorities. In order to avoid bias on behalf of the authors choosing just what they think is important in future primary research, results of the survey of 25 researchers and clinicians with an interest in atopic eczema and six consumers with atopic eczema are shown in *Table 41*. There was remarkable similarity between the different groups in calling for research on similar themes. Research themes fall mainly into assessing the things that we already have rather than assessing the role of newer agents. Research that evaluates the delivery of whole packages of care such as involvement of nurses was also highlighted. This type of research is important when extrapolating from cost-effectiveness studies of motivated patients in secondary care to a primary care setting. It may be the case that an inexpensive single treatment delivered with a simple package of care may be more effective than an expensive therapy without any such support.

Clearly it is impossible to commission all of these proposals, and the authors prioritisation of the six most urgent research themes are shown in *Table 42*. Studies on disease prevention also need to be considered.

Secondary research

Perhaps one of the most useful aspects of this scoping review is that it will serve as a generator of other more detailed specific systematic reviews. Already therefore, titles for reviews on the reduction of house dust mite, antihistamines, Chinese herbs and dietary approaches have been registered with the Cochrane Skin Group, and it is hoped that others will use the data contained within this review as a backbone for additional systematic reviews.

Methodological

There is a clear need for a programme of methodological research to accompany the primary research if patients and their carers are to make sense of the study findings. Further research, such as the current research by this team to identify a simple list of patient-derived outcome measures for atopic eczema, is needed. A recent review[32] of 'named' outcome scales used in atopic eczema identified 13 different instruments, none of which had undergone full testing for validity, repeatability and responsiveness. In addition to completing the validity testing of such 'named' scales, further research involving consumers and carers is required to determine a minimum list of similar outcome measures, for example a quality-of-life measure, patient-rated global disease improvement and the 'best' of the current named objective doctor-rated scales for use in future atopic eczema trials. This will vastly aid the comparability of studies providing such a list has been derived using the best quality external evidence with ownership from a wide range of stakeholders. Drug regulatory authorities could occupy a key role in recommending the use of such measures.

The RCTs highlighted in this study also provide an opportunity to explore more generic issues such as the relationship between magnitude of benefit and study quality or design issues. Future RCTs in dermatology can also consider using a Bayesian approach, particularly where there is pre-existing

TABLE 41 *Primary research questions identified by 25 clinicians and six consumers*

Intervention	Question
Disease prevention	What is the role of vaccination in triggering atopic eczema expression? Role of maternal dietary manipulation and house dust mite avoidance
Emollients	Does regular use of emollients reduce disease relapse?
Topical corticosteroids	What is the most optimal use of topical steroids? Do topical steroids suppress growth? Are the 'newer' once-daily topical steroids more effective than older preparations? Do topical corticosteroids cause long-term skin damage when used appropriately?
Tacrolimus and ascomycin	How do the newer topical agents such as tacrolimus and ascomycin compare with topical corticosteroids? Should tacrolimus or ascomycin be used after inducing a remission with topical steroids?
Diets	Role of exclusion diets
Factors affecting treatment response	Do different patterns of atopic eczema (discoid, reverse pattern, flexural) require different treatments? How important is the presence of *S. aureus* in managing disease? Are there any genetic markers for predicting treatment response?
Trigger factors	What are the most important modifiable trigger factors?
Treatments for severe disease	How does ultraviolet treatment compare with oral immunomodulatory treatment in severe disease? Should potentially toxic treatments be used on a rotational basis? Efficacy of agents such as azathioprine, methotrexate, anti-leukotrienes, naltrexone
Disease dimensions	What are the most effective interventions at reducing the itch of atopic eczema? Does any treatment alter the natural history of disease if used properly and for long enough? Which is the best treatment approach for mild-to-moderate disease?
The role of tests	What is the usefulness of allergy tests in disease management What is the role of allergic contact dermatitis in topic eczema?
Environmental manipulation	Are water softeners effective? Does removal of pets influence disease activity? How important is control of humidity and excessive heat in the home?
Psychological approaches	Which are the most psychological/psychotherapeutic approaches and how well do patients respond to such approaches outside the hands of enthusiasts?
Bandages	How effective are wet-wraps, with and without emollients or topical steroids?
Organisation of care/education	How effective are educational approaches in improving the correct use of first-line treatments? What is the role of specialist nurses in helping people with atopic eczema? How effective is a multiprofessional team approach compared with a dermatologist alone? How important is patient concordance in predicting disease control?
Bathing	Are salt baths helpful? Is there an optimal frequency of bathing?
Issues of safety	Long-term adverse effects of cyclosporin in children Long-term adverse effects of ultraviolet light in children

TABLE 42 *The six most urgent primary research priorities*

Question	Justification
How effective are wet-wrap bandages with topical steroids or emollients vs the same treatment and no wet-wraps?	Widespread use with no RCT backing. Potentially large and useful treatment effect but also greater potential for local and systemic adverse effects of topical steroids
How useful are blood allergy tests at predicting benefits from allergen avoidance?	Large demand for such tests matched by lack of evidence that they mean anything useful in terms of eczema outcomes
Does the installation of a water-softening device improve atopic eczema?	Sold widely to eczema sufferers. Some epidemiological evidence that hard water might be important. Modifiable environmental factor
What is the role of specialist nurses in managing patients with atopic eczema?	Some observational evidence of benefit in some centres. May be a cost-effective complement to current doctor-dominated approach
Head-to-head cost-effectiveness comparison of topical corticosteroids against topical tacrolimus or ascomycin	Newer agents likely to be taken up eagerly in view of corticosteroid 'phobia', but true benefit and cost–benefit unclear
Trials aimed at prevention of atopic eczema	Large potential health gains in high-risk populations

epidemiological evidence (e.g. as in the case of house dust mite and water hardness) to inform the prior probabilities. In other areas where there is a multiplicity of new interventions being introduced constantly, consideration should be given to more flexible and pragmatic approaches such as the use of tracker studies.

Implications for healthcare

The strength of evidence supporting the various interventions have already been summarised in the key points of the results chapters. The strength of evidence in relation to those interventions which are commonly used in the UK are summarised qualitatively in *Table 43*. Given the virtual absence of long-term studies, the data can only refer to short-term control of disease.

Some 'health' warnings

Table 43 gives the authors' opinion on the value of the evidence base for the interventions considered. It is not intended as a substitute for the dose examination of the original studies in the context of local guideline and policy development. Any attempt at summarising the RCT evidence (or lack of such evidence) for such a wide range of interventions is fraught with hazard, perhaps the most important of which is that absence of RCT evidence for an intervention is not the same as providing evidence to reject that intervention. Therefore it might be entirely reasonable to continue to use a range of emollients in atopic eczema based on lower hierarchies of evidence until appropriate RCTs are done, given the fact that they have become 'consecrated' through usage. On the other hand, some RCTs have failed to show any benefit for some interventions and these could perhaps be looked at carefully in terms of the rationale for their continued widespread use. This is easier said than done as advice such as avoidance of synthetic fibres and enzyme-containing washing powders, and frequent bathing have all become deeply engrained in the rituals of atopic eczema advice. Similarly, use of twice-daily topical corticosteroids or dilutions of topical corticosteroids have also become deeply embedded in clinical practice. Crucial factors such as patient choice, adverse effects and cost also have to be taken into account when making recommendations.

Trying to split *Table 43* into further first-line, second-line and third-line treatment guidelines is beyond the scope of this systematic review and is an approach that is hazardous without a much wider consultation and more detailed synthesis of adverse effect data, patient preference data and cost data, which by definition is always contextual and limited in time. Decision analysis approaches should also be used to determine which interventions are amenable to change in the future.

Summary

- RCTs of interventions for atopic eczema have often not answered the questions of most importance to patients and their carers.
- This mismatch is possibly due to the lack of independent investment into primary atopic eczema research.

TABLE 43 *Results of systematic review of treatments and prevention of atopic eczema*

Interventions with reasonably established efficacy (based on at least one high-quality RCT and a clinically useful effect)	**Interventions with insufficient evidence to make recommendations** (only one small RCT or conflicting RCTs where the largest and best-quality RCTs do not suggest a clear and clinically useful benefit)	**Interventions for which RCT evidence does not support a clinically useful benefit** (at least one RCT that fails to show a convincing benefit on overall disease activity)	**Interventions with no RCT evidence whatsoever**
• Oral cyclosporin • Topical corticosteroids • Psychological approaches • Ultraviolet light	• Maternal antigen avoidance for disease prevention during and after pregnancy • Antihistamines • Chinese herbs • Dietary restriction in established atopic eczema • House dust mite reduction • Homeopathy • Massage therapy • Hypnotherapy • Evening primrose oil • Emollients • Topical coal tar • Topical doxepin	• Avoidance of enzyme washing powders • Cotton clothing as opposed to soft-weave synthetics • Biofeedback • Twice-daily as opposed to once-daily topical corticosteroids • Topical antibiotic/steroid combinations vs topical steroids alone • Antiseptic bath additives	• Short bursts of potent vs longer-term weaker topical steroids • Dilution of topical corticosteroids • Oral prednisolone • Azathioprine • Salt baths • Impregnated bandages • Wet-wrap bandages • Water-softening devices • High filtration as opposed to ordinary vacuuming • Routine patch testing • Combinations of different treatments • Different approaches to organisation of care

- There are some glaring gaps in our current knowledge regarding the use of some interventions that are commonly used such as emollients and wet-wrap bandages.
- This review has identified some lesser known RCTs, which suggest that some interventions such as bioresonance and avoidance of synthetic clothing are ineffective.
- The review has also failed to find any evidence to support the use of twice-daily as opposed to once-daily topical steroids or topical antibiotic/steroid combinations as opposed to topical steroids alone in infected atopic eczema.
- The review has helped to place non-pharmacological treatments in their context alongside conventional drug approaches.
- Future RCTs should consider using a parallel group design and be of longer duration.
- A profusion of outcome measures should be avoided in favour of a few clinically understandable and patient-orientated ones.
- There is much scope for improving the standard of clinical trial reporting in atopic eczema by journals adopting CONSORT and by registering ongoing trials with the Cochrane Skin Group.
- This review has identified several primary research gaps, which need to be addressed mainly by RCTs.
- The review is likely to be a useful generator of future more detailed systematic reviews.
- The RCT database contained within this report provides a good opportunity to conduct some general research into the relationship between study quality and treatment benefit.

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Colette Hoare performed all of the searches, checked for eligible studies, obtained hard copies of studies, conducted the focus group, abstracted data from included studies, wrote the section on complementary therapies, managed the references and finalised the appendices and report layout.

Hywel Williams wrote the study proposal, supervised the day-to-day running of the project, handsearched conference proceedings, checked on excluded studies, abstracted and summarised data from most of the included studies, and wrote the final report with help from Colette Hoare.

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Appendix 1

Search strategies

The Cochrane Collaboration highly sensitive electronic search string for MEDLINE (OVID)

#1 RANDOMIZED CONTROLLED TRIAL.pt.
#2 CONTROLLED CLINICAL TRIAL.pt.
#3 RANDOMIZED CONTROLLED TRIALS.sh.
#4 RANDOM ALLOCATION.sh.
#5 DOUBLE BLIND METHOD.sh.
#6 SINGLE BLIND METHOD.sh.
#7 or/1-6
#8 (ANIMAL not HUMAN).sh.
#9 7 not 8
#10 CLINICAL TRIAL.pt.
#11 exp CLINICAL TRTIALS/
#12 (clin$ adj25 trial$).ti,ab.
#13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
#14 PLACEBOS.sh.
#15 placebo$.ti,ab.
#16 random$.ti,ab.
#17 RESEARCH DESIGN.sh.
#18 or/10-17
#19 18 not 8
#20 19 not 9
#21 COMPARATIVE STUDY.sh.
#22 exp evaluation studies/
#23 follow up studies.sh.
#24 prospective studies.sh.
#25 (control$ or prospectiv$ or volunteer$).ti,ab.
#26 or/21-25
#27 26 not 8
#28 26 not (9 or 20)
#29 9 or 20 or 28

#30 explode dermatitis, atopic/
#31 dermatitis, atopic.ti,ab,rw,sh.
#32 eczema, atopic.ti,ab,rw,sh.
#33 eczema.ti,ab,rw,sh.
#34 atopic eczema.ti,ab,rw,sh.
#35 atopic dermatitis.ti,ab,rw,sh.
#36 infantile eczema.ti,ab,rw,sh.
#37 childhood eczema.ti,ab,rw,sh.
#38 neurodermatitis.ti,ab,rw,sh.
#39 besniers prurigo.ti,ab,rw,sh.
#40 or/30-39

#42 29 and 40

Date of last search using this strategy for this report was end of June 2000

General skin search (EMBASE and MEDLINE)

#1 drug
#2 dermatological agent/
#3 skin/
#4 dermatology/
#5 dermatolog$.mp.
#6 skin disease$.mp.
#7 or/2-6
#8 1 and 7

Date of last search using this strategy for this report was end of November 1999

Search string for EMBASE (OVID) developed by the BMJ Publishing Group for its Clinical Evidence series

#1 exp clinical trial/ or clinical trial.ti,ab,hw,tn,mf.
#2 exp controlled study/
#3 (clinical trial$ or controlled clinical trial$).ti,ab,hw,tn,mf.
#4 (random$ or placebo$).ti,ab,hw,tn,mf.
#5 double blind.ti,ab,hw,tn,mf.
#6 exp Randomized Controlled Trial/
#7 or/1-6
#8 limit 7 to human
#9 explode dermatitis, atopic/
#10 dermatitis, atopic
#11 eczema, atopic
#12 eczema
#13 atopic eczema
#14 atopic dermatitis
#15 infantile eczema
#16 childhood eczema
#17 neurodermatitis
#18 besniers prurigo

#19 8 and 18

Date of last search using this strategy for this report was end of June 2000

Appendix 2

Excluded studies

TABLE 44 *Table of excluded studies for trials of topical steroids*

Author	Date	Interventions	Reason for exclusion
Topical steroid vs 'placebo' vehicle			
Cullen	1973	Betamethasone benzoate gel 0.025% vs placebo gel	Atopic dermatitis not separated from other dermatoses in results
Rosenthal	1980	Clocortolone pivalate 0.1% cream vs placebo cream base	Atopic dermatitis not separated from other dermatoses in results
Gartner	1984	Diproderm cream 0.05% vs placebo vehicle	Atopic dermatitis not separated from other dermatoses in results
Guzzo	1991	Halobetasol propionate 0.05% ointment vs vehicle	Atopic dermatitis not separated from other dermatoses in results
Lebwohl	1996	Fluticasone propionate 0.005% ointment vs vehicle	Unclear if 'eczema' is atopic dermatitis in this study, especially as most of the subjects were adult – author has been contacted for clarification
Schachner	1996	Hydrocortisone 17-butyrate ointment vs vehicle	No randomisation mentioned
Heuck	1997	Topical bedesonide vs base	The atopic dermatitis patients (study one) were part of an open case series. The two remaining RCTs in this study were all on asthma patients
Topical steroid vs another topical steroid			
Zimmerman	1967	Betamethasone 17-valerate 0.05% ointment vs fluocinolone acetonide 0.025%	First study was a case series, and it is unclear if randomisation occurred in second study
Grater	1967	Flumethasone vs 0.1% triamcinolone vs 1% hydrocortisone	Atopic dermatitis not separated from other dermatoses in results
Rosenberg	1971`	0.05% fluocinonide vs 0.1% betamethasone valerate	Atopic dermatitis not separated from other dermatoses in results
Bluefarb	1972	Desonide cream 0.05% vs betamethasone valerate cream 0.1%	Atopic dermatitis not separated from other dermatoses in results
Meenan	1972	Flucinonide 0.05% vs betamethasone 17 valerate cream 0.1%	Atopic dermatitis not separated from other dermatoses in results
Borelli	1973	Clocortolone (C168) vs fluocinolone	'Eczema' group not specified sufficiently
McCuiston	1973	Fluocinonide 0.01% and 0.05% vs betamethasone valerate	Not clear if randomised, outcome measures not described at all
Polano	1973	Hydrocortisone butyrate 0.1% vs triamcinolone acetonide 0.1% vs hydrocortisone acetate 1%	Atopic dermatitis not separated from other dermatoses in results
Stewart	1973	Desonide vs triamcinolone acetonide vs betamethasone 17-valerate	Atopic dermatitis not separated from other dermatoses in results
Nordwell	1974	Betamethasone 17, 21-dipropionate 0.05% cream vs fluocortolone caproate 0.25% plus fluocortolone pivalate 0.25% cream	Atopic dermatitis not separated from other dermatoses in results
Sparkes	1974	Clobetasol propionate 0.05% vs betamethasone 17-valerate ointment and cream vs fluclorolone acetonide ointment and cream and fluocinonide	Atopic dermatitis not separated from other dermatoses in results
Laurberg	1975	1% hydrocortisone in a stabilized 10% urea cream vs betamethasone 17-valerate 0.1% cream	Atopic dermatitis results mixed up with patients with 'atopic winter feet'
Lundell	1975	Desoximetasone 0.25% vs fluocinolone acetonide 0.025% cream	Nature of 'endogenous eczema' unclear. Inadequate description to classify as atopic dermatitis
Ludvigsen	1975	Calmuril-hydrocortisone 1% cream vs triamcinolone acetonide 0.1% cream	Unclear if randomised. No study results given!
Meyer-Rohn	1975	Desoximetason 0.25% vs betamethasone-valerate 0.1%	Atopic dermatitis not separated from other dermatoses in results
Sudilovsky	1975	Halcinonide cream 0.1% vs fluocinonide 0.05% cream	Disease definition, i.e. 'eczematous dermatoses which would normally be treated with topical steroids' not acceptable as a term synonymous with atopic eczema

continued

TABLE 44 contd *Table of excluded studies for trials of topical steroids*

Author	Date	Interventions	Reason for exclusion
Parish	1976	Betamethasone benzoate 0.025% gel vs betamethasone valerate 0.1% cream	Cannot be sure that study subjects with 'eczematous dermatoses' had atopic eczema
Thormann	1976	Hydrocortisone 17-butyrate vs betamethazone 17-valerate	Results of five different skin disorders mixed up and only one patient with atopic eczema
Roessel	1977	Triamcinolone acetonide benzoyl-β-amino-isobutyrate vs betamethasone dipropionate	Atopic dermatitis not separated from other dermatoses in results
Khan	1978	1% hydrocortisone plus 10% urea vs 0.05% fluocinonide	Dry eczematous dermatoses in adults mixed up with atopic dermatitis
Lassus	1979	Clobetasone butyrate 0.05% cream vs hydrocortisone butyrate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Helander	1982	Hydrocortisone 17-butyrate 0.1% cream vs betamethasone 17-valerate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Hersle	1982	Diflorasone diacetate 0.05% vs betamethasone valerate	Atopic dermatitis not separated from other dermatoses in results
Turnbull	1982	Locoid vs Betnovate lotion	Study of seborrhoeic and atopic dermatitis of the scalp with results not separated
Gip	1983	Hydrocortisone 17-butyrate 0.1% cream vs betamethasone 17-valerate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Schmidt	1984	D-homosteroids domoprednate 0.1% ointment vs 0.1% betamethasone valerate ointment	Atopic dermatitis not separated from other dermatoses in results
Gip	1987	Hydrocortisone 17-butyrate 0.1% cream vs betamethasone 17-valerate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Schmidt	1987	Domoprednate 0.1% ointment vs hydrocortisone butyrate ointment	Atopic dermatitis not separated from other dermatoses in results
Handa	1988	Alcometasone dipropionate 0.05% ointment vs 1% hydrocortisone ointment	Atopic dermatitis not separated from other dermatoses in results
Panja	1988	Alclometasone dipropionate 0.05% cream vs 1% hydrocortisone cream	Atopic dermatitis not separated from other dermatoses in results
Celleno	1990	Alclometasone dipropionate 0.1% vs 0.1% hydrocortisone 17-butyrate	Atopic dermatitis not separated from other dermatoses in results
Viglioglia	1990	Mometasone furoate 0.1% cream once daily vs betamethasone valerate 0.1% cream twice daily	Atopic dermatitis not separated from other dermatoses in results
Brunner	1991	Halobetasol propionate 0.05% ointment vs 0.1% diflucortolone valerate ointment	Atopic dermatosis results mixed up with patients with lichen simplex
Datz	1991	Halobetasol propionate ointment 0.05% vs clobetasol 17-propionate ointment 0.05%	Atopic dermatitis results mixed up with lichen simplex
Rajka	1993	Mometasone furoate 0.1% fatty cream vs betamethasone valerate 0.1% cream	Atopic dermatitis not separated from other dermatoses in results
Schäfer-Korting	1993	Prednicarbate 0.025% -0.25% vs hydrocortisone aceponate vs hydrocortisone buteprate 0.1% vs betamethasone 17-valerate 0.1% vs hydrocortisone 1% vs 2 drug-free vehicles	Conducted in healthy volunteers not atopic eczema subjects
Blum	1994	Betamethasone dipropionate 0.05% in propylene glycol vs clobetasol propionate 0.05% ointment	Atopic dermatitis not separated from other dermatoses in results
Delescluse	1996	Fluticasone propionate ointment 0.005% vs betamethasone 17, 21-dipropionate ointment 0.05%	Atopic dermatitis not separated from other dermatoses in results
Juhlin	1996	Fluticasone propionate 0.05% cream vs hydrocortisone 17-butyrate 0.1% cream	Atopic dermatitis results not separated from patients with other eczemas of a known cause
Meffert	1999	Topical methylprednisolone aceponate vs amcinonide, betamethasone valerate, hydrocortisone butyrate and vehicle	Whole range of 'acute eczemas' not separated in results
Topical steroid vs another topical			
Bjornberg	1967	Crotamiton vs Crotamiton/hydrocortisone combo	Atopic eczema not specified/separated
Christiansen	1977	Bufexamac vs 0.1% triamcinolone acetonide, 1% hydrocortisone cream and placebo	Atopic dermatitis results not separated from other dermatoses

continued

TABLE 44 contd *Table of excluded studies for trials of topical steroids*

Author	Date	Interventions	Reason for exclusion
Topical steroid plus additional active agents			
Bjornberg	1966	Topical flumethasone plus vioform vs hydrocortisone with 5, 7-Dichlor-8-hydroxy-2-methylquinolin 3%	Besnie's prurigo included, results not separated
Sasagawa	1970	Betamethasone valerate plus gentamicin sulphate vs betamethasone	Atopic dermatitis not separated from other dermatoses in results
Weitgasser	1972	Topical dexamethasone vs topical nandrolone plus chlorhexadine	Rag bag of dermatoses (atopic dermatitis not among them) and results not separated
Aertgeerts	1973	Topical dexamethasone vs topical nandrolone plus chlorhexdine	Various dermatoses lumped together
Carpenter	1973	Vioform-hydrocortisone cream vs components alone and base cream vehicle	Atopic dermatitis not separated from other dermatoses in results
Aertgeerts	1976	Dexamethasone plus chlorhexidine vs flumethasone – pivalate 0.02% plus iodochlorohydroxy-quinolone	Atopic dermatitis not separated from other dermatoses in results
Cunliffe	1976	Fluclorolone acetonite 0.025% in FAPG vs betamethasone 17-valerate plus 0.5% neomycin	Atopic dermatitis not separated from other dermatoses in results
Strategos	1986	Fusidic acid/betamethasone combination vs gentamicin – betamethasone combination	Only five patients with atopic eczema all present in only one treatment arm
Weitgasser	1993	Halometasone/triclosan cream vs betamethasone dipropionate/getamicin sulphate cream	Atopic dermatitis not separated from other dermatoses in results
Poyner	1996	Fusidic acid/hydrocortisone cream vs miconazole/hydrocortisone cream	Unclear if patients with 'clinically infected eczema' had atopic eczema. Author contacted for clarification
Comparison of different formulations of the same topical steroids			
Pilgaard	1980	Hydroderm™ vs hydrokortison DAK™	Atopic dermatitis not separated from other dermatoses in results
Once-daily vs more frequent application of topical steroids			
Tharp	1996	Fluticasone propionate 0.05% once vs twice daily	Eczema unspecified
Fredricksson	1980	Halcinonide cream 0.1% once daily vs same cream three times daily	Psoriasis and atopic dermatitis results mixed up
Schmid	1981	Topical fluocinoloneacetonid 0.025% once daily, twice daily or interval therapy	Not clearly atopic dermatitis patients
English	1989	Betamethasone dipropionate once vs twice daily	Atopic dermatitis not separated from other dermatoses in results
Topical steroids in the prevention of relapse			
Vickers	1976	Maintenance on low-potency topical steroids switching to high-potency for short periods vs use of high-potency steroid throughout treatment vs high-potency steroid regularly once daily using a low-potency steroid for the second application	Not an RCT, though a clear intention to conduct one. Subsequent RCT never published
Moller	1983	Clobetasol proprionate vs flupredniden acetate	Atopic dermatitis not separated from other dermatoses in results

FAPG, fatty acid propylene glycol
Diproderm™, not available in the UK; Hydroderm™, Schering Corp., Denmark; Betnovate™, Glaxo-Wellcome, UK

TABLE 45 *RCTs of 'eczema' excluded for other reasons*

Author	Date	Interventions	Reason for exclusion
Smith	1961	Trimeprazine vs methdilazine	Atopic eczema data not separated in results
Brown	1971	Psychiatric treatment	Only one case of atopic eczema
Chan-Yeung	1971	DSCG	Asthma study
Anonymous	1973	Carbamide in hyperkeratosis	Atopic eczema results not separated
D'Souza	1973	House dust mites	People had asthma or hay fever
Baraf	1976	Antihistamines: cyproheptadine vs hydroxyzine	Atopic eczema results not separated from other dermatoses
Baertschi	1976	Antibiotic prophylaxis	'Eczema' only mentioned as adverse effect
Friedman	1978	Monoamione oxidase inhibitors	Unclear if any of the neurodermatits patients had atopic eczema
Buch-Rasmussen	1979	Hydrocortisone alcoholic solutions	Study of external otitis
Newbold	1980	Emollients	Atopic eczema results not given separately
Anonymous	1981	5% butyl flufenamate vs bufexamac	Atopic dermatitis not separated from other dermatoses in results
Bazex	1982	Terfenadine vs clemastine	Atopic eczema results not separated from other dermatoses in results
Cooper	1983	Thymopoietin pentapeptide	No clinical outcomes measured or reported
Archer	1984	Adrenoreceptor agonists	Not a therapeutic trial
Fairris	1984	Superficial X-Ray therapy (of the feet)	Unclear if patients had atopic eczema
Fairris	1985	Superficial X-Ray therapy (of the hands)	Unclear if patients had atopic eczema
Meyrick-Thomas	1985	Ranitidine	Healthy atopic volunteers
Svensson	1985	Diagnostic tool based on clinical criteria	Diagnostic study 'subjects randomly collected'
Bernstein	1986	Doxepin hydrochloride	Abstract only
Niimura	1988	Oral acyclovir	Study of eczema herpeticum
Roberts	1988	PAF antagonist vs placebo	Not atopic eczema patients
Warren	1988	The importance of bradykinin and histamine in the skin response to antigen	Not atopic eczema patients, not a therapeutic trial
Burr	1989	Risk factors for atopic eczema	Not an RCT of an intervention for atopic eczema, instead, an observational study of risk factors for atopic eczema within another breastfeeding RCT
Ebden	1989	Evening primrose oil	Asthma not atopic eczema
Monroe	1989	Nalmefene opiate antagonist vs placebo	Atopic eczema results not presented separately
Sheehan-Dare	1989	PUVA vs superficial radiotherapy	Not clear atopic dermatitis
Brandrup	1990	Occlusive dressing	'Eczema' only mentioned as adverse effect
Markey	1990	PAF	Atopic subjects without evidence of atopic eczema
Michel	1990	Cetirizine	Pollen sensitive patients unspecified
Heyer	1991	Substance P and topical mustard oil	Not a therapeutic trial
Peter	1991	Ketaconazole	Study of seborrhoeic dermatitis
Schafer	1991 (a)	Evening primrose oil	No clinical outcomes
Schafer	1991 (b)	Phospholipid fatty acid composition and LTB_4 release of neutrophils	No clinical outcomes
Kerscher	1992	Topical steroids	Healthy volunteers
Korting	1992	Prednicarbate cream	Healthy volunteers
Nierop	1992	Auranofin	Study of asthma only
Olsen	1992	Systemic steroids with 2% minoxidil	Study of alopecia areata with eczema mentioned as adverse effect
Couser	1993	Surfactant	Unspecified eczema as outcome measure
Lutsky	1993	Loratadine syrup vs terfenadine suspension	Atopic eczema results not given separately
Rombo	1993	Malaria prophylaxis	'Eczema' mentioned as adverse effect

continued

TABLE 45 contd *RCTs of 'eczema' excluded for other reasons*

Author	Date	Interventions	Reason for exclusion
Zepelin	1993	Omega-3 fatty acid	Psoriasis patients
Lee	1994	Surfactant mixturesHealthy volunteers	
Lovegrove	1994	Milk-free diet vs normal diet	No separate data on atopic eczema
Nakagawa	1994	Tacrolimus ointment 0.03, 0.1 and 0.3%	Randomisation not described, three actives compared in hand and neck area, unblinded
Soyland	1994	n-3 omega fatty acid supplementation	Atopic eczema severity outcome data not given
Syed	1994	Podophyllotoxin cream	Study of molluscum
Tegner	1994	Skin blanching by hydrogen peroxide	Adverse effect study of skin blanching of hydrogen peroxide
Zimmermann	1994	Balneophototherapy with daily 15% synthetic Dead Sea Salt bath and selective ultraviolet phototherapy vs balneophototherapy with daily 3% NaCl salt bath and selective ultraviolet phototherapy	Atopic dermatitis not separated from other dermatoses in results
Roquet	1995	Loratidine	Atopic subjects not necessarily having eczema
Simon	1995	Ioxaglate vs Iopamidol	Not a study of atopic eczema outcomes. A study to see if allergic reactions are commoner in one type of contrast medium in patients with atopic disease
Simon	1995	Gamma-interferon	No clinical outcomes
Snyman	1995	Betahistine	Simply 'atopic volunteers' not necessarily atopic eczema
Verwimp	1995	Whey-protein hydrolysate based formulas	Unclear if atopic eczema patients
Wahlgren	1995	Interleukin-2	Laboratory experiment with no clinical outcomes, not a therapeutic trial
Anonymous	1997	Cetirizine vs placebo	No atopic eczema outcomes
Kalpakliogu	1997	Heparin	Asthma study
Heyer	1997	Opiate and H1 antagonist effects	Healthy volunteers
Kekki	1997	Skin-prick and patch-test reactivity	Diagnostics
Lippert	1997	Antigen-induced cytokine release	Not a clinical trial of a therapeutic agent. Only cytokines measured
Pigatto	1997	Colloidal grain suspensions	Not a therapeutic trial
Rukwied	1997	Cetirizine vs placebo	Experimentally-induced flare responses
Sabroe	1997	Doxepin vs terfenadine	No atopic eczema outcomes
Frossard	1998	Cetirizine	Healthy volunteers
Hill	1998	Betamethasone plus clioquinol cream vs betamethasone plus fusidic acid cream	Hand eczema
Lippert	1998	Certirizine	Laboratory experiment with no clinical outcomes
Sorensen	1998	Intravenous immunoglobulin	Study of multiple sclerosis with eczema mentioned as side effect
Syed	1998	Imiquimod 1%	Study of molluscum
Warnecke	1998	Ichthyol oil	Healthy volunteers
Weisshaar	1998	Topical capsaicin vs placebo	Effect of capsaicin on experimentally induced whealing from histamine icthyosis
Darsow	1999	Aeroallergen sensitization	Diagnostics
Goh	1999	Mometasone furoate cream vs clobetasol propionate cream	Unspecified chromic limb eczema
Grundmann-Kollmann	1999	PUVA bath vs PUVA cream	Atopic eczema results not separated
Ortonne	1999	SDZ ASM 981 vs topical steroids and vehicle	Healthy volunteers
Rudofsky	1999	Intravenous prostaglandin	Study of venous ulcers with eczema mentioned as adverse effect

TABLE 46 *RCTs excluded at an early stage because eczema was unspecified*

Author	Date	Interventions	Reason for exclusion
Topical steroids			
Leo Pharmaceuticals unpublished data on file	–	Fucicort® vs Betnovate	Unspecified hand eczema
Stahle	1965	Fluocinolone vs tumenol prednisolone	Description of 'patches of eczema' unclear
Stahle	1965	Full vs half strength betamethasone 17-valerate	Description of 'patches of eczema' unclear
Munro	1967	Betamethasone 17-valerate vs fluocortolone caproate ointment	'Eczema' unspecified
Anonymous	1969	Flurandrenolone with clioquinol in 2 different strengths	Unclear if 'eczema' included atopic eczema
Lloyd	1969	Fluocinolone acetonide 0.025% vs flucinolone containing neomycin	Nature of inflammatory dermatitis unclear
Portnoy	1969	1% hydrocortisone vs 0.2% fluocortolone	'Eczema' unspecified
Ashurst	1970	Beclomethasone dipropionate vs betamethasone 17-valerate	'Conditions responsive to topical applications of steroids' – unclear if this included atopic eczema
Ashurst	1972	Hydrocortisone 17-butyrate vs fluocinolone acetonide vs hydrocortisone butyrate with chlorquinaldol	Inadequate description of 'eczema'
Hall-Smith	1972	Betamethasone valerate vs betamethasone benzoate	Description of 'steroid-responsive dermatoses' insufficient
Harman	1972	Fluclorolone acetonide vs betamethasone 17-valerate	Various types of 'dermatitis' unclear
Neering	1972	Betamethasone 17-valerate vs triamcinolone acetanide under occlusive dressing	'Eczema' unspecified
Sarkany	1972	Fluocinonide vs betamethasone valerate	Type of 'eczema' unclear
Alexander	1973	Hydrocortisone 17-butyrate vs betamethasone valerate 0.1%	Nature of 'eczema' unclear
Craps	1973	Clocortolone pivalate vs controls in 17 double-blind trials	Non-specific 'eczema'
Cullen	1973	Betamethasone benzoate vs placebo gel	'Eczematous dermatoses' not separated
Marks	1973	Betamethasone 17-valerate 0.1% vs formocortal 0.025%	'Eczema of the hands' unclear
Wilson	1973	Betamethasone 17-valerate ointment lanolin-free vs original formulation vs fluclorolone acetonide ointment	Type of eczema unclear
Garretts	1975	Fluprednylidene acetate cream vs base	Inflammatory skin disease unspecified
Ronn	1976	Betamethasone vs fluocinonide	'Eczema' unspecified
Munro	1977	Betamethasone valerate ointment vs fluocinonide FAPG	'Eczema' unspecified
Palmerio	1977	Halopredone acetate vs betamethasone valerate	Nature of 'eczema' unclear
Dotti	1978	Dexamethasone 17-valerate vs 0.1% betamethasone vs 1% hydrocortisone acetate	Nature of 'eczematous lesions' unclear
Afzelius	1979	Betamethasone diapropionate 0.05% vs fluocinolone acetonide 0.025%	Unclear if atopic eczema included
Doherty	1979	Diflucortolone valerate 0.3% oily cream vs clobetasone propionate 0.05% cream	'Chronic severe eczema' too non-specific
Rosenberg	1979	Amcinonide vs betamethasone valerate	'Eczematous dermatitis' unclear
Vollum	1979	Betamethasone valerate vs halcinonide	Nature of eczema lesions unclear
Allenby	1981	Clobetasone butyrate 0.05% vs hydrocortisone butyrate 0.1%	Unclear if atopic eczema
Anonymous	1981	Hydrocortisone 17-butyrate vs betamethasone 17-valerate creams	Unspecified uninfected eczema
Guenther	1981	Amcinonide cream 0.1% vs halcinonide cream 0.1%	Nature of 'eczematous dermatitis' unclear
Bickers	1984	Amcinonide vs halcinonide	Nature of 'subacute eczematous dermatitis' unclear
Johansson	1984	Diflorasone diacetate vs betamethasone valerate	Nature of 'eczematous dermatitis' unclear

continued

TABLE 46 contd *RCTs excluded at an early stage because eczema was unspecified*

Author	Date	Interventions	Reason for exclusion
August	1985	Diflucortolone vs betamethasone cream	Unspecified symmetrical eczema
Jegasothy	1985	Clobetasol propionate vs fluocinonide cream	Nature of 'chronic eczema' unclear
Jaffé	1986	Hydrocortisone plus potassium hydroxyquinoline vs 1% hydrocortisone plus 2% miconazole cream	Nature of 'infected eczema' unclear
Barry	1987	Desonide 0.05% and 0.1% cream	'Non-infected hand eczemas' unclear
Williamson	1987	Hydrocortisone/urea cream vs betamethasone valerate cream	Nature of 'dry eczema' unclear
Lutsky	1993	Loratadine syrup vs Terfenadine suspension	Atopic dermatitis not separated from other dermatoses in results
Gip	1994	Betamethasone 17-valerate 0.1% lipocream vs betamethasone 17-valerate 0.1% cream	Nature of 'dry chronic dermatitis' unclear
Kejda	1994	1% hydrocortisone cream vs Locoid 0.1%	Nature of 'chronic eczema' unclear
Nakagawa	1994	Tacrolimus ointment 0.03, 0.1 and 0.3%	Randomisation not described, unblinded open study
Tharp	1996	Fluticasone once daily vs twice daily	Unspecified eczema
Jorizzo	1997	Clobetasol propionate 0.05% vs emollient vehicle	'Eczema' unspecified
Radiation			
King	1984	Superficial radiotherapy vs simulated therapy	Nature of 'palmar' eczema unclear
Cartwright	1987	Grenz vs placebo	Nature of 'bilateral hand ezcema' unclear if atopic eczema
Cromoglycate			
Dannaeus	1977	SCG vs placebo	Unspecified eczema
Pacor	1992	DSCG vs oxatomide	Nature of eczema unspecified
Antihistamines			
Hellier	1963	Trimeprazine vs amylobarbitone	Unspecified eczema
Laugier	1978	Mequitazine vs placebo	Unspecified 'dermatological conditions'
Miscellaneous			
de Gregorio	1970	Topical bendazac vs placebo vs 3% hydrocortisone acetate	Nature of 'eczematous eruptions' unclear
Fredrikksson	1975	Urea creams	Nature of eczematous dermatitis of hands unclear
Zimmermann	1981	Intravenous demetindenmaleat vs clemastine	Nature of 'allergic dermatoses' unclear
Fairris	1984	Superficial X-ray therapy	Nature of unspecified constitutional eczema of the hands unclear
Veien	1985	Oral challenge with balsam of Peru vs placebo	Various types of 'dermatitis' unclear
Lauharanta	1991	Emuslion cleansing vs washing with soap	Nature of 'hand eczema' unclear
Drake	1995	5% doxepin cream vs vehicle cream	Description of study subjects suggests that 'eczematous dermatitis' did not include atopic dermatitis

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Appendix 3

Studies of steroid therapy

TABLE 47 *RCTs of topical corticosteroid vs placebo*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Brock & Cullen, 1967[126] USA	0.5% triamcinolone acetonide o.d. in flexible collodion vs 'flexible collodion' placebo o.d.	40 patients in total two atopic eczema patients	Prospective, randomised, double-blind parallel study	Lesion improvement	Out of two atopic eczema patients one found active site better and one found neither site better	Method and concealment of randomisation unclear, study described as double-blind, no withdrawals or drop-outs	Scant details Patient preference study gives little indication of magnitude of effect
Gehring & Glooer, 1996[71] Germany Translated	Water-in-oil emulsion b.d. for 2 weeks vs water-in-oil emulsion plus1% hydrocortisone for 1 week followed by the emulsion only in the second week	69 patients with atopic dermatitis	Prospective, randomised, double-blind parallel-group study for 2 weeks	Doctor-assessed erythema, patient-assessed roughness and itching Other biological measures	Both groups improved substantially for all parameters Trend toward greater improvement in hydrocortisone groups but not statistically significant	69 patients enrolled, 12 did not meet all study critieria yet 63 were used in final assessment	The study demonstrates the large vehicle/ placebo response in atopic eczema trial
Vanderploeg, 1976[105] 	0.05% betamethasone dipropionate ointment b.d. vs vehicle placebo	36 patients with moderate-to-severe atopic dermatitis	Prospective, randomised, double-blind study of 3 weeks' duration	Amount of scale, erythema, pruritus, thicknes of lesions and crusting on a 0–4 scale (0 = none, 4 = very severe) Global evaluation <25% = worse to 100% = excellent	Improvement over baseline for mean total symptom score was 11.4 for dipropionate and 11.2 for placebo decreasing to 1.6 for dipropionate and 8.4 for placebo at week 3; $p < 0.0001$	Method and concealment of randomisation unclear, study described as double blind 'code', three drop-outs, no ITT	Large treatment effect
Roth & Brown, 1978[87] USA	Hydrocortisone valerate cream 0.2% vs placebo t.d.s.	20 atopic eczema patients	Prospective, randomised, left/right, parallel study of 4 weeks' duration	Pruritus, erythema, scaling, excoriation, lichenification Overall condition and severity of disease	No actual data given for hydrocortisone valerate vs placebo. 75% of the patients showed excellent improvement or were better with the hydrocortisone valerate cream compared with 20% with the placebo Overall ratings at the end of the therapy showed hydrocortisone valerate to be significantly more effective than the placebo ($p < 0.001$)	Method and concealment of randomisation unclear, study described as double-blind Withdrawals and drop-outs not mentioned	Difficult to estimate magnitude of benefit

continued

TABLE 47 contd *RCTs of topical corticosteroid vs placebo*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Sudilovsky *et al.*, 1981[95]	0.1% halcinonide cream o.d. plus cream base placebo b.d. vs cream base placebo t.d.s.	58 atopic eczema patients	Prospective, randomised, right/ left, parallel study of 3 weeks' duration	Comparative and absolute therapeutic responses: erythema, oedema, changes in size of thickness of lesions Physician global response	Of 54 evaluable patients at week 3, 13 (24%) were markedly improved for halcinonide comparative clinical response vs 1 (2%) for placebo patients ($p < 0.001$)	Method and concealment of randomisation unclear, study described as double-blind, four drop-outs Withdrawals, no ITT	Patients with a previous history of poor response to topical corticosteroids were excluded
Lupton *et al.*, 1982[94]	Halcinonide ointment 0.1% vs t.d.s. ointment base placebo t.d.s.	233 patients with mild, moderate and severe atopic dermatitis	Prospective, randomized, double-blind paired comparison study of 2 weeks' duration	Therapeutic response of lesions on each side evaluated as excellent, good, fair, poor Lesion resolution evaluated for lesion size, erythema, oedema, transudation and lichenification Therapeutic response four-point scale (4 = excellent, 1 = poor)	In Halcinonide group 64% excellent, 21% good, 10% fair and 5% poor response In placebo group 23% excellent, 21% good, 36% fair and 20% poor response	Method and concealment of randomisation unclear, study described as double-blind 19 lost to follow-up, no ITT	Big treatment effect Only 4 weeks' duration
Sefton *et al.*, 1984[114]	Hydrocortisone valerate 0.2% ointment b.d. vs vehicle placebo	64 patients with mild-to-moderate atopic dermatitis	Prospective, randomised, double-blind left/right parallel study of 2 weeks' duration	Pruritus, erythema, scaling, papulation, lichenification and vesiculation Global evaluation using an VAS 0–100, 100 most severe	Mean global evaluation severity scores on 0–100 VAS: hydrocortisone valerate baseline score of 34.6 decreasing to 10.3 and placebo baseline score of 34.1 decreasing to 28.9 after 14 days treatment ($p < 0.01$)	Method and concealment of randomisation unclear, study described as double-blind (identical coded tubes), three drop-outs, no ITT	Six trials described in this paper (three RCTs) only one of which had not been published elsewhere
Wahlgren *et al.*, 1988[100]	Betamethasone dipropionate 0.05% cream b.d. vs base cream placebo b.d.	30 adult patients with persistent atopic dermatitis and chronic pruritis	Prospective, randomised, double-blind crossover study of 4 days' duration	Intensity of pruritus using Pain-Track and distribution and activity of eczema determined and excoriations counted	'No pruritus' on Days 3–4 was 35.8% during betamethasone and 21.5% during placebo therapy ($p = 0.0062$)	Method and concealment of randomisation unclear, study described as double-blind, four drop-outs, no ITT	Very short duration (4 days) using a novel approach to measure itch

continued

TABLE 47 contd *RCTs of topical corticosteroid vs placebo*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Stalder *et al.*, 1994[91]	Desonide o.d. vs excipient o.d.	40 children with atopic dermatitis	Prospective, randomised, double-blind parallel study of 7 days' duration	Global physician score based on extent and severity of lesion Local lesion score based on target area Various bacteriological assessments	66.7% desonide group showed improvement or resolution compared with 15.8% in the placebo group ($p < 0.001$) *S. aureus* density decreased by log 2.2 compared with log 0.6 in the placebo group ($p < 0.05$)	Method and concealment of randomisation unclear, study described as double-blind No mention of withdrawals and drop-outs	Paper suggests that use of topical steroids alone has a big impact on bacterial colonisation
Lebwohl *et al.*, 1996[76] USA (Study 1)	Fluticasone propionate ointment 0.005% vs placebo vehicle	203 patients with atopic eczema	Prospective, randomised, parallel study of 29 days' duration	Patient's self assessment of treatment efficacy Physician's gross assessment, severity scores of five signs and one symptom	Patient's self assessment at Day 29, 81% ($n = 74$) found fluticasone excellent or good vs 37% ($n = 28$) found vehicle excellent or good Drug-related adverse effects were rare	Method and concealment of randomisation unclear, study described as double-blind Large number of withdrawals and drop-outs ($n = 101$); no ITT analysis	Unclear why two identical large multicentre trials conducted and repeated concurrently
Lebwohl *et al.*, 1996[116] USA (Study 2)	Fluticasone propionate ointment 0.005% vs placebo vehicle	169 patients with atopic eczema	Prospective, randomised, parallel study of 29 days' duration	Patient's self assessment of treatment efficacy Physician's gross assessment, severity scores of five signs and one symptom	Patient's self assessment at day 29, 84% ($n = 63$) found fluticasone excellent or good vs 48% ($n = 26$) found vehicle excellent or good Drug-related adverse effects were rare	Method and concealment of randomisation unclear, study described as double-blind Large number of withdrawals and drop-outs ($n = 80$); no ITT analysis	Unclear why two identical large multicentre trials conducted and repeated concurrently

continued

TABLE 47 contd *RCTs of topical corticosteroid vs placebo*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Sears *et al.*, 1997[81]	Hydrocortisone buteprate 0.1% cream vs cream base placebo o.d.	194 patients with atopic dermatitis	Prospective, randomised, double-blind parallel study of 14 days' duration	Seven disease signs (infiltration, scaling, erythema, lichenification, vesicles, papules, and excoriation) were evaluated on a four-point scale (0 = absent, 3 = severe) Pruritus evaluated separately on same four-point scale Overall improvement on a seven-point scale (1 = cleared, 7 = worse) and global treatment efficacy on a four-point scale (1 = good and 4 = poor)	Seven sign lesion scores improvement over baseline of 9.13 for hydrocortisone reduced to 2.67 at Day 14, and placebo baseline of 9.95 reduced to 6.69 at Day 14	Method and concealment of randomisation unclear, study described as double-blind 26 drop-outs; no ITT	Large study with big treatment effects
Maloney *et al.*, 1998[132]	Clobetasol propionate 0.05% b.d. cream vs vehicle placebo b.d.	81 patients with moderate-to-severe atopic dermatitis	Randomised, double-blind parallel study of 43 days' duration	Physician gross assessment based on % improvement of target lesion plus changes from baseline in mean severity scores for erythema, pruritus, induration/papulation, lichenification, erosion/oozing/crusting, and scaling/dryness and for total signs and symptoms	Gross assessment at Day 43 showed 78% of clobetasol-treated patients were good, excellent or cleared compared with 33% of placebo-treated patients	Method and concealment of randomisation unclear, study described as double-blind 20 drop-outs; no ITT	Baseline scores not given

o.d., once daily

TABLE 48 *Patient characteristics and interventions of included studies (potentially poolable topical steroid versus another topical steroid)*

Study	Design	No. of subjects	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawals and drop-outs
Duke *et al.*, 1983[108]	Parallel, RCT	68	> 14	3 weeks	Not specified	Alclometasone dipropionate ointment 0.05% b.d.	Clobetasone butyrate ointment 0.05% b.d.	Unspecified	Four However, 65 included in efficacy study
Fisher & Kelly, 1979[96]	Parallel, left/right, RCT	(240) 107 atopic eczema	2–73	3 weeks	Not specified	Fluocininide 0.05% emollient cream t.d.s.	Betamethasone valerate 0.1% cream t.d.s.	Unspecified	11 atopic eczema patients
Lassus, 1983[115]	Parallel, RCT	40	5–11	2 weeks	Stable or worsening > 1 week	Alclometasone dipropionate cream 0.05% b.d.	Hydrocortisone butyrate cream 0.1% b.d.	Unspecified	None
Lassus, 1984[135]	Parallel, RCT	43	No data	2 weeks	Stable or worsening > 1 week	Alclometasone dipropionate cream 0.05% b.d.	Clobetasone butyrate cream 0.05% b.d.	Unspecified	None
Roth & Brown, 1978[97]	Parallel, L/R, RCT	19	No data	4 weeks	Not specified	Hydrocortisone valerate cream 0.2% t.d.s. Hydrocortisone valerate cream 0.2% t.d.s.	Betamethasone valerate cream 0.1% t.d.s. Hydrocortisone cream 1.0% t.d.s.	Antihistamines (for allergic rhinitis); insulin, antibiotics and tranquilisers	Unspecified
Sefton & Kyriakopoulos, 1983[136]	Parallel, L/R, RCT	145	No data	2 weeks	Mild to moderate	Hydrocortisone valerate ointment 0.2%	Betamethasone valerate 0.1% ointment Fluocinolone acetonide 0.025% ointment Triamcinolone acetonide 0.1% ointment	Unspecified	14: loss to follow-up or protocol violations
VanDelRey *et al.*, 1983[139]	Not translated (Spanish)								
Veien *et al.*, 1984[113]	Parallel, L/R, RCT	40	< 10	4 weeks	Not specified	Hydrocortisone 17-butyrate (Locoid) cream 0.1%	Hydrocortisone (Uniderm™) 1% cream	None specified	None
Yasuda, 1976[99]	Parallel, L/R, RCT	144	No data	7 days	Not specified	Hydrocortisone 17-butyrate 0.1% Locoid ointment	Triamcinolone acetonide 0.1% ointment Hydrocortisone acetate 1% ointment	'No local or systemic medications were permitted that could conceivably affect the dermatoses'	39 (seven drop-outs, 32 'not yet evaluated')

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TABLE 49 *Outcome measures*

Study	Outcome measure	Scale
Duke *et al.,* 1983[108]	Clinical signs and disease sign score: erythema, induration, pruritus	0–3 scale (0 = absent, 3 = severe)
	Physician's global assessment: cleared, marked improvement, moderate improvement, slight improvement, no change, exacerbation	Clear = 100%, <50% = slight improvement
Fisher & Kelly, 1979[96]	Clinical response relative to status of lesion (moderate improvement, slight improvement, no significant change, worse)	Five-point scale (5 = clear, 1 = worse)
	Adverse effects recorded	
	Patient and physician preference regarding efficacy of one agent over the other excluding cosmetic preferences	
Lassus, 1983[115]	Erythema, induration, pruritus	0–3 scale (0 = absent, 3 = severe)
	Physician global evaluation of improvement: cleared, marked improvement, moderate improvement, slight improvement, no change, exacerbation	Clear = 100%, <50% = slight improvement
Lassus, 1984[135]	Erythema, induration, pruritus	0–3 scale (0 = absent, 3 = severe)
	Investigator globally evaluated improvement in overall disease condition	
	Patients examined for adverse reactions	
Roth & Brown, 1978[97]	Overall condition evaluation	Eight-point scale: severely worse (1) to cleared (8)
	Severity scored	Four-point scale: 1 = clear, 2 = slight, 3 = moderate, 4 = severe
	Five symptoms: pruritus, erythema, scaling, excoriation, lichenification	Ten-point scale (0–9) 0 = clear
Sefton & Kyriakopoulos, 1983[136]	Investigator-assessed pruritus, erythema, scaling, papulation, lichenification, vesiculation (the distance of the mark made by an investigator from the end of the scale labelled none or clear indicated the degree of severity of the particular sign or symptom)	VAS digitalised into 0–100, 100 most severe
VanDelRey *et al.,* 1983[139]		
Veien *et al.,* 1984[113]	Global severity of all lesions	Five-point scale (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe)
	Therapeutic results assessed using three different degrees of improvement	Moderate, good, excellent associated with score reductions of at least 1, 2 and 3 points on the rating scale, respectively
Yasuda, 1976[99]	Investigator-assessed decrease in erythema, scaling, oedema, subjective symptoms, such as pruritus and burning sensation	
	Rapidity of onset of any therapeutic response, maximum degree of improvement of lesions and maintenance of response during the remainder of the treatment period were also rated as criteria for the overall evaluations of the treatment	

TABLE 50 *Outcome measures signs and symptoms*

Study	Erythema	Purulence	Excoriation	Dryness	Xerosis	Scaling	Lichenification	Cracking	Fissuring	Exudation	Vesiculation	Pustules/papules	Oozing/weeping	Oedema	Inflammation	Crusts	Infiltration	Induration	Itch	Sleep loss	Physician global severity assesssment	Patient global severity assessment	Area assessment (method used)	Scale named (if modified specify)
Duke *et al.*, 1983[108]	●																	●	●		●			
Fisher & Kelly, 1979[96]																								
Lassus, 1983[115]	●																	●	●		●			
Lassus, 1984[135]	●																	●	●		●			
Roth & Brown, 1978[97]	●		●			●	●												●		●			
Sefton & Kyriakopoulos, 1983[136]	●					●	●				●	●							●		●			
VanDelRey *et al.*, 1983[139]																								
Veien *et al.*, 1984[113]																								
Yasuda, 1976[99]	●					●								●					●					

Note:
Additional outcomes: Yasuda[99] also burning sensation

TABLE 51 *Results*

Study	Main reported results	Authors' conclusions	Quality
Duke *et al.*, 1983[108]	75% improvement in alclometasone dipropionate vs 68% improvement in clobetasone butyrate for mean clinical scores erythema, induration, pruritus ($p > 0.10$)	Clinical sign scores improved continuously during the study period and, at the end of therapy, favoured alclometasone conclusively over clobetasone	Method and concealment of randomisation unclear, 'blind evaluator technique' suggests single-blind study No ITT
Fisher & Kelly, 1979[96]	Mean clinical response 4.5 for fluocinonide and 4.38 for betamethasone on a scale of 1–5, where 5 = excellent or clear	Clinical responses favoured fluocinonide for the atopic dermatitis group ($p = 0.021$)	"Randomisation correlated with sequential numbers"; study described as double-blind No ITT
Lassus, 1983[115]	Eight out of 20 patients in alclometasone dipropionate group and seven out of 20 patients in hydrocortisone butyrate group showed 76–100% (marked or cleared) improvement in signs and symptoms (erythema, induration, pruritus)	Both creams were effective treatments for atopic dermatitis, however, alclometasone dipropionate was judged slightly more efficacious	Method and concealment of randomisation unclear, study described as double-blind No drop-outs or withdrawals
Lassus, 1984[135]	85% improvement for alclometasone dipropionate group and 86% improvement for clobetasone butyrate group of signs and symptoms (erythema, induration and pruritus)	Both treatments were effective	Method and concealment of randomisation unclear, study described as double-blind No drop-outs or withdrawals
Roth & Brown, 1978[97]	14 out of 19 patients showed clear or excellent improvement for both hydrocortisone valerate 0.2% cream and betamethasone valerate 0.1% cream (t.d.s.)	Hydrocortisone valerate 0.2% cream was found to be as effective as betamethasone valerate cream 0.1% cream	Method and concealment of randomisation unclear, study described as double-blind Withdrawals and drop-outs not mentioned
Sefton & Kyriakopoulos, 1983[136]	Hydrocortisone valerate 0.2% scored 12.6 compared with 10.7 for betamethasone valerate 0.1% VAS (mean) Hydrocortisone valerate 0.2% scored 15.6 compared with 14.5 for triamcinolone acetonide 0.1% VAS (mean) Hydrocortisone valerate 0.2% scored 4.7 compared with 4.6 for fluocinolone acetonide 0.1% VAS (mean)	Hydrocortisone valerate 0.2% ointment is a safe and effective perparation for use in mild-to-moderate atopic dermatitis	"The allocation treatments in each study was accomplished by a restricted randomisation process to ensure equal frequencies of the treatments to each side in small sequences of consecutively numbered patients". "The test preparations were supplied to investigators in coded identical tubes" No ITT carried out
VanDelRey *et al.*, 1983[139]	Needs translating		
Veien *et al.*, 1984[113]	Complete clearance of skin symptoms was found in 60% Locoid 0.1% treated patients and in 30% of Uniderm 1% treated patients	Locoid cream is significantly superior to Uniderm cream in the treatment of atopic dermatitis in children	Treatment assignment followed 'randomised double-blind code' No withdrawals or drop-outs
Yasuda, 1976[99]	Improvement over baseline as reported by investigator: 11 patients found hydrocortisone 17-butyrate superior to triamcinolone, 17 found drugs comparable 17 patients found hydrocortisone 17-butyrate superior to hydrocortisone acetate, nine found them comparable (for clinical effects)	Hydrocortisone 17-butyrate 0.1% ointment proved more effective than hydrocortisone acetate 1% ointment and triamcinolone acetonide 0.1% ointment	Table of numbers assured randomisation Study described as double-blind No ITT

TABLE 52 *Non-pooled topical steroid versus another topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Binder & McCleary, 1972[102]	Fluocinonide cream 0.05% q.d.s. vs betamethasone valerate cream 0.10% q.d.s.	Ten atopic eczema patients	Prospective, randomised, left right parallel study of 2 weeks' duration	Lesion improvement	Fluocinolone was superior to betamethasone in 70% of patients	Table of randomised numbers used. Study described as double-blind No withdrawals or drop-outs	Difficult to interpret magnitude of effect.
Almeyda & Fry, 1973[122]	10% urea and 1% hydrocortisone vs cream 0.1% betamethasone 17-valerate cream	50 atopic eczema patients	Prospective, randomised, left, right, parallel study of 3 weeks' duration	Lesion response: excellent, good, none, deterioration	Mean response of good or excellent outcome 76% urea hydrocortisone and 78% betamethasone 17-valerate	Method and concealment of randomisation unclear. Study described as double-blind. No withdrawals or drop-outs	Study which claimed equivalence of a very mild corticosteroid preparation against a potent one. Study grossly under-empowered to establish equivalence
Leibsohn & Bagatell, 1974[93]	Halcinonide cream 0.1% t.d.s. betamethasone 17-valerate cream 0.1% t.d.s.	Nine patients with atopic dermatitis	Prospective, randomised. Left right parallel study of 3 weeks' duration	Decrease of lesion size, reduction in erythema, oedema, transudation, lichenification and scaling, relief of pruritus and pain	An excellent or good response was recorded in 63% halcinonide patients and 38% betamethasone patients for overall evaluation of therapeutic response	"Randomised according to patient's study number" Study described as double-blind. One lost to follow-up, no ITT	Study of 88 patients with mixed dermatoses, some responding differently to the treatment
Almeyda & Burt, 1974[92]	Hydrocortisone 1% UHc powder-cream vs 0.1% betamethasone 17-valerate	36 adults and children with mild, moderate and severe atopic eczema	Prospective, randomised, left, right, parallel study of 4 weeks' duration	Clinical condition assessed as excellent if completely cleared and good if partially cleared, no improvement and deterioration	97% 'excellent' or 'good' improvement for hydrocortisone 1% and 94% 'excellent' or 'good' improvement for betamethasone	Method and concealment of randomisation unclear. Study described as double-blind. No withdrawals or drop-outs	Another study which assumes that no evidence of a statistical difference is the same as therapeutic equivalence
Lundell, 1974[419] (German)	0.1% fluprednylidenaceate in vs 0.25% fluocortolone	42 patients with severe atopic dermatitis	Prospective, randomised, left/right, parallel study of 4 weeks' duration	Erythema, scaling, weeping, itching (composite score therapeutic index)	Good effect for both preparations; fluprednylidenacetate significantly better than fluocortolone after 2nd week; therapeutic index 0.96 vs 0.86 after 4 weeks	Method and concealment of randomisation unclear, study described as double-blind Three withdrawals/ drop-outs, no ITT	Difficult to interpret treatment effect without placebo control

continued

TABLE 52 contd *Non-pooled topical steroid versus another topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Bjornberg & Hellgren, 1975[121] Germany (translated)	0.25% Desoximetasone cream b.d. vs 0.1% betametasone valerate cream b.d.	22 patients with atopic dermatitis and 24 patients with psoriasis	Prospective, randomised, double-blind controlled side-to-side comparison for 1-2 weeks	0–5 scale assessment of skin morphology Scoring of superior treatment (a>b, or b>a or a=b)	For atopic dermatitis patients: Desoximetason treated side was rated superior 11 times; betamethasone treated side rated superior eight times No difference three times	Randomisation unclear	Very short duration
Bleeker, 1975[70]	Halcinonide 0.1% cream b.d. vs clobetasol propionate 0.05% cream b.d.	27 moderate-to-severe atopic eczema patients	Prospective, randomised, left/right, parallel study of 2 weeks' duration	Lesions assessed for decrease in erythema, oedema, transudation, lichenification, scaling, pruritus and pain	92% 'excellent' or 'good' overall clinical response for both halcinonide and clobetasol	Table of random assignment Study described as double-blind No drop-outs or withdrawals	No placebo arm
Morley *et al.*, 1976[120]	0.05% clobetasone butyrate cream or ointment b.d. vs 0.0125% flurandrenolone cream or ointment b.d.	71 atopic eczema patients children only	Prospective, randomised, left/right, parallel study of 1 week duration	Clinician-assessed lesions as healed, improved, static or worse plus clinician/patient preference for right/left side	No data on clinician rated healing of lesions given Patient preference data only reported, which indicated a non-statistically significant preference in favour of clobetasone butyrate	Method and concealment of randomisation unclear, implies double blinding (neither clinician nor patient aware of identification) No withdrawals or drop-outs	No data to indicate magnitude of treatment effect
Savin, 1976[150]	Betamethasone dipropionate ointment 0.05% vs hydrocortisone ointment 1% b.d.	27 patients with atopic dermatitis 26 moderate, one very severe	Prospective, randomised, parallel study of 3 weeks' duration	Clinical effectiveness: excellent(>75%), good (50–75%), fair (25–50%), poor (<25%)	50% betamethasone 'excellent' or 'good' response compared with 22% hydrocortisone	Method and concealment of randomisation unclear, study described as double-blind Five drop-outs; no ITT	Clear categorical data and seperation of atopic eczema and psoriasis

continued

TABLE 52 contd *Non-pooled topical steroid versus another topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Yasuda, 1976[99]	Hydrocortisone 17-butyrate 0.1% locoid ointment vs triamcinolone acetonide 0.1% ointment or hydrocortisone acetate 1% ointment	144 atopic dermatitis patients	Prospective, randomised, left/right, parallel study of 7 days' duration	Decrease in erythema, scaling, oedema, subjective symptoms such as pruritus and burning sensation and improvement of lesions	Hydrocortisone 17-B superior to triamcinolone 10%, comparable 16%, inferior 3% Hydrocortisone 17-B superior to hydrocortisone acetate 16%, comparable 9% and inferior 3%	Table of numbers assured randomisation Study described as double-blind Seven drop-outs; 32 not yet evaluated hence no ITT	Well reported with useful data on placebo and psoriasis groups
Mali, 1976[137]	Betamethasone dipropionate cream vs locacorten 0.02% b.d.	16 atopic dermatitis patients from a total of 66 steroid-responsive dermatoses	Prospective, randomised, parallel study of 3 weeks' duration	Much better, slightly better, no change, slightly worse, much worse	19% betamethasone group much better compared with 13% Locacorten group ($p > 0.10$)	Method and concealment of randomisation unclear, study described as double-blind 16 withdrawals, unclear from which group	Useful to have data separated by diseases but only 16 atopic eczema patients
Bluefarb *et al.*, 1976[119]	Diflorasone diacetate 0.05% cream vs flucinonide 0.05% cream b.d.	210 atopic/ neurodermatitis patients	Prospective, randomised, parallel study of 3 weeks' duration	Degree of therapeutic response 1–25%, 26–50%, 51–75%, 76–100% clinical resolution, no change in severity or deterioration of lesions	Improvement over baseline >50% improvement: 71% for both diflorasone and fluocinonide	Method and concealment of randomisation unclear, study described as double-blind Nine+ withdrawals, no ITT	Some reservation on whether atopic/ neurodermatitis is the same as atopic eczema
Roth & Brown, 1978[97] Study 1	Hydrocortisone valerate cream 0.2% vs betamethasone valerate cream 0.1% t.d.s.	19 atopic eczema patients	Prospective, randomised, left/right parallel study of 4 weeks' duration	Symptoms pruritus, erythema, scaling, excoriation, lichenification Overall condition and severity	74% showed clear or excellent improvement for both hydrocortisone valerate and betamethasone valerate	Method and concealment of randomisation unclear, study described as double-blind Withdrawals and drop-outs not mentioned	Underpowered study

continued

TABLE 52 contd *Non-pooled topical steroid versus another topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Roth & Brown, 1978[97] Study 2	Hydrocortisone valerate cream 0.2% vs hydrocortisone cream 1% t.d.s.	29 atopic eczema patients	Prospective, randomised, left/right parallel study of 4 weeks' duration	Symptoms pruritus, erythema, scaling, excoriation, lichenification Overall condition and severity	No actual data given for this study Overall judgement of the response to the two medications (defined as cleared, excellent, good, no effect, or worse) showed hydrocortisone valerate to be statistically superior to hydrocortisone ($p < 0.05$)	Method and concealment of randomisation unclear, study described as double-blind Withdrawals and drop-outs not mentioned	Difficult to evaluate without any data
El-Hefnawi *et al.*, 1978[118]	Halcinonide-neomycin-amphotericin ointment 0.1% vs hydrocortisone 1% ointment	Five atopic dermatitis patients	Prospective, randomised, left/right parallel study of 3 weeks' duration	Subjective and objective evaluations of responses Global evaluation	100% improved or cleared for both halcinonide and hydrocortisone (cleared: 80% and 60%, respectively)	Pre-designed randomisation chart Study described as double-blind Withdrawals and drop-outs not mentioned	Very few atopic eczemna patients mixed up with other inflammatory skin diseases
Fisher & Kelly, 1979[96]	Fluocinonide 0.05% emollient cream t.d.s. vs betamethasone valerate 0.1% cream t.d.s.	107 atopic eczema patients	Prospective, randomised, left/right parallel study of 3 weeks' duration	Clinical response relative to status of lesion	Mean clinical response 4.5 for fluocinonide and 4.38 for betamethasone on a scale of 1–5, where 5 = excellent or clear	Randomisation correlated with sequential numbers Study described as double-blind 11 withdrawals/ drop-outs; no ITT	Suspect randomisation method
Ramelet, 1982[420] (Switzerland)	Betamethasone dipropionate 0.05% vs diflucortolone valerate 0.3% b.d.	12 adults with resistant atopic dermatitis	Prospective, randomised, parallel study of 14 days' duration	Physician-assessed erythema, induration, scaling, crusting, pruritus, excoriation, and pain Physician global assessment of therapeutic response % improved	For overall therapeutic efficacy 83% had cleared or marked improvement in both betamethasone and diflucortolone groups	Method and concealment of randomisation unclear, study described as double-blind No drop-outs or withdrawals	Very small number of patients over very short period of time

continued

TABLE 52 contd *Non-pooled topical steroid versus another topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Sefton & Kyriakopoulos, 1983[136] Study 1	Hydrocortisone valerate ointment 0.2% vs betamethasone valerate 0.1% ointment t.d.s.	68 mild-to-moderate atopic eczema patients	Prospective, randomised, left/right parallel study of weeks duration	Investigator-assessed pruritus, erythema, scaling, papulation, lichenification, vesiculation on an VAS of 1–100 (100 being most severe)	Improvement over baseline for hydrocortisone 44.1 reduced to 12.6 betamethasone 43.4 reduced to 10.7	Allocation by a restricted randomisation process in coded identical tubes 14 initially lost to follow-up, plus three from this part of study No ITT carried out	Magnitude of efficacy of 0.2% hydrocortisone valerate similar to that of a potent preparation
Sefton & Kyriakopoulos, 1983[136] Study 2	Hydrocortisone valerate ointment 0.2% vs triamcinolone acetonide 0.1% ointment t.d.s.	37 mild-to-moderate atopic eczema patients	Prospective, randomised, left/right parallel study of weeks duration	Investigator-assessed pruritus, erythema, scaling, papulation, lichenification, vesiculation on VAS of 1–100 (100 being most severe)	Improvement over baseline for hydrocortisone 46.4 reduced to 15.6 triamcinolone 47.9 reduced to 14.5	Allocation by a restricted randomisation process in coded identical tubes 14 initially lost to follow-up, plus one from this part of study No ITT carried out	Three studies described in same paper
Sefton & Kyriakopoulos, 1983[136] Study 3	Hydrocortisone valerate ointment 0.2% vs flucinolone 0.025% ointment t.d.s.	26 mild-to-moderate atopic eczema patients	Prospective, randomised, left/right parallel study of weeks duration	Investigator-assessed pruritus, erythema, scaling, papulation, lichenification, vesiculation on VAS of 1–100 (100 being most severe)	Improvement over baseline for hydrocortisone 27.1 reduced to 4.7, fluocinolone 26.9 reduced to 4.6	Allocation by a restricted randomisation process in coded identical tubes 14 initially lost to follow-up, plus one from this part of study No ITT carried out	Three studies described in same paper
Lassus, 1983[115]	Alclometasone dipropionate cream 0.05% b.d. vs hydrocortisone butyrate cream 0.1% b.d.	40 children with atopic eczema	Prospective, randomised, parallel study of 2 weeks' duration	Erythema, induration, pruritus Physician global evaluation of improvement	76–100% improvement or 'marked-cleared' was seen in 40% of alclometasone patients and 35% of hydrocortisone patients	Method and concealment of randomisation unclear, study described as double-blind No withdrawals or drop-outs	Useful to have outcome data presented as categories
Bagatell *et al.*, 1983[79]	Alclometasone dipropionate cream 0.05% vs hydrocortisone cream 1.0% t.d.s.	249 atopic eczema patients	Prospective, randomised parallel study of 3 weeks' duration	Erythema, induration, pruritus Investigator global evaluation	71% alclometasone patients showed cleared or marked improvement compared to 69% for hydrocortisone patients	Method and concealment of randomisation unclear, study described as double-blind 20 withdrawals/ drop-outs; no ITT carried out	Although written up as a study supporting superiority of the newer alclometasone, there is not much difference when % who are markedly improved or clear is evaluated

continued

TABLE 52 contd *Non-pooled topical steroid versus another topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Van DelRey *et al.*, 1983[139] Spain (translated)	Alclometasone cream 0.05% vs hydrocortisone butyrate	30 patients over 12 years old, more than 1 year disease duration and resistant to treatment	Parallel double-blind prospective randomised trial lasting 3 weeks	Doctor-assessed erythema, hardening of the skin and scaling After treatment improvement evaluated on a scale 1–6, where 1 = 100% improvement	Both treatments gave similar results of efficacy Total sign score fell from 7.20 to 1.00 in the alclometasone group and from 7.14 to 0.93 in the hydrocortisone group	Described as double-blind and randomised but method not clear One patient excluded from hydrocortisone group as he had seborrheic dermatitis	Difficult to establish equivalence in such a small study
Harder & Rufli, 1983[149] Switzerland (Basel) (translated)	Diflorasonediacetate 0.05% ointment o.d. vs betamethasone 17 valerate 0.1% ointment t.d.s.	98 patients with eczema' (probably atopic eczema but this is not specified in the paper)	Prospective, randomised, single-blind parallel-group study for 3 weeks	Improvement as assessed by: erythema, oedema, lichenification, induration, scaling, excoriation, itching, exulceration; each assessed with four-point scale	(Only summary data reported) Both groups achieved good results No significant difference between groups	26 drop-outs (detailed description given), no ITT analysis	One of the first studies to evaluate o.d. application vs more frequent application of a standard treatment
Konzelmann & Harms, 1983[147] Switzerland (Zurich) (translated)	Diflorasone diacetate 0.05% cream o.d. vs betamethasone dipropionate 0.1% cream	120 patients with acute or subacute eczema	Prospective, randomised, open parallel-group study for 3 weeks	Improvement assessed by doctor on five-point scale 0–100% improvement	85% of all patients showed grade 4 improvement (75–100%), no significant difference between groups	18 drop-outs, which were not assessed	Similar to above study
Duke *et al.*, 1983[108]	Alclometasone dipropionate ointment 0.05% b.d. vs clobetasone butyrate ointment 0.05% b.d.	68 atopic eczema patients	Prospective, randomised parallel study of 3 weeks' duration	Clinical score erythema, induration, pruritus, and physician global assessment	75% improvement in alclometasone group compared with 68% improvement in clobetasone group for mean clinical score	Method and concealment of randomisation unclear, blind evaluator technique suggests single-blind study No ITT	A small equivalence study
Lassus, 1984[135]	Alclometasone dipropionate cream 0.05% b.d. vs clobetasone butyrate cream 0.05% b.d.	43 atopic eczema patients	Prospective, randomised parallel study of 2 weeks' duration	Erythema, induration, pruritus and physician global evaluation of improvement	85% improvement for alclometasone group compared with 86% improvement for clobetasone group for three signs	Method and concealment of randomisation unclear, study described as double-blind No withdrawals or drop-outs	Little difference in treatment effect
Veien *et al.*, 1984[113]	Hydrocortisone 17-butyrate (Locoid) cream 0.1% vs hydrocortisone (Uniderm) 1% cream	40 atopic eczema patients	Prospective, randomised, left/right parallel study of 4 weeks' duration	Global severity of all lesions	Complete clearance of skin symptoms was found in 60% hydrocortisone 17-butyrate-treated patients compared with 30% hydrocortisone 1%-treated patients	Method and concealment of randomisation unclear, study described as double-blind No withdrawals or drop-outs	Treatment benefit of hydrocortisone butyrate increased as study progressed

continued

TABLE 52 contd *Non-pooled topical steroid versus another topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Nolting, 1985[138] Germany (translated)	Betamethasone dipropionate 0.05% vs desoximetasone 0.25% ointment	33 atopic eczema patients with resistant or severe disease in a trial, which also included psoriasis patients	Prospective, randomised, parallel RCT of 2 weeks' duration	Physician global rating	41% and 53% had clearance in the betamethasone vs desoximetasone groups, respectively ($p > 0.05$)	Method and concealment of randomisation unclear, study described as double-blind No ITT	Numbers of atopic eczema patients too small to make any specific comments
Rajka & Verjans, 1986[110]	Hydrocortisone 17-butyrate (Locoid) 0.1% fatty cream vs desonide (Apolar) 0.1% ointment b.d.	30 moderate-to-severe atopic dermatitis patients	Prospective, randomised, left/right, parallel study of 4 weeks' duration	Investigator-assessed global severity and severity grades of erythema, induration and scaling	Mean global severity score over baseline of 2.8 reduced to 1.3 for hydrocortisone and 1.7 for desonide ($p < 0.05$)	Method and concealment of randomisation unclear, study described as double-blind No drop-outs	Scaling scores not given on nine out of 30 patients because they did not experience scaling throughout the trial
Majerus & Reiffers-Mettelock, 1986[85]	Halometasone 0.05% cream or ointment vs betamethasone valerate 0.1% cream or ointment b.d.	75 atopic dermatitis patients	Prospective, randomised, parallel study of 3 weeks' duration	Inflammation, crusting, scaling, lichenification, excoriation, induration, exudate, pruritus, pain (healing, improvement, failure)	Healing was reported in 70% of patients with halometasone cream, 60% with halometasone ointment compared with 90% on betamethasone cream, and 80% on betamethasone ointment	Method and concealment of randomisation unclear, study described as double-blind 33 drop-outs/ withdrawals; no ITT	RCT mixed inflammatory dermatoses
Ulrich & Andresen, 1991[41] Germany (translated)	0.05% Halomethasone cream b.d. vs 0.25% Prednicarbate cream b.d. (both topical steroids)	165 patients with active episode of atopic dermatitis suitable for exclusively topical treatment	Prospective, randomised, double-blind parallel group study for 2 weeks	1. clinical effectiveness (doctor-assessed, five-point scale) 2. onset of clinical effectiveness (doctor-assessed) 3. adverse effects 4.cosmetic acceptability (patient-assessed five-point scale)	1. clinical effectiveness: no significant difference between groups 2. onset: no difference at Day 1 or 4 between groups 3. adverse effects: none reported 4 cosmetic acceptability: 51% vs 46% rated it 'excellent' (NS)	Randomisation criteria unclear Authors tried to create subgroup of severely affected patients, probably retrospectively They then claim significant advantage for Halomethasone in severely affected patients	One of authors was an employee of the company that produces Halomethasone cream
Haneke, 1992[75] Germany Study 1	0.1% methylprednisolone aceponate ointment o.d vs 0.1% betamethasone valerate b.d.	94 adults with atopic dermatitis	Prospective, randomised, left/right, parallel study of 4 weeks' duration	Patient and doctor global assessments Doctor assessed 11 signs and symptoms	No actual data for o.d. methylprednisolone vs b.d. betamethasone given	Method and concealment of randomisation unclear Study described as double-blind, no ITT	Results of all three studies impossible to disentangle

continued

TABLE 52 contd *Non-pooled topical steroid versus another topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Haneke, 1992[75] Germany Study 2	0.1% methylprednisolone aceponate ointment b.d. vs 0.1% betamethasone valerate b.d.	94 adults with atopic dermatitis	Prospective, randomised, left/right, parallel study of 4 weeks' duration	Patient and doctor global assessments Doctor assessed 11 signs and symptoms	No actual data for b.d. methylprednisolone vs b.d. betamethasone given	Method and concealment of randomisation unclear Study described as double-blind, no ITT	Results of all three studies impossible to disentangle
Rampini, 1992[123] Study 1	Methylprenisolone aceponate 0.1% cream b.d. vs prednicarbate 0.25% cream b.d.	80 children with atopic dermatitis	Prospective, randomised, parallel study of 3 weeks' duration	Objective and subjective symptoms of erythema, exudation, scaling, hyperkeratosis, itching, burning Global therapeutic response	97.3% methylprenisolone patients achieved complete healing or distinct improvement compared with 100% prednicarbate patients	Method and concealment of randomisation unclear, study described as double-blind Two drop-outs/ withdrawals; no ITT	Three studies of three different comparisons in different age groups
Rampini, 1992[123] Study 2	Methylprenisolone aceponate 0.1% o.d. ointment vs prednicarbate 0.25% cream b.d.	120 children with atopic dermatitis	Prospective, randomised, parallel study of 3 weeks' duration	Objective and subjective symptoms of erythema, exudation, scaling, hyperkeratosis itching, burning Global therapeutic response	96.3% methylprenisolone patients achieved complete healing or distinct improvement compared with 98.1% prednicarbate patients	Method and concealment of randomisation unclear, study described as double-blind 12 drop-outs/ withdrawals; no ITT	Three studies of three different comparisons in different age groups
Hoybye *et al.*, 1991[124]	Momethasone furoate o.d. vs hydrocortisone 17-butyrate b.d.	96 atopic dermatitis patients	Prospective, randomised, parallel study of 6 weeks' duration	No information given	85% momethasone patients significantly greater improvement vs 71% hydrocortisone group ($p = 0.0025$)	Method and concealment of randomisation unclear, study described as investigator blind Drop-outs/ withdrawals no data given	Published in abstract form only
Gelmetti *et al.*, 1994[80] Italy (translated)	0.025% budesonide cream vs 0.1% alclometasone dipropionate b.d.	40 children with atopic dermatitis	Prospective, randomised, parallel study of 2 weeks' duration	% of patients who were good or excellent Composite scale of signs and symptoms and tolerability	83% good or excellent for budesonide vs 94% good or excellent for alclometasone (No formal statistical comparison done)	Method and concealment of randomisation unclear; blinding unclear; no ITT	No final analysis Very similar effects, small numbers over very short term

continued

TABLE 52 contd *Non-pooled topical steroid versus another topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Jorizzo *et al.*, 1995[88]	Desonide 0.05% ointment vs hydrocortisone 1% ointment b.d.	113 children with atopic dermatitis	Prospective, randomised, parallel study of 5 weeks' duration	Physician global improvement, erythema, lichenification excoriations, oozing and crusting, induration and papules Pruritus assessed subjectively	68% desonide patients and 40% hydrocortisone had clearing or marked improvement at 5 weeks	Method and concealment of randomisation unclear, study described as investigator blind Two drop-outs/ withdrawals; no ITT	Study followed-up by a longer 6-month follow-up study, which did not show any signs of skin thinning in either group
Camacho *et al.*, 1996[68] Spain (translated)	0.25% prenicarbate cream vs 0.2% flucortolone monhydrate cream b.d.	49 out-patients with atopic dermatitis aged 19–65 years	Prospective, randomised, double-blind parallel right/left comparison of 3 weeks' duration	Itch, erythema, eczema, vesicles/papules lichenification, on a scale of 0–3 Also physician and patient global evaluation of whether one side better than the other	Physicians rated the prednicarbate side better in 12 patients, the flucortolone side better in seven patients and no difference in 16 patients ($p = 0.30$) at the end of 3 weeks 80% of patients recorded good to excellent improvement on the prednicarbate side compared with 63% for the flucortolone side ($p = 0.10$) No statistical difference between signs and symptoms were noted Stinging similar in both groups	Randomisation method and concealment not described Stated to be double-blind No ITT analysis (14/49 drop-outs)	Sponsored study of very short duration Drop-outs were not included in analysis, which is worrying given the high drop-out rate (29%) and the fact that at least two dropped out because they worsened
Lebwohl *et al.*, 1999[116] USA	0.1% mometasone furoate cream o.d. vs 0.2% hydrocortisone valerate cream b.d.	219 children with moderate-to-severe atopic dermatitis	Prospective, randomised, parallel study of 21 days' duration	Investigator assessed seven signs and symptoms on a 0–3 scale (0 = none, 3 = severe) and global assessment % improved	Mean improvement in severity score (no baselines given) at day 21 (% of patients with 100% clearance), 87.4% for mometasone and 79.7% for hydrocortisone valerate at Day 21	Method and concealment of randomisation not clear, study described as evaluator-blind	Unclear if the o.d. vs b.d. cream was blinded (probably not) End-points given but unclear what they are

TABLE 53 *RCTs of topical steroids versus another topical*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Hiratsuka *et al.*, 1996[84] Japan	Beclomethasone dipropionate t.d.s. vs topical SCG t.d.s.	43 children with moderate-to-severe atopic dermatitis	Prospective, randomised, parallel study of 2 weeks' duration	Severity of inflammation, lichenification and cracking over 15 body areas Patient diary cards for itch and sleep loss Laboratory tests	Itch and sleep disturbance estimated from graph SCG baseline score 2.3 and 2.4 reduced to 0.7 and 0.5 for itch and sleep disturbance, respectively, at 2 weeks and beclomethasone baseline 2.2 and 2.3 reduced to 0.9 and 0.6 for itch and sleep loss, respectively, at 2 weeks	Method and concealment of randomisation unclear, study described as double-blind No information of withdrawals or drop-outs	Study mainly concerned with cellular and immunological changes
Korting *et al.*, 1995[86] Germany	Hamamelis distallate 5.35 g plus 0.64 mg ketone/100 g vs vehicle or 0.5% hydrocortisone	72 patients with moderate-to-severe atopic dermatitis	Prospective, randomised, left/right, parallel study of 2 weeks' duration	Physician and patient global assessments 0–5 scale, where 0 = healed and 5 = worse Itch, erythema, scaling, oedema, papules, pustules, exudation, lichenification, excoriations, fissuring	There was no clinical or statistical difference between hamamelis and vehicle for reduction of itching at 2 weeks Mean itch score changed from 2.1 to 0.8 for hydrocortisone and from 2.1 to 1.2 for hamamelis ($p < 0.01$) Patient recorded efficacy was also significantly improved in hydrocortisone group when compared with hamamelis There were no differences between hamamelis and vehicle	Method and concealment of randomisation unclear, study described as double-blind Seven withdrawals/drop-outs; no ITT	Useful study with a placebo arm, which provided no evidence to support efficacy of hamamelis
Munkvad, 1989[83] Denmark	Clinitar coal tar vs 1% hydrocortisone	30 patients with mild-to-moderate atopic eczema	Prospective, randomised, left/right, parallel study of 4 weeks' duration	Infiltration, erythema, lichenification, excoriations, dryness, doctor and patient global assessments	All five parameters reduced significantly over the 4-week period but no significant differences between the two treatments	Method and concealment of randomisation unclear No mention of blinding No withdrawals/drop-outs	Difficult to blind due to smell of coal tar Difficult to evaluate significance of change in scores due to small sample size and lack of data No placebo arm

continued

TABLE 53 contd *RCTs of topical steroids versus another topical*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Wolf-Jürgensen, 1979[74] Norway	5% bufexamac b.d. vs 0.1% hydrocortisone or placebo b.d.	10 atopic eczema patients within a study of 72 patients with various forms of dermatoses	Prospective, randomised, parallel study of 2 weeks' duration	Patient and investigator global assessment Severity of inflammation, induration, lichenification, crusts, scaling, pruritus	Change in global score was very similar for the three patients allocated to placebo, betamethasone and bufexamac	Method and concealment of randomisation unclear, study described as double-blind One withdrawal/ drop-out; no ITT	Impossible to interpret differences in such a small subsample of atopic eczema patients

TABLE 54 *Topical steroid plus additional active agents*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Addition of antimicrobials							
Wachs & Maibach, 1976[90] USA	Betamethasone valerate cream vs gentamicin/betamethasone valerate vs gentamicin cream t.d.s.	83 infected moderate-to-severe atopic dermatitis patients	Prospective, randomised parallel study of 22 days	Global assessment and overall severity, degree of inflammation, degree of infection, erythema, pruritus, pustules, crusting, exudation, vesiculation, lichenification	Improvement over baseline on a scale of 0–10 Betamethasone/ gemtamicin group baseline score of 6.1 reduced to 1.0, betamethasone group 6.1 reduced to 1.8 and gentamicin group 6.6 baseline reduced to 4.2	Method and concealment of randomisation unclear, study described as double-blind Four drop-outs; no ITT	Treatment responses were very slightly larger for steroid/ antibiotic combination but none statistically significant Bacterial growth similar in all three groups
Hjorth *et al.*, 1985[111]	Betamethasone 17-valerate 0.1% vs betamethasone 17-valerate plus 2% fusidic acid	60 atopic dermatitis patients with potentially infected atopic eczema	Prospective, randomised, left/right, parallel study of 7 days' duration	Bacteriological swabs Clinical symptoms: vesicles, oedema, erythema, excoriation, crusting, lichenification, itching	Data for mean atopic dermatitis not given, only result is investigator preference: 29 no preference, 22 preferred betamethasone plus fusidic acid and nine preferred betamethasone alone	Method and concealment of randomisation unclear, study described as double-blind No drop-outs or withdrawals	Author contacted for more data but has sadly deceased Study provides no evidence of improved efficacy of betamethasone/ fusidic acid combination above betamethasone alone in infected atopic eczema

continued

TABLE 54 contd *Topical steroid plus additional active agents*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Wilkinson & Leigh 1985[117] UK	0.1% betamethasone plus 2% fusidic acid cream vs 0.1% betamethasone plus 0.5% neomycin cream b.d. or t.d.s.	43 infected or potentially infected atopic eczema patients	Prospective, randomised, parallel study of 2 weeks' duration	Severity of lesions assessed by patient and doctor as either very severe, severe, moderate, mild, minimal, or absent Swabs taken for infection	95% patients (91% doctors) felt lesions improved after betamethasone plus fusidic acid after 2 weeks vs 100% patients (100% doctors) felt betamethasone plus neomycin No separate data for bacteriological efficacy for atopic dermatitis	Method and concealment of randomisation unclear, study described as double-blind Nine withdrawals and drop-outs but unclear which type of eczema these patients had (seven types of dermatoses reported)	Difficult to interpret in the absence of a betamethasone only arm
Meenan, 1988[107]	Hydrocortisone 17-butyrate 0.1% plus 3% chlorquinaldol vs 0.1% triamcinolone acetonide plus 0.25% neomycin plus 0.025% gramicidin nystatin	40 children with eczema for 3 months to 14 years with secondary infection	Prospective, randomised parallel study of 14 days' duration	Pruritus, erythema, lichenification, oozing/crusting, scaling Skin swabs for infection Patient and physician global score	Both treatments produced a highly significant ($p < 0.001$) linear reduction in the scores for all parameters, no significant difference between treatments Highly significant reduction in infection for both treatments ($p < 0.001$)	Method and concealment of randomisation unclear, study described as double-blind No data given on withdrawals or drop-outs	Both agents contain an antimicrobial/ antiseptic, and no steroid-only comparator
Zienicke, 1993[146]	Prednicarbate 0.25% cream vs prednicarbate 0.25% cream plus didecyldimethyl-ammoniumchloride 0.25%	180 superinfected atopic eczema patients	Prospective, randomised, parallel study of 34 days' duration	Redness, swelling, papulovesicles, vesicles, pustules, bullae, papules, status madidans, crusting and scaling on a score of 1–5	Clinical score over baseline of 25 for both drugs reduced to 13.5 for prednicarbate and 13 for prednicarbate plus didecyl dimethyl-ammoniumchloride 30% patietns still had *S. aureus* at day 34 compared with 100% at start	Method and concealment of randomisation unclear, study described as double-blind 44 withdrawals/ drop-outs; no ITT carried out	Duplicate publication of Korting 1994 No clinical or statistical difference between groups

continued

TABLE 54 contd *Topical steroid plus additional active agents*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Ramsay *et al.*, 1996[128] Study 1	Fusidic acid and 1% hydrocortisone vs 1% hydrocortisone	186 mild-to-moderately severe atopic dermatitis	Prospective, randomised, parallel study of 2 weeks' duration	Primary: percentage patients not failing treatment (included signs, withdrawal and various bacteriological criteria) Secondary: erythema, scaling, oedema, itching, serous discharge, crusting, extent of lesions and overall clinical response	63.7% fusidic acid plus hydrocortisone did not fail treatment compared with 50.6% in the hydrocortisone group ($p = 0.11$) Mean change in clinical scores not statistically significant ($p = 0.21$)	Method and concealment of randomisation unclear, study described as double-blind 32 drop-outs/ withdrawals; no ITT	No evidence to support a clear benefit of combination over plain hydrocortisone
Ramsay *et al.*, 1996[128] Study 2	Fusidic acid and 1% hydrocortisone vs 2% fusidic acid	68 mild to moderately severe atopic dermatitis	Prospective, randomised, parallel study of 2 weeks' duration	Erythema, scaling, oedema, itching, serous discharge, crusting, extent of lesions and overall clinical response Swabs taken	36.4% fusidic acid plus hydrocortisone failed treatment and 65.6% fusidic acid failed treatment ($p = 0.04$)	Method and concealment of randomisation unclear, study described as double-blind Three drop-outs/ withdrawals; no ITT	Some evidence of benefit of fucidin/hydrocortisone over fucidin alone
Thaci, 1999[77] Germany	Fusidic acid 2% plus 0.1% betamethasone cream vs fusidic acid 2% plus 0.1% betamethasone ointment vs ointment vehicle b.d.	59 patients with potentially infected atopic dermatitis	Prospective, randomised, parallel study of 10 days' duration	Bacteriological tests, signs and symptoms on a four-point scale, investigator-assessed overall clinical response	Overall clinical response assessed by invrestigator as 'clearance' or 'marked improvement' in 92% fusidic acid/betamethasone cream patients, in 84% fusidic acid/ betamethasone ointment patients, and 25% ointment vehicle patients No statistically significant difference between the two formulations	Method and concealment of randomisation unclear, study described as double-blind No withdrawals or drop-outs mentioned	Abstract only Only results reported in text given

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TABLE 54 contd *Topical steroid plus additional active agents*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Addition of antifungal							
Anon, 1967[127]	Triamcinolone acetonide 0.1% and neomycin sulphate 0.35% vs triamcinolone acetonide 0.1% and neomycin sulphate 0.35% plus undecylenic acid 2.5%	Ten infantile eczema patients within a study of 100 patients with various skin disorders	Prospective, randomised, parallel study	No change, some improvement, marked improvement, cured	Cured or marked improvement 17% for triamcinolone acetonide and neomycin sulphate compared with 100% for triamcinolone acetonide 0.1% and neomycin sulphate plus undecylenic acid	Method and concealment of randomisation unclear, study described as double-blind Drop-outs/ withdrawals: no data given no ITT Length of study not given	Difficult to make any conclusion in such a small subset
Topical steroids plus something else vs topical steroids alone							
Kaplan *et al.*, 1978[89]	Hydrocortisone 0.5% plus 30% caffeine vs hydrocortisone 0.5% vs betamethasone valerate 0.1%	90 atopic dermatitis patients	Prospective, randomised, parallel study of 3 weeks' duration	Pruritus, erythema, scaling, lichenification, oozing, excoriation, overall global impression	Mean improvement over baseline global impression on a scale 0–5: 2.6 to 1.6 for hydrocortisone, 2.1 to 0.8 for caffeine and hydrocortisone, 2.7 to 0.6 for betamethasone	Method and concealment of randomisation unclear, study described as double-blind Seven drop-outs/ withdrawals; no ITT	Some evidence to suggest the addition of caffeine might have a small additional benefit
Chapman, 1979[125]	0.1% hydrocortisone butyrate ointment vs 1% hydrocortisone alcohol with 10% urea b.d.	40 atopic eczema patients split into two studies One group applied creams to dry skin, the other after wetting the skin first	Prospective, randomised, left/right parallel study of 3 weeks' duration	Erythema, scaling, oedema	Mean clinical improvement dry skin 73% hydrocortisone alcohol vs 80% hydrocortisone 17-butyrate ($p > 0.05$) wet skin 67% hydrocortisone alcohol vs 68% hydrocortisone 17-butyrate ($p > 0.05$)	Method and concealment of randomisation unclear, study described as double-blind Drop-outs/ withdrawals; no data given	No evidence to support efficacy of the combination treatment
Norén & Melin, 1989[106]	Hydrocortisone vs betamethasone valerate plus hydrocortisone vs hydrocortisone plus habit reversal vs betamethasone valerate plus hydrocortisone plus habit reversal	45 moderate-to-severe atopic dermatitis patients	Prospective, randomised, parallel study of 5 weeks' duration	Primary: reduction in scratching, secondary: dryness, scaling, erythema, infiltration, frequency of scratching	At end of 5-week evaluation period total skin status scores (not defined in paper) fell in all four groups but more so in groups that included habit reversal (data only presented in graphical form) Similar changes for other skin signs presented in graphical form	Method and concealment of randomisation unclear, no blinding Two drop-outs/ withdrawals; no ITT	Useful RCT which evaluates combinations of different treatment approaches which suggests an additional benefit of habit reversal

TABLE 55 *RCTs comparing different formulations of the same topical steroid*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Andersen *et al.*, 1988[144] Denmark	Mildison® 1% hydrocortisone vs Uniderm 1% hydrocortisone	96 children with atopic dermatitis	Prospective, randomised, left/right parallel study of 4 weeks' duration	Global severity of symptoms, global improvement of skin lesions, investigator and patient preference	Mean reduction in severity score over baseline of 1.7 for Mildison and Uniderm reduced to 0.7 and 0.8, respectively	Method and concealment of randomisation unclear, study described as double-blind No withdrawals or drop-outs	Little efficacy difference between treatments, yet patients preferred the Mildison preparation
Korting *et al.*, 1090[103] Germany	0.039% liposomal betamethasone dipropionate vs 0.054% commercial propylene glycol gel	12 patients with atopic dermatitis	Prospective, randomised, left/right, parallel study of 2 weeks' duration	Investigator assessed ten signs and symptoms of eczema and proportion of patients with major improvement or healed and global effect on a 0–5 scale. where 0 = healed and 5 = worse	Although data not reported in text, estimates from the figure showed that 80% evaluable patients noted healed or major improvement in liposome group compared with 60% patients in reference group at Day 14	Method and concealment of randomisation unclear, study described as double-blind Two withdrawals/ drop-outs; no ITT	Small study where ten parameters measured and data only given for some to support enhanced benefit for test substance
Malzfeldt *et al.*, 1989[130] Germany	Betamethasone 17-valerate 0.0056% in liquid paraffin vs betamethasone 17-benzoate 0.00056% in neutral oil	16 patients with atopic eczema	Prospective, randomised, left/right parallel study of 5–7 days' duration	Investigator assessed five signs on a 0–3 scale (max. score 15)	In low solution capacity group mean global score fell from 11.9 at baseline to 3.8 at Day 7 compared with 11.9 to 8.2 at baseline and Day 7, respectively, for high solution capacity ($p \leq 0.01$)	Method and concealment of randomisation unclear, study described as double-blind Withdrawals or drop-outs not mentioned	Study suggests that vehicle can markedly affect efficacy
Olholm *et al.*, 1988[143] Denmark	Mildison 1% hydrocortisone vs Uniderm 1% hydrocortisone	60 atopic dermatitis patients	Prospective, randomised, left/right parallel study of 4 weeks' duration	Lesions: global severity of atopic dermatitis, investigator and patient preference of therapeutic efficacy	Physician global assessment for those aged <10 years: the proportion of those with moderate, severe, or very severe dermatitis was 94% at baseline and 14% at 4 weeks for Mildison compared with 94% at baseline and 16% at 4 weeks for Uniderm For >10 years 89% baseline to 12% at 4 weeks for Mildison and Uniderm	Method and concealment of randomisation unclear, study described as double-blind Five drop-outs and withdrawals; no ITT	Very similar to Andersen *et al.*,[144] study, but this time no patient preference with regards to cosmetic acceptibility

Mildison®, Yamanouchi, UK

TABLE 56 *RCTs of once-daily versus more frequent application of steroids (trials involving the same active compound)*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Sudilovsky *et al.*, 1981[95] USA	0.1% halcinonide cream o.d. vs 0.1% 0.1% halcinonide cream t.d.s.	149 atopic eczema patients	Prospective, randomised, right/left, parallel study of 3 weeks' duration	Comparative and absolute therapeutic responses: erythema, oedema, changes in size of thickness of lesions Physician global response	Based on 116 evaluable patients at week 3 86.2% noticed good or excellent clearance in t.d.s. vs 85.3% in o.d. group No statistical differences	Method and concealment of randomisation unclear, study described as double-blind 33 drop-outs/ withdrawals; no ITT	Table of random numbers used Implies double blinding by use of placebo
Richelli *et al.*, 1990[145] Italy	Clobetasone 17-butyrate lotion b.d. (8 am and 3 pm) vs b.d. (3 pm and 8 pm) or o.d. (9 pm)	30 children with atopic eczema	Prospective, randomised, right/left, parallel study of 3 weeks' duration	Itching, burning, pain, erythema, oedema, exudation, blisters, bullae, scabs, scaling, lichenification, pooled into a mean score Serum cortisol and ACTH tests	Data on severity scores only presented in graphical form No obvious differences between three groups No supporting statistics given	Method and concealment of randomisation unclear Blinding not described Unclear of ITT	Method and concealment of randomisation unclear Blinding not described Unclear of ITT
Haneke, 1992[75] Germany	Methylprednisolone aceponate ointment o.d. vs b.d.	88 adults with atopic dermatitis	Propsective, randomised, left/right, parallel study of 4 weeks' duration	Patient and doctor global assessments Doctor assessed 11 signs and symptoms	No actual data for o.d. vs b.d. methylprednisolone aceponate given	Method and concealment of randomisation unclear Study described as double-blind No ITT	Results of all three studies impossible to disentangle
Koopmans *et al.*, 1995[69] Finland	0.1% hydrocortisone 17-butyrate cream b.d. vs o.d. plus vehicle o.d.	150 adults and children over the age of 12 years suffering from atopic dermatitis	Prospective, randomised, parallel study of 4 weeks' duration	Patient and doctor assessed overall severity Clinical features assessed were erythema, induration, pruritus and excoriation	78% o.d. vs 93% b.d. (p = 0.006) noticed considerable improvement or clearance according to patient	Method and concealment of randomisation unclear Study described as double-blind No ITT but only one drop-out	Method and concealment of randomisation unclear Study described as double-blind No ITT but only one drop-out
Bleehen *et al.*, 1995[87] UK	Fluticasone propionate 0.05% cream o.d. vs b.d.	270 moderate-to-severe atopic dermatitis patients	Prospective, randomised, parallel study of 4 weeks' duration	Patient diary cards for itch, rash and sleep disturbance Physician assessed six signs and global assessment	Patient diary cards revealed improvement in rash, itch and sleep loss for both treatment groups within first week. 80% in o.d. and 85% in b.d. groups defined as clinical success on ITT analysis (p = 0.35)	Method and concealment of randomisation unclear Probably investigator blinded but unclear ITT carried out	Method and concealment of randomisation unclear Probably investigator blinded but unclear ITT carried out

ACTH, adrenocorticotrophic hormone

TABLE 57 *Once- versus twice-daily application of different topical corticosteroids (trials involving different active compounds)*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Hoybye *et al.*, 1991[142] Denmark	Mometasone furoate cream o.d. vs hydrocortisone 17-butyrate cream b.d.	96 adult atopic eczema patients	Prospective, randomised, parallel study of 6 weeks' duration	Patient VAS for severity of eczema, 0–3 score for doctor-assessed erythema, infiltration and pruritus, global evaluation scores of 1–6	A comparison of the evaluations made by patients on a VAS after 6 weeks showed no difference in efficacy between the two treatments ($p = 0.30$)	Method and concealment of randomisation unclear, study described as single-blind Ten drop-outs/ withdrawals, no ITT	Difficult to blind a o.d. treatment with a b.d. treatment Posology of treatments not given
Vernon *et al.*, 1991[101] USA	Mometasone furoate 0.1% cream vs hydrocortisone 1.0% cream o.d.	48 children with moderate-to-severe atopic dermatitis	Prospective, randomised, parallel study of 6 weeks' duration	Doctor-assessed erythema, lichenification, skin surface disruption (crusting, scaling), excoriation, and pruritus on a 0–3 scale, % body surface area and global evaluation	For the 12 evaluable patients mean percentage improvement in total sign/ symptom score was 95% for mometasone vs 75% for hydrocortisone ($p = 0.01$) The group with more than 25% body surface area involvement showed a wider difference in favour of mometasone (92% vs 62%; $p = 0.01$)	Method of randomisation unclear, study described as single blind with an 'unblinded investigator' evaluations were carried out by a 'blinded' investigator 36 patients experienced clearing of eczema prior to end of study so were withdrawn; no ITT carried out	Efficacy advantage of mometasone (classified as potent in UK) not surprising when compared against a very mild product
Rafanelli *et al.*, 1993[129] Italy	Mometasone furoate 0.1% cream o.d. vs clobetasone 0.05% cream b.d.	60 children with atopic dermatitis	Prospective, randomised, parallel study of 3 weeks' duration	Parent-assessed efficacy of treatment on a four-point scale (excellent to poor) Investigator-assessed erythema, induration and pruritus, global percentage improvement	Total sign/symptom score improvement over baseline, 7.8 to 1.1 ($p < 0.01$) for mometa-sone vs 7.2 to 2.4 for clobetasone (NS)	Method of randomisation unclear, study described as third party blind No withdrawals or drop-outs	Uncertain what type of clobetasone was tested This is important as the propionate is super potent whereas butyrate is moderately so
Marchesi *et al.*, 1994[131] Italy	Mometasone furoate ointment 0.1% o.d. vs betamethasone dipropionate ointment 0.05% b.d.	60 adult patients with atopic eczema of at least moderate severity	Prospective, randomised, parallel study of 3 weeks' duration	Investigator assessed erythema, induration and pruritus on a 0–3 scale, global evaluation % improvement	100% of mometasone and betamethasone patients had cleared or experienced good improvement by week 3 No baseline values given	Method of randomisation unclear, study described as third-party blind evaluator No withdrawals or drop-outs	Pity there was no comparison between o.d. betamethasone

continued

TABLE 57 contd *Once- versus twice-daily application of different topical corticosteroids (trials involving different active compounds)*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Reidhav & Svensson, 1996[72] Sweden	Betamethasone valerate 0.1% cream o.d. vs mometasone furoate 0.1% cream o.d.	30 patients with atopic dermatitis aged 15–66 years	Prospective, randomised, left/right, parallel study of 4 weeks' duration	Patient assessed pruritus and smarting pain on 0–3 scale, evaluator assessed erythema, scaling, lichenification, excoriation, papules, and vesicles on a 0–3 scale (max. score 18)	No significant differences were found for any of the symptoms scored following 4 weeks' treatment with betamethasone valerate or mometasone furoate	Method and concealment of randomisation unclear, study described as double-blind Ten drop-outs/ withdrawals; no ITT carried out	No actual efficacy data reported, only patient preference data given
Traulsen, 1997[73] Denmark Study 1	Hydrocortisone buteprate cream 0.1% o.d. vs betamethasone valerate 0.1% cream o.d.	86 atopic dermatitis patients 12+ years	Prospective, randomised, left/right parallel study of 2 weeks' duration	Erythema, infiltration, lichenification, scaling, vesiculation, papules, excoriations and pruritus on a 0–4 scale Patient-assessed efficacy and investigator global assessment	The sum of scores of 8 symptoms showed a mean reduction from 13.1 to 2.3 after 2 weeks' treatment There were no significant differences between the two treatments	Method and concealment of randomisation unclear, study described as double-blind Three withdrawals/ drop-outs; no ITT carried out	No differences between treatments but effect sizes similar to studies of b.d. usage
Traulsen, 1997[73] Denmark Study 2	Hydrocortisone buteprate ointment 0.1% o.d. vs betamethasone valerate 0.1% ointment o.d.	82 atopic dermatitis patients 12+ years	Prospective, randomised, left/right parallel study of 2 weeks' duration	Erythema, infiltration, lichenification, scaling, vesiculation, papules, excoriations and pruritus on a 0–4 scale Patient-assessed efficacy and investigator global assessment	The mean sum of scores of five symptoms (erythema, scaling, vesicles, papules, pruritus) decreased from baseline 8.3 to 1.6 after 2 weeks for hydrocortisone buteprate vs 8.3 to 1.4 for betamethasone valerate A statistically significant difference was found in favour of betamethasone	Method and concealment of randomisation unclear, study described as double-blind Four withdrawals/ drop-outs; no ITT carried out	
Amerio *et al.*, 1998[78] Italy	Mometasone furoate 0.1% o.d. vs betamethasone valerate b.d.	97 atopic dermatitis patients	Prospective, randomised, parallel study of 15 days' duration	Erythema, oedema, essudate, scaling, excoriation, lichenification (objective symptoms) and pruritus and burning (subjective symptoms)	83.1% mometasone furoate patients and 89.2% betamethasone valerate patients experienced a reduction in signs and symptoms (NS)	Method and concealment of randomisation unclear from abstract, study described as double-blind Unclear from abstract if any withdrawals or drop-outs	A study reported in Italian; all information abstracted from the English abstract only Pity there was no o.d. betamethasone

continued

TABLE 57 contd *Once- versus twice-daily application of different topical corticosteroids (trials involving different active compounds)*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Wolkerstorfer *et al.*, 1998[82] The Netherlands	Fluticasone propionate 0.05% cream o.d. vs clobetasone butyrate 0.05% cream b.d.	22 children with atopic dermatitis	Prospective, randomised, parallel study of 4 weeks' duration	SCORAD composite scale of extent and intensity of eight signs	At week 4, three fluticasone patients and one clobetasone patient were clinically healed (SCORAD <9)	Method and concealment of randomisation unclear, study described as double-blind Only one drop-out; no ITT analysis carried out	Small sample over a short period of time

TABLE 58 *RCTs of topical steroids in the prevention of relapse*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
VanDerMeer, 1999[104] The Netherlands	Fluticasone propionate 0.005%(g/g) vs placebo	54 patients with moderate-to-severe atopic dermatitis patients identified from a larger set of 112 on the basis of enhanced steroid responses	Prospective, randomised, parallel study of 16 weeks' duration	Risk of relapse and time to relapse Clinical assessment SCORAD: erythema, oedema/ papulation, oozing/ crusts, excoriations, lichenification, dryness, pruritus and sleep loss Skin thickness on biopsy specimens	68% of patients in the placebo group and 39% in the fluticasone group withdrew because of recurrence and relapse Risk of relapse was 2.6 times greater in active group (95% CI, 1.2 to 5.7) No significant changes were detected in either treatment group in serum cortisol levels or in skin thickness measurements	Method and concealment of randomisation unclear, study described as double-blind 17 withdrawals/ drop-outs; no ITT Only data up to first relapse analysed	Good to see a longer-term study evaluating relapse as well as short-term efficacy Difficult to say how much of the benefit in preventing realpse was due to treating old healed sites as opposed to treatment of new sites

TABLE 59 *Trials that specifically set out to examine adverse effects of topical corticosteroids*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Lucky *et al.*, 1997[133] USA	Desonide 0.05% ointment vs hydrocortisone 2.5% ointment b.d.	20 children	Prospective, randomised, parallel study of 4 weeks' duration	Hypothalamic pituitary–adrenal (HPA) axis (cortisol levels)	–1.6 and –1.3% change in cortisol levels over baseline at 28 days for desonide and hydrocortisone groups, respectively	Method and concealment of randomisation unclear, study described as open label Five drop-outs; no ITT	No evidence of HPA suppression in either group Short-term study
Sanabria-Silva *et al.*, 1991[148] Spain (translated)	Hydrocortisone 1% vs betamethasone dipropionate 0.05% vs cold cream placebo	45 children with atopic dermatitis	Prospective, randomised, open study of 4 weeks' duration with 10 days suspended treatment	'Rebound phenomenon' reactivation of lesions with greater intensity than their pre-treatment state a few (<10) days after suspending the treatment with topical steroids, which had controlled them The extensiveness of lesions according to three signs Photographs taken before and after treatment	Sudden suspension of topical steroids was followed by relapse in every case but in no case was there rebound There was no statistical difference between the frequency of relapse in the three groups ($p < 0.055$)	Method and concealment of randomisation unclear, open study, no blinding No mention of withdrawals and drop-outs	Although rebound is often referred to, there was no evidence of such a phenomenon in this study
Kuokkanen & Sillantaka, 1987[109] Finland	Alclometasone dipropionate 0.05% vs hydrocortisone 1.0% b.d.	37 children with eczema	Prospective, randomised, left/right, parallel study of 3 weeks' duration	Cutaneous atrophy: skin thinning, shininess, striae and fine blood vessels (telangiectasia) as assessed under magnification	Signs of cutaneous atrophy were not observed at any test site either at beginning or at 3-week evaluation period Efficacy similar in both groups with 88% improvement signs and symptoms in alclometasone-treated sites vs 86% hydrocortisone-treated sites	Method and concealment of randomisation unclear, study described as double blind Three withdrawals/drop-outs; no ITT	No evidence of skin thinning, though study duration very short

TABLE 60 *Trials that evaluated oral steroids*

Study	Interventions	Study population and sample size	Trial design, description and follow-up	Outcome measures	Main reported results	Quality of reporting	Comment
Dickey, 1976[98] USA	Betamethasone sodium phosphate 4.0 mg/ml injection vs dexamethasone sodium phosphate 4.0 mg/ml injection o.d.	22 patients with moderate-to-severe atopic dermatitis	Prospective, randomised, parallel study of 24 hours' duration	Inflammation, vesiculation, pruritus, exudation, excoriations, overall evaluation	Overall evaluation on a four-point rating scale: baseline 3.44 for betamethasone reduced to 2.89 and 3.62 for dexamethasone reduced to 2.69	Method and concealment of randomisation unclear, study described as double-blind Withdrawals and drop-outs not mentioned	Although a placebo group might have been ethically difficult, patient-based views on treatment response would have been useful
Heddle *et al.*, 1984[112] UK	Oral plus nasal beclomethasone dipropionate q.d.s. vs placebo	27 children with moderate-to-severe atopic eczema	Prospective, randomised, crossover study of 4 weeks' duration	Patient assessed itch and sleep loss (VAS) Doctor assessed redness, vesiculation, crusting, excoriation, lichenification	Parental scores for itch and antihistamine use were significantly lower on beclomethasone than placebo, but use of topical steroids and sleep loss did not show any significant change Other significant changes especially surface damage	Method and concealment of randomisation unclear, study described as double-blind One withdrawal; no ITT	Crossover study with significant treatment order interactions Large treatment effects
La Rosa *et al.*, 1995[140] Italy	Systemic flunisolide 640–1200 µg b.d. vs placebo	20 children with severe atopic dermatitis	Prospective, randomised, crossover study of 2 weeks' duration	Pruritus, erythema/oedema, excoriation, papulation/erosion/scaling, lichenification	Improvement over baseline for total clinical severity score: group A 75 reduced to 34 and group B 74 reduced to 29	Method and concealment of randomisation unclear, study described as double-blind Withdrawals/drop-outs not mentioned	Big treatment effects

Appendix 4

Duplicate and triplicate publications

TABLE 61

Interventions	Duplicate or triplicate publications
Fish oils	Bjorneboe 1989[254] = Bjorneboe 1987[251]
Evening primrose oil	Wright 1985[245] = Wright 1982[242]
Evening primrose oil	Ferreira 1998a[233] = Ferreira 1998b[234]
Cyclosporin A	Sowden 1991[295] = Salek 1993[293] = Allen 1991[298]
Corticosteroids	Sefton 1984[114] = Sefton 1983[136]
Corticosteroids	Korting 1995[86] = Zienicke 1993[146]
House dust mites	Friedmann 1998[267] = Tan 1996[263]
Allergen–antibody complexes	Leroy 1993[284] = Leroy 1992[285]
Topical corticosteroids	Ottevanger 1992 = Hoybye 1991[124]

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We look forward to hearing from you.

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