DOI 10.1111/J.1365-2133.2005.06410.X

Topical corticosteroids for atopic eczema: clinical and cost effectiveness of once-daily vs. more frequent use

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Accepted for publication
17 August 2004

Key words:
atopic eczema, clinical effectiveness, cost effectiveness, frequency, systematic review, topical corticosteroids

Summary

Background Topical corticosteroids remain the mainstay of treatment for atopic eczema, yet there is uncertainty over the frequency of their use in terms of clinical and cost effectiveness.

Objectives To assess the clinical and cost effectiveness of once-daily vs. more frequent use of same-potency topical corticosteroids in atopic eczema.

Methods A systematic review of the clinical and cost-effectiveness literature was undertaken, together with a cost-minimization analysis.

Results The review identified a sparse literature, comprising one previous systematic review and 10 randomized controlled trials (RCTs). No published cost-effectiveness studies were identified. RCTs were focused on potent topical corticosteroids (eight RCTs), with no trials (RCTs/controlled clinical trials) identified on mild potency products. There was broad heterogeneity in trial methods, and therefore we considered outcomes according to: (i) at least a good response or 50% improvement, and (ii) eczema rated as cleared or controlled. Studies found little difference between once-daily and more frequent use of topical corticosteroids. The literature on moderately potent and potent corticosteroids offered no basis for favouring once-daily or more frequent use, although some significant differences favouring twice-daily treatment were identified. One RCT on very potent products favoured three times daily use on the basis of clinical response, but reported no difference in the numbers with at least a good response. Given the similar outcomes seen in clinical effectiveness a cost-minimization approach was adopted to consider cost effectiveness, in order to identify the least-cost option. However, cost-minimization analysis proved complex due to wide variations in product price, with the relative cost of product comparisons by frequency proving the most important factor in determining the least-cost alternative.

Conclusions This review has not identified any clear differences in outcomes between once-daily and more frequent application of topical corticosteroids. We would encourage prescribing clinicians to consider the once-daily use of topical corticosteroids when making treatment decisions for patients with atopic eczema. However, we find that the literature on clinical effectiveness is limited and a broader understanding of compliance and phobia associated with topical steroids is needed to inform on this issue.

Atopic eczema (atopic dermatitis) is a chronic inflammatory skin condition, a relapsing condition characterized by frequent flares on the skin. It is a widespread condition, thought to affect about 15–20% of school-age children at some stage,[1] and 2–10% of adults,[2] giving a likely patient group in excess of 2 000 000 people in England and Wales. It presents a major cause of morbidity and a major area of resource use for the U.K. National Health Service (NHS).

The severity of atopic eczema can vary enormously, from an occasional dry, scaly patch of eczema, easy to treat with emollients, to a debilitating disease, with much of the body being covered by excoriated, bleeding, infected lesions, and

the patient severely distressed.[3] Most patients, about 80%, experience mild disease, with 2–5% of patients having severe atopic eczema.[4] The condition is associated with considerable morbidity, which varies with disease severity.[5]

Research to date has suggested that atopic eczema costs the U.K. NHS in excess of £125 million per year[6] (189 million Euros), and the condition can also impose a substantial cost burden on individuals and society well in excess of the costs falling on the NHS.[6,7]

Treatment of atopic eczema involves a combination of preventive measures aimed at suppressing the symptoms of disease and individualized treatment for controlling and preventing complications. The successful management of atopic eczema requires a multipronged approach, with topical corticosteroids the mainstay of treatment, particularly in the control of flares.

When prescribing topical corticosteroids the frequency of application is a key clinical issue; there are many products available and they vary in terms of recommended frequency of use from one to four applications per day. Most products in the *British National Formulary* (BNF)[8] are recommended for use once or twice daily, yet there are few empirical data to assess the patterns of prescribing with respect to frequency of application. The generally accepted twice-daily regimen seems to have developed empirically.[9] Over recent years, newer topical corticosteroids have been specifically marketed for once-daily use (e.g. mometasone furoate and fluticasone propionate cream).[1] These 'once-daily' products have demonstrated similar effectiveness in comparisons with more frequent use, but they have a premium price and may not be the most cost-effective treatment option. Identifying the most effective and cost-effective approach could have benefits for patients and the NHS. If once-daily use is as effective as more frequent use, as trials have suggested,[10,11] then patients will benefit from greater convenience and reduced exposure to potential side-effects, with potential cost savings for the NHS. In view of the continuing uncertainty, the National Institute for Clinical Excellence (NICE) in the U.K., which provides patients, health professionals and the public with guidance on current best practice, was asked to provide national guidance on the merits of once-daily vs. more frequent application of topical corticosteroids.[12] This study reports the results of a systematic review and economic evaluation commissioned to assist the NICE in its deliberations.

The primary objectives of this review were to assess the clinical and cost effectiveness of once-daily use of topical corticosteroids vs. more frequent use of same-potency topical corticosteroids in the treatment of individuals with atopic eczema, and thereafter to make recommendations for future research. We use the widely used U.K. BNF classification of potency (mild, moderate, potent and very potent),[8] but note that potency categories are based on a number of factors (e.g. vasoconstriction, side-effects) and may not fully differentiate between different formulations.

Materials and methods

Search strategy for identification of studies

Electronic databases were searched from inception to October 2003. These included the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, NHS Centre for Reviews and Dissemination (CRD, University of York) databases (including DARE, NHS EED and HTA database), Medline (Ovid), EMBASE, National Research Register, Science Citation Index, BIOSIS, EconLit, MRC Trials database, Early Warning System, and Current Controlled Trials. The search terms used included a variety of disease-related terms and corticosteroid product names. The full search strategy has been reported elsewhere.[13] Bibliographies of included studies and related papers were checked for relevant studies and experts were contacted for advice and peer review and to identify published and unpublished studies. Manufacturer submissions to the NICE appraisal programme were also reviewed.

Inclusion/exclusion criteria

Systematic reviews and meta-analyses of randomized controlled trials (RCTs), as well as individual RCTs were included. Controlled clinical trials (CCTs) were included in our search where there were no RCTs in product potency groupings. Studies were included if they compared once-daily vs. more frequent application of topical corticosteroids of the same potency in patients with atopic eczema (atopic dermatitis). Studies comparing corticosteroids with different potencies were excluded, as were studies that included patients with other types of eczema such as contact dermatitis, seborrhoeic eczema, varicose eczema and discoid eczema. We have excluded from the review those topical corticosteroids classified as being compound preparations and products containing antimicrobials (as specified in the NICE Scope[12]). Studies were included in the review if they reported one or more of the following outcomes: overall response to treatment (e.g. using severity scores), impact on clinical features of the condition (e.g. erythema, induration, pruritus, excoriation, thickening); relapse/flare rate; side-effects; compliance; tolerability; patient preference measures; and quality of life. Cost-effectiveness studies were included if they were full economic evaluations, comparing costs and consequences of alternative options related to frequency of application of topical corticosteroids. Reports available only as abstracts and non-English language studies were excluded.

Methods of review

The review was undertaken following the general principles outlined by the NHS CRD.[14] Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any differences in opinion

resolved through discussion. The quality of included studies was assessed using criteria developed by the NHS CRD (e.g. method of randomization, allocation concealment, blinding and the inclusion of an intention-to-treat analysis).

Results

Quantity and quality of research available

Initial searches identified 4429 references. Of these, only one systematic review (Hoare *et al.*[15]) and 10 RCTs matched the criteria for inclusion in this systematic review. One RCT compared moderately potent corticosteroids,[16] eight RCTs compared potent corticosteroids[10,11,17–22] and one RCT compared very potent corticosteroids.[23] One of these RCTs was unpublished and was made available for inclusion in this review by GlaxoSmithKline (GSK).[19] No RCTs or CCTs of mild corticosteroids were eligible for inclusion. Most studies compared once- vs. twice-daily application, but one study compared once vs. three times daily application of corticosteroids.[23] Seven of the RCTs compared once-daily application of the same active compound, and three RCTs compared once-daily application of different active compounds. A summary of the products compared in the studies can be seen in Table 1.

Apart from the GSK study[19] and the study by Berth-Jones *et al.*[18] the quality of the reporting and methodology of the included RCTs was generally poor. The method of randomization was adequate in only three studies,[18,19,23] with concealment of allocation not reported in one of these.[23] Six trials were described as double-blind:[10,11,17–19,23] four used identical tubes for treatment and placebo and were judged to be adequately blinded, while two studies simply described the trial as double-blind without further description of the procedures.[11,18] Only three studies[10,18,19] adequately reported the point estimates and measures of variability and included an intention-to-treat analysis.

Although our literature search was comprehensive we found no cost-effectiveness studies reporting on frequency of use of topical corticosteroids. Previous reviews have also reported an absence of cost-effectiveness literature.[24,25]

Clinical effectiveness

Outcomes

We found broad heterogeneity in the reporting of outcomes, many of which were subjective in nature. Owing to the variations used to report outcomes we selected two outcome measures that were commonly used, in some form, across trials: (i) at least a good response or 50% improvement, and (ii) eczema rated as cleared or controlled. All but two studies (Richelli *et al.*[16] and Rajka *et al.*[21]) present results using these two outcomes, with findings reported by patient numbers (assessed by the physician and/or the patient).

Patients with at least a good response or 50% improvement

Seven studies reported the number of patients with at least a good response or 50% improvement by the end of the study (Fig. 1a). Clinical and statistical heterogeneity between the studies meant that meta-analysis was inappropriate for this group. Little difference was found between once and more frequent application of topical corticosteroids. Only one study[19] found a statistically significant difference, where once-daily application of fluticasone propionate ointment reduced the chance of success, as assessed by the physician, by 12% (relative risk, RR 0·86, 95% confidence interval, CI 0·75–0·99) compared with the twice-daily group. However, when assessed by patients this difference was no longer statistically significant (RR 0·87, 95% CI 0·75–1·02).

Eczema rated as cleared or controlled

Six studies reported the number of patients rated cleared/controlled or as showing an excellent response (Fig. 1b). It was considered inappropriate to combine these studies in a meta-analysis due to heterogeneous measures of effect. Koopmans *et al.*[11] reported a significant difference in physician assessment of lesion clearance in favour of twice-daily treatment (RR 0·69, 95% CI 0·52–0·91). However, this finding was not supported by the patient assessment of lesion clearance (RR 0·83, 95% CI 0·64–1·07). In the GSK study, where a statistically significant difference had been reported against response rate, there was no significant difference against physician assessment of cleared or controlled eczema; the result, although favouring twice-daily treatment, was no longer statistically significant (once-daily vs. twice-daily 17% vs. 23%; RR 0·73, 95% CI 0·44–1·23).[19]

When comparing once daily and three times daily application of the very potent corticosteroid halcinonide cream 0·1%, Sudilovsky *et al.*[23] found that a more favourable comparative response (slightly superior or markedly superior response) of similar lesions on each side of the body was observed with three times daily application. Overall, 31·5% of patients had a better response to three times daily application, 21·5% had a better response to once-daily application, and 47% had an equal response ($P < 0·05$).

Severity of signs and symptoms

Eight studies present data on severity of signs and symptoms,[10,11,16,17,19–22] with results presented across a broad spectrum of clinical features. Differences by frequency are generally not statistically significant, and where statistical significance is reported against a number of signs and symptoms (e.g. pruritus, erythema), studies are regarded as being of poor quality.[20–22] Full details on the reporting of signs and symptoms have been presented elsewhere.[13]

Table 1 Clinical effectiveness of once-daily vs. more frequent use of topical corticosteroids (numbers responding to treatment or with eczema cleared or controlled)

Study	Treatment/comparison	Outcomes	Once daily	More frequent	Significance
Berth-Jones *et al.*[18]	Fluticasone propionate cream 0·05% once daily (n = 95) vs. twice daily (n = 91)	Patients with controlled atopic dermatitis at end of stabilization stage (absent or mild)	Cream: 80% (76/95)	Cream: 84% (76/91)	P = 0·546
	Fluticasone propionate ointment 0·005% once daily (n = 100) vs. twice daily (n = 90)		Ointment: 77% (77/100)	Ointment: 71% (64/90)	P = 0·249
	Patients: age 12–65 years, moderate to severe				
Bleehen *et al.*[10]	Fluticasone propionate cream 0·05% once daily (n = 137) vs. twice daily (n = 133)	No. of patients with at least a good response (> 50% improvement)	80% (110/137)	85% (113/133)	95% CI −14·2 to 5·0, P = 0·35
	Patients: children and adults. At least moderate severity	Intent-to-treat analysis	79% (108/137)	83% (110/133)	95% CI −14·7 to 6·2, P = 0·42
		Per-protocol analysis			
GSK[19]	Fluticasone propionate ointment 0·005% once daily (n = 123) vs. twice daily (n = 122)	No. with success (%)			
	Patients: children and adults. At least moderate severity	*Investigators' assessment*			
		Visit 2	69% (80/116)	71% (83/117)	2·0% (−9·8, 13·7) P = 0·74
		Visit 3	79% (77/98)	78% (83/106)	−0·3% (−11·6, 11·0) P = 0·96
		Visit 4	74% (70/94)	86% (78/91)	11·2% (−0·1, 22·6) P = 0·056
		Visit 5	78% (64/82)	85% (68/80)	7·0% (−4·9, 18·8) P = 0·25
		Last visit	72% (86/119)	84% (99/118)	11·6% (1·2, 22·1) P = 0·031
		Patients' assessment			
		Visit 2	67% (79/118)	69% (81/118)	1·7% (−10·2, 13·6) P = 0·78
		Visit 3	78% (81/104)	83% (88/106)	5·1% (−5·6, 15·8) P = 0·35
		Visit 4	76% (73/96)	80% (74/92)	4·4% (−7·4, 16·2) P = 0·47
		Visit 5	74% (61/82)	80% (63/79)	5·4% (−7·6, 18·3) P = 0·42
		Last visit	69% (82/118)	79% (93/117)	10·0% (−1·1, 21·1) P = 0·079
Hoybye *et al.*[20]	Mometasone furoate in fatty cream base once daily (n = 49) vs. hydrocortisone 17-butyrate in fatty cream base twice daily (n = 45)	Cleared or improved markedly	88% (43/49)	78% (35/45)	P = 0·28
	Patients: adults. Severity score at least 4·5 out of 9	1 (cleared)	10/49	7/45	Others not reported
		2 (marked improvement)	33/49	28/45	
		3 (moderate improvement)	6/49	7/45	
		4 (slight improvement)	0	0	
		5 (no change)	0	3/45	
		6 (exacerbation)	0	0	
Koopmans *et al.*[11]	Hydrocortisone 17-butyrate 0·1% once daily (n = 75) vs. twice daily (n = 75)	Overall improvement in skin disease:			
	Patients: aged over 12 years	*Investigators' opinion*			
		Clearance of lesions	49% (36/74)	70% (52/74)	
		Considerable improvement	35% (26/74)	20% (15/74)	
		Definite improvement	12% (9/74)	9% (7/74)	
		Minimal improvement	4% (3/74)	0 (0/74)	
		No change	0 (0/74)	0 (0/74)	
		Worse	0 (0/74)	0 (0/74)	
		Patients' opinion			
		Clearance of lesions	55% (41/73)	68% (51/75)	
		Considerable improvement	23% (17/73)	25% (19/75)	
		Definite improvement	16% (12/73)	5% (4/75)	
		Minimal improvement	3% (2/73)	0 (0/75)	

Table 1 (Contd.)

Study	Treatment/comparison	Outcomes	Once daily	More frequent	Significance
		No change	1% (1/73)	1% (1/75)	
		Worse	0 (0/73)	0 (0/75)	
		Total clearance of lesions:			
		2 weeks	12% (9/73)	19% (14/74)	P = 0·29
		4 weeks	27% (20/73)	47% (35/75)	P = 0·02
Marchesi *et al.*[22]	Mometasone furoate ointment 0·1% once daily (n = 30) vs. betamethasone dipropionate ointment 0·05% twice daily (n = 30) Patients: adults. At least moderate severity	Physicians' global evaluation of response to treatment: Cleared Good improvement	53% (16/30) 47% (14/30)	50% (15/30) 50% (15/30)	Not reported
Tharp[17]	Fluticasone propionate cream 0·05% once daily (n = 79) vs. twice daily (n = 79) Patients: aged over 12 years. Moderate to severe	Patients' subjective assessment (patients rating treatment excellent or good)			
		Day 8	74% (56/76)	76% (58/76)	P = NS
		Day 15	73% (53/73)	84% (61/73)	P = 0·01
		Day 22	72% (50/69)	81% (55/68)	P = 0·02
		Day 29	74% (48/65)	71% (43/60)	P = NS
		Physician's gross assessment (patients with target lesion response rated cleared or excellent)			
		Day 8	29% (22/76)	39% (30/76)	P = NS
		Day 15	42% (31/73)	62% (45/73)	P = NS
		Day 22	57% (39/69)	70% (48/68)	P < 0·014
		Day 29	69% (45/65)	78% (47/60)	P = NS
Sudilovsky *et al.*[23]	Halcinonide cream 0·1% once daily (n = 149) vs. three times daily (n = 149) Patients: unclear	Absolute therapeutic response (excellent or good, at least 50% improvement)	85·3% (99/116)	86·2% (100/116)	P = NS
		Comparative clinical response (markedly or slightly superior):			
		Week 1 (n = 149)	Markedly 5	Markedly 11	P = NS
		(equal response: 85)	Slightly 21	Slightly 27	
		Week 2 (n = 138)	Markedly 3	Markedly 15	P < 0·05
		(equal response: 87)	Slightly 18	Slightly 15	
		Week 3 (n = 116)	Markedly 2	Markedly 12	P < 0·01
		(equal response: 81)	Slightly 9	Slightly 12	
		Overall (n = 149)	Markedly 2 (1·3%)	Markedly 12 (8·1%)	P < 0·05
		(equal response: 70)	Slightly 30 (20·1%)	Slightly 35 (23·5%)	
		Total with better response:	32 (21·5%)	47 (31·5%)	
Studies included but not reporting response to treatment					
Richelli *et al.*[16]	Clobetasone 17-butyrate 0·05% lotion once daily (n = 9) vs. twice daily (n = 21) Patients: children	Authors report severity of signs and symptoms			
Rajka *et al.*[21]	Mometasone furoate fatty cream 0·1% once daily (n = 57) vs. betamethasone valerate cream 0·1% twice daily (n = 60) Patients: aged over 16 years. Mild to moderate severity	Authors report severity of signs and symptoms			

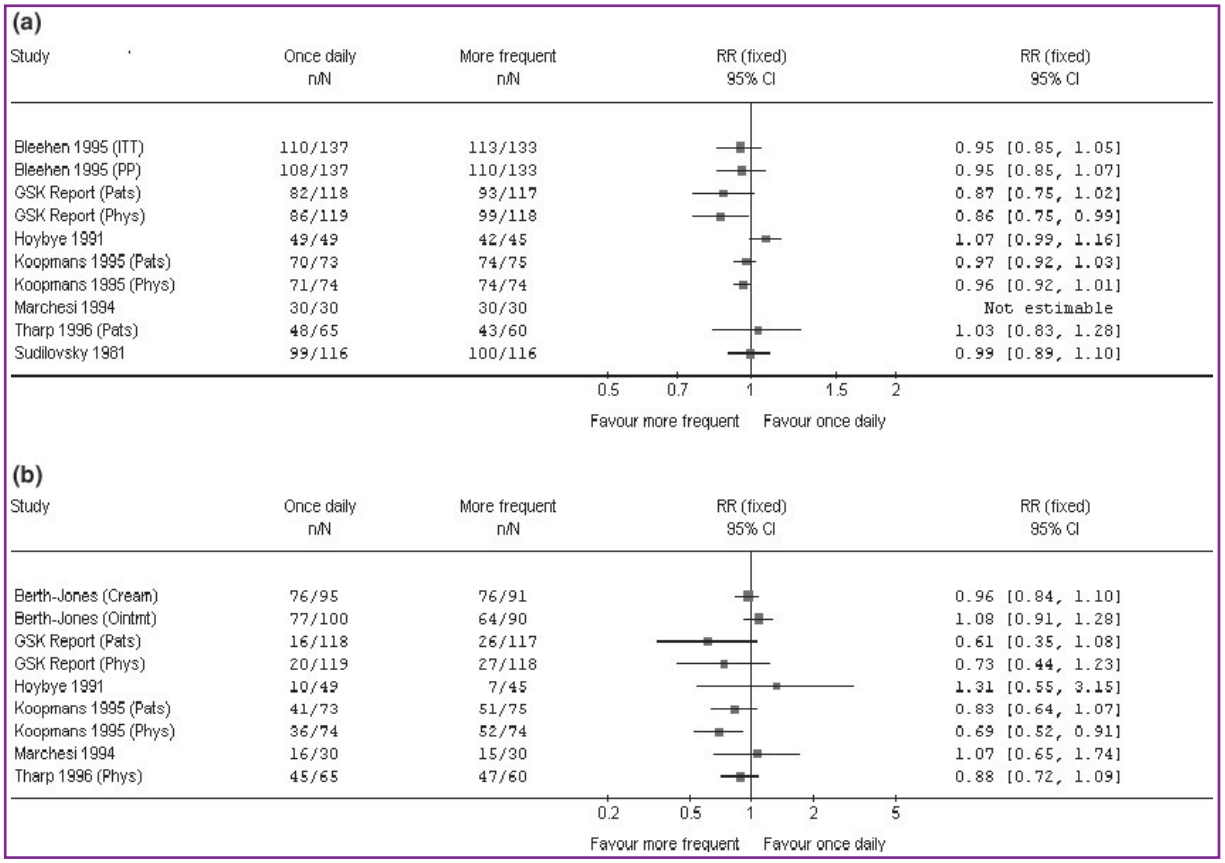

Fig 1. Effectiveness of once daily vs. more frequent use of topical corticosteroids (forest plot illustrations). **(a)** Patients with at least a good response (at least 50% improvement) at end of treatment. **(b)** Patients with controlled or cleared atopic eczema. Note: the patients in the studies by Bleehen *et al.*,[10] GSK Report[19] and Koopmans *et al.*[11] are included twice for illustration of different assessments. See Table 2 for details of treatment duration. RR, relative risk; CI, confidence interval; ITT, intention-to-treat analysis; PP, per-protocol analysis; Pats, patients' assessment; Phys, physicians' assessment.

Adverse events

The quality and extent of reporting adverse effects was variable between studies. Adverse effects were not reported in any detail in the moderate or very potent corticosteroid studies,[16,23] and only seven of the eight RCTs concerned with potent corticosteroids reported adverse effects. Table 2 summarizes the reporting of adverse effects. Overall, there appeared to be little evidence of any differences in frequency or severity of short-term adverse events between once-daily and more frequent application of potent or very potent corticosteroids; however, data were limited.

Cost effectiveness

Cost-effectiveness analysis considers the difference in resource use and cost of an intervention in the context of differences in effect. As we have not found any cost-effectiveness studies to inform on the frequency of use of topical corticosteroids we have examined the cost issues associated with once vs. more frequent use of products, and have considered them against the findings from our review of the clinical effectiveness.

Product costs

The cost for topical corticosteroids, per patient per year, will vary according to the prescribed topical corticosteroid and the number of flares that the patient needs to treat, both of these being associated with the severity of the disease. Table 3 presents an estimate of product costs across a range of topical corticosteroids eligible for inclusion in this review, using prices listed in the BNF[8] (applying the largest pack size available). There are wide variations in product costs: the cost per 30 g/30 mL can vary from £0·66 (for generic hydrocortisone) to £4·59 (for fluticasone propionate: Cutivate®). One observation is the relatively high cost of the newer 'once-daily' topical corticosteroids fluticasone propionate cream (Cutivate®) and mometasone furoate (Elocon®), at £4·59 and £4·22, respectively, per 30 g/30 mL, with comparator potent products such as betamethasone valerate (Betnovate®) or hydrocortisone butyrate (Locoid®) costing £1·31 and £2·27, respectively, per 30 g/30 mL. Figure 2 presents data from the U.K. Department of Health[26] on the general pattern/distribution of community dispensed prescriptions (during 2002) for relevant topical corticosteroids. Data are not limited to

Table 2 Adverse events in trials comparing frequency of topical corticosteroids

Study details (duration of treatment)	Adverse effects	Once daily	More frequent
Richelli *et al.*[16] (7 days)	Adverse effects not reported	(n = 9)	(n = 21)
Berth-Jones *et al.*[18] (4 weeks)	No. of patients: cream	(n = 95)	(n = 91)
	No. of patients: ointment	(n = 100)	(n = 90)
	Most common adverse event: Ear, nose and throat infection: 9 (group not specified)		
	Visual signs of atrophy related to study treatment[a]		
	Telangiectasia: cream	0	1
	Telangiectasia: ointment	1	0
	Striae: cream	0	0
	Striae: ointment	1	0
Bleehen *et al.*[10] (4 weeks)	No. of patients	(n = 137)	(n = 133)
	Most common adverse event		
	Skin disorder	34	21
	Exacerbation of eczema	7	2
	Skin irritation following drug administration	5	2
	Exacerbation of itching	4	1
	Total no. of reports	68	64
	Total no. of patients (%)	46 (33·6)	45 (33·8)
	Events possibly, probably, or almost certainly related to study medication (mostly skin disorders)	26	24
GSK[19] (4 weeks)	No. of reports	(n = 123)	(n = 122)
	Most common adverse event		
	Skin disorder	32	24
	Exacerbation of eczema	13	6
	Pruritus	6	4
	Total no. of reports	86	75
	Total no. of patients (%)	54 (44)	49 (40)
	Relationship to study medication (no. of reports)		
	Unrelated	44	47
	Unlikely	21	14
	Possibly	6	8
	Probably	9	3
	Almost certain	6	3
	Total no. of reasons	86	75
	Total no. of patients (%)	54 (44)	49 (40)
Hoybye *et al.*[20] (3 weeks)	No. of patients States that treatment-related side-effects were few, and these weresimilar in both groups. Reported side-effects were stinging, burning, itching, dryness, acne, folliculitis and hair growth. None showed evidence of skin atrophy	(n = 49)	(n = 45)
Koopmans *et al.*[11] (4 weeks)	No. of patients Total no. reporting adverse events (%)	(n = 75) 4 (5·3)	(n = 75) 4 (5·3)
Marchesi *et al.*[22] (3 weeks)	No. of patients (%)	(n = 30)	(n = 30)
	Telangiectasias of mild severity in last 2 weeks of treatment	4 (13·3)	5 (16·7)
	Loss of skin marks and reduced elasticity	0	1 (3·3)
	Neither systemic nor local reactions occurred. In all patients checked for blood tests, values varied within a very narrow range		
Rajka *et al.*[21] (3 weeks)	No. of patients Adverse events not reported for atopic dermatitis separately	(n = 57)	(n = 60)
Tharp[17] (4 weeks)	No. of patients	(n = 77)	(n = 77)
	Total no. reporting adverse events (%)	4 (5)	3 (4)
	None of the adverse events was judged to be serious or unexpected		
Sudilovsky *et al.*[23] (3 weeks)	No. of patients Side-effects generally of a mild nature, the most common being burning, pruritus and erythema, with no differences in incidence between once daily and three times daily regimens. However, adverse events not reported for eczema and psoriasis separately. No systemic effects were observed	(n = 149)	3 × daily (n = 149)

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

Table 3 Product cost for topical corticosteroids (eligible for inclusion in the review), by *British National Formulary* (BNF) potency classification (BNF list price)[8]

Potency	BNF chemical name	Product name	Cost per 30 g/30 mL[b]
Mild	Hydrocortisone (generic[a])	Hydrocortisone cream/ointment 0·5%	£0·66
	Hydrocortisone (generic[a])	Hydrocortisone cream/ointment 1%	£0·74
	Hydrocortisone (proprietory)	Efcortelan cream/ointment 0·5%	£0·66
	Hydrocortisone (proprietory)	Efcortelan cream/ointment 1%	£0·81
	Hydrocortisone (proprietory)	Efcortelan cream/ointment 2·5%	£1·83
	Hydrocortisone (proprietory)	Mildison Lipocream 1%	£2·63
	Hydrocortisone (proprietory)	Dioderm cream 0·1%	£2·69
	Fluocinolone acetonide	Synalar cream 1/10, 0·0025%	£1·15
Moderate	Alclometasone dipropionate	Modrasone cream/ointment 0·05%	£1·69
	Betamethasone valerate	Betnovate RD cream/ointment 0·025%	£1·08
	Clobetasone butyrate	Eumovate cream/ointment 0·05%	£1·70
	Desoxymethasone	Stiedex LP oily cream 0·05%	£2·46
	Fluocinolone acetonide	Synalar cream/ointment 1/4, 0·00625%	£1·22
	Fluocortolone	Ultralanum cream/ointment plain	£1·77
	Flurandrenolone	Haelan cream/ointment 0·0125%	£1·63
Potent	Beclomethasone dipropionate	Propaderm cream/ointment 0·025%	£1·74
	Betamethasone dipropionate	Diprosone cream/ointment/lotion 0·05%	£2·05
	Betamethasone valerate	Betnovate cream/ointment 0·1%	£1·31
	Betamethasone valerate	Bettamousse foam 0·12%	£2·25
	Betamethasone valerate	Betacap scalp application 0·1%	£1·27
	Betamethasone valerate (generic)	Betamethasone valerate cream/ointment 0·1%	£1·54
	Diflucortolone valerate	Nerisone cream/ointment 0·1%	£1·59
	Fluocinolone acetonide	Synalar cream/ointment 0·025%	£1·74
	Fluocinonide	Metosyn FAPG cream/ointment 0·05%	£1·54
	Fluticasone propionate	Cutivate cream/ointment 0·05%	£4·59
	Hydrocortisone butyrate	Locoid Lipocream 0·1%	£2·38
	Hydrocortisone butyrate	Locoid cream/ointment 0·1%	£2·27
	Hydrocortisone butyrate	Locoid Crelo 0·1%	£2·72
	Mometasone furoate[c]	Elocon cream/ointment/scalp lotion 0·1%	£4·22
Very potent	Clobetasol propionate	Dermovate cream/ointment 0·05%	£2·48
	Diflucortolone valerate	Nerisone Forte ointment/oily cream 0·3%	£2·09
	Halcinonide	Halciderm cream 0·1%	£3·40

prescribing in atopic eczema—they cover prescribing of these products generallybut the data do show that regardless of the wide range of products available, prescribing was most frequent in a small number of product groupings. There may have been changes in prescribing practice from 2002 to the present day but the data do offer an indication of current practice.

Quantity of topical corticosteroid used

Quantity of topical corticosteroid used, by frequency, is reported in only two of the clinical trials included in our review of clinical effectiveness. Bleehen *et al.*[10] report that the amount of active treatment used by the once-daily group was roughly half of that used by the twice-daily group; however, data were not reported. The GSK study[19] presents data on the estimated amount of topical corticosteroid used per week, on a twice-daily regimen over a 4-week period, reporting usage ranging from 32 to 36 g in week 1 to about 21–30 g in week 4 (a mean amount of 28·3 g per week).

In addition to the above review a few other studies report limited data on the amount of topical corticosteroid product used.[27–30] However, we find that information to guide us on product use is varied and it is difficult to draw conclusions due to differences in study duration (i.e. 4 weeks vs. 18 weeks), patient groups and products used. It is clear from the general literature on the treatment of atopic eczema that product use varies by severity of disease, patient group (child vs. adult) and setting (hospital vs. community).

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

Cost-effectiveness analysis

The above review of clinical effectiveness shows no clear difference between once-daily vs. more frequent use of topical corticosteroids: outcomes appear broadly similar. Therefore, for the purposes of the cost-effectiveness analysis

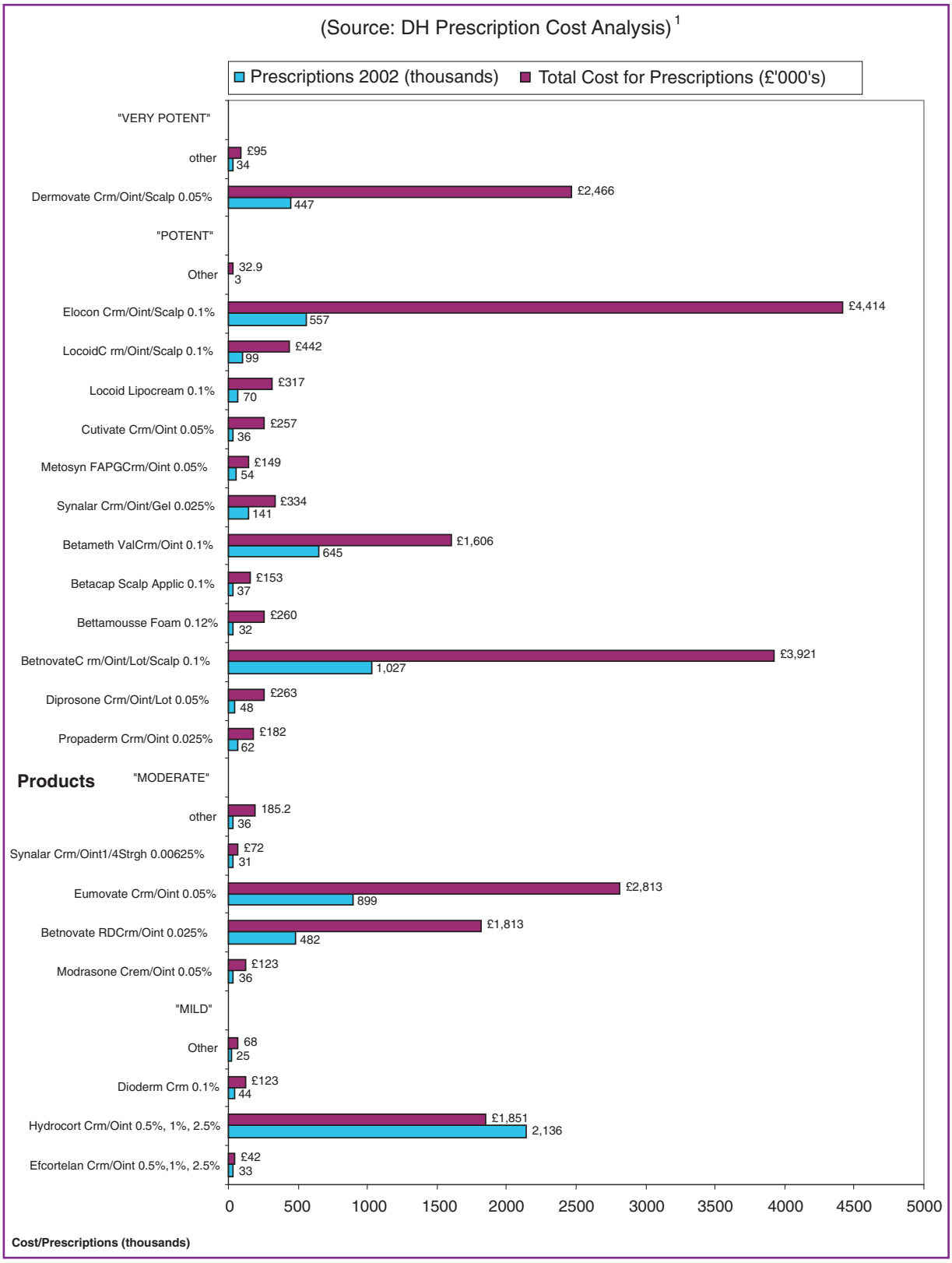

Fig 2. Prescribing patterns for eligible topical corticosteroids (community dispensed prescriptions, 2002).

discussed here the effectiveness of once-daily and more frequent application of topical corticosteroids is assumed to be equivalent. With equivalent outcomes the issue of cost effectiveness becomes a question of 'cost-minimization analysis' (CMA): essentially a search for the 'least-cost' alternative where the principle is an efficiency comparison based

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

In some cases same-potency products may be more costly overall on a once-daily regimen than alternative products on a twice-daily regimen, with an associated additional cost to the NHS. For example, where fluticasone propionate cream (Cutivate®) or mometasone furoate (Elocon®) once daily is substituted for betamethasone valerate, betamethasone dipropionate or hydrocortisone butyrate twice daily, the once-daily regimen would be expected to be more costly than the twice-daily regimen.

When applying a CMA approach in 'same product' comparisons the once-daily treatment option would be expected to dominate in the CMA; this is the case in four of the seven trials that report findings on response rates for 'at least a good response or 50% improvement'. However, in two of the seven comparisons (Hoybye *et al.*[20] and Marchesi *et al.*[22]) the twice-daily treatment regimen dominates as costs are expected to be less for the products in these regimens (i.e. cost per g mL^{-1} in the once-daily regimen is greater than twice that in the twice-daily regimen).

Where studies report an effectiveness difference (greater number of patients responding to treatment) a judgement is required over the cost effectiveness of treatment. This is the case in the study reported by GSK[19] which indicates that twice-daily use of fluticasone propionate ointment offers an improved outcome over once-daily use of the same product (72% success in the once-daily group compared with 84% success in the twice-daily group; $P = 0{\cdot}031$). From this study we estimate the cost per additional successfully treated flare to be £38·50 (based on the difference in effect in the GSK study[19]), assuming four flares per year, with each flare treated over a 2-week period with 30 g of fluticasone propionate per week on a twice-daily regimen and 15 g per week on a once-daily regimen. Where the outcome 'success' is regarded as a meaningful and beneficial outcome, this would indicate that the additional cost of a twice-daily regimen would be regarded as a cost-effective use of NHS resources. Furthermore, any difference in product costs would be largely offset by the opportunity cost of additional visits to the general practitioner (regardless of other NHS costs) where treatment is regarded as a failure.

Discussion

When prescribing topical corticosteroids as part of the management of atopic eczema, the clinician is faced with a wide range of products, classified by potency, available in various formulations and preparations (over 30 different products included in this review with numerous alternative formulations and preparations). Prescribers are faced with a dilemma as the literature to inform on the relative merits of available products is not extensive, and there is a lack of comparative data to help clinicians decide what may be the best treatment option for their patient.[31] On the question of frequency, this review of the comparative clinical effectiveness has not identified any clear differences in outcomes between once-daily and more frequent application of topical corticosteroids. Only one study (GSK) found a statistically significant difference in response rates between different regimens. Findings on severity of symptoms are very similar, with no clear differences between frequency strategies. These findings are important, indicating that clinical effectiveness may be similar. Although we cannot rule out a small benefit for twice-daily treatment, we believe this is unlikely to be clinically important.

The strength of the evidence and the conclusions on effectiveness are limited, due to the small number of studies and their poor quality. The outcomes were found to be subjective and varied between studies. Furthermore, there are difficulties translating differences in outcome measure and severity scores into clinically meaningful effects. Treatment response rates tended to be similar between once-daily and more frequent application of potent or very potent corticosteroids. Although some statistically significant differences favouring more frequent application were identified, these were inconsistent between outcome assessors, depending on whether they were assessed by the physician or patient, and varied according to the outcome selected for analysis.

The number and severity of adverse events appeared to be similar between once-daily and more frequent applications, although data are limited. None of the studies reported data on late-onset or long-term adverse events, such as skin atrophy, and we expect such events, although rare, to be a major concern to patients and carers. Studies have reported that a large proportion of patients expresses anxiety and fear over the use of topical steroids.[24,32] There is an intuitive belief that less frequent use of topical corticosteroids will be beneficial in reducing the incidence of adverse events, and will lead to a reduction in patient and carer anxiety and fear over use of corticosteroids, with subsequent improvements possible in adherence.

In our examination of cost effectiveness (CMA) we suggest that treatment decisions (i.e. once vs. more frequent use) may revert to a selection of the cost-minimizing option. However, it would be unfair to think that once-daily use of steroids could be regarded broadly as the expected cost-minimizing option, on the basis of the CMA approach we consider in the context of the trials examined in this review. The included

clinical trials are dominated by same-compound comparisons and to get a broader feel for the CMA it would be interesting to see comparisons of the newer and relatively expensive once-daily products and the less expensive products, where we would expected, assuming similar clinical effectiveness, the twice-daily option to be the cost-minimizing option. A further worthwhile comparison would be a large well-conducted trial investigating the use of betamethasone valerate (the most commonly prescribed product) on a once-daily regimen vs. more frequent use. It would also be interesting to see a wider selection of comparative trials looking at once-daily treatment options.

One important issue for budget holders is the extent to which there may be potential for cost savings on the prescribing budget, if once-daily use of topical corticosteroids were to become more common. Cost savings at a patient level will be relatively small, and issues related to pack size and product waste can easily erode any potential cost savings. Furthermore, a proportion of patients will pay a fee for their medication, as they will be subject to the standard per-item prescription charge applied in the U.K. Given the very large number of people treated for atopic eczema, about 1·5–2 million school-age children and in the region of 1 million adults, we feel that crude estimates for cost savings could range from £300 000 to £3·5 million (450 000–5·3 million Euros), based on a variety of assumptions, i.e. products used, the quantity of product used by frequency, and the number of patients affected. However, a switch to newer and relatively expensive products specifically marketed for once-daily use (i.e. mometasone furoate and fluticasone propionate cream) could result in additional NHS costs.

In conclusion, this review has not shown an important difference in the clinical effectiveness of once-daily vs. more frequent use of topical corticosteroids: outcomes and adverse events appear similar. These findings are similar to those of Hoare *et al.*[15] However, we have used broader eligibility criteria allowing for the inclusion of additional studies, including comparisons of different products of the same potency. The addition of such studies adds weight to the conclusions of our review. This study has also offered context and guidance on the important issue of cost effectiveness with respect to the application of topical corticosteroids, an area of prescribing which represents significant expenditure and budget impact for the U.K. NHS. We suggest that prescribers consider the product costs in alternative treatment regimens, in order to select the least-cost option (everything else being equal).

We find that there is a need for further research on the clinical effectiveness of a broader range of topical corticosteroids by frequency of use. There is currently a limited number of trials involving mild, moderate and very potent products, and further information is needed on the relative merits of treatment frequency in these potency groups. Furthermore, trials to establish whether once-daily use of older/cheaper generic products is equivalent to more frequent use would be helpful, as the majority of the literature is currently concerned with comparisons of more traditional twice-daily treatment options. Importantly, further research is also required regarding the impact on quality of life, compliance, and phobia of topical steroids, of once-daily vs. more frequent use of products.

Acknowledgments

The authors thank Ms Liz Payne for assistance with literature searching. This review was funded by the NHS R & D Health Technology Assessment Programme, and was commissioned on behalf of the National Institute for Clinical Excellence. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

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