ClinicalEvidence

Psoriasis (chronic plaque)

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ABSTRACT

INTRODUCTION: Psoriasis is a chronic inflammatory skin disease that affects 1% to 3% of the population, in some people causing changes to the nails and joints as well as skin lesions. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of non-drug (other than ultraviolet light), topical drug, ultraviolet light, and systemic drug treatments for chronic plaque psoriasis? What are the effects of combined treatment with drugs plus ultraviolet light for chronic plaque psoriasis? What are the effects of combined systemic plus topical drug treatments for chronic plaque psoriasis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 122 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: acupuncture, adding calcipotriol (topical) to psoralen plus ultraviolet light A or ultraviolet light B, adding oral retinoids to psoralen plus ultraviolet A (PUVA), alefacept, balneotherapy, ciclosporin, dithranol, T cell-targeted therapies, cytokine blocking agents, emollients (alone or plus ultraviolet light B), etanercept, fish oil supplementation, fumaric acid derivatives, Goeckerman treatment, heliotherapy, infliximab, Ingram regimen, keratolytics (salicylic acid, urea), leflunomide, methotrexate, oral pimecrolimus, oral retinoids (alone or with ultraviolet light B), phototherapy plus balneotherapy, psoralen plus ultraviolet A, psychotherapy, systemic drug treatments plus topical vitamin D derivatives, tars, tazarotene, topical corticosteroids (alone or plus oral retinoids), topical Vitamin D derivatives, ultraviolet light A, and ultraviolet light B.

QUESTIONS

INTERVENTIONS

NON-DRUG TREATMENTS (NOT UV LIGHT)

Unknown effectiveness

TOPICAL TREATMENTS

Beneficial

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

UV LIGHT

Likely to be beneficial

Unknown effectiveness

SYSTEMIC TREATMENTS

Trade off between benefits and harms

Unknown effectiveness

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Footnote

*Based on consensus.

Key points

- Psoriasis affects 1% to 3% of the population, causing changes to the nails and joints in addition to skin lesions in some people.
- We don't know whether treatments that might affect possible triggers, such as acupuncture, balneotherapy, fish oil supplementation, or psychotherapy, improve symptoms of psoriasis, as we found few studies.
- There is consensus that topical emollients and salicylic acid are effective as initial and adjunctive treatment for people with chronic plaque psoriasis, but we don't know whether tars are effective.

  Dithranol may improve lesions compared with placebo. It may be less effective than topical vitamin D derivatives such as calcipotriol.

  Topical potent corticosteroids may improve psoriasis compared with placebo, and efficacy may be increased by adding tazarotene, oral retinoids, or vitamin D and derivatives, or by wrapping in occlusive dressings. Short-term, placebo-controlled randomised trials of topical corticosteroids and vitamin D derivatives are still currently performed in psoriasis, mainly for regulatory purposes. From a clinical point of view, there is no need for further trials of this sort; however, there is still a need for additional long-term or comparative trials.

  We don't know whether tars are more effective than ultraviolet light or vitamin D derivatives in people with chronic plaque psoriasis.
- CAUTION: Tazarotene, vitamin D and derivatives, and oral retinoids are potentially teratogenic and are contraindicated in women who may be pregnant.
- Heliotherapy, PUVA, and ultraviolet B (UVB) may improve lesions and reduce relapse, but increase the risks of photo-ageing and skin cancer.
- There is consensus that heliotherapy and UVB are beneficial.
- Methotrexate and ciclosporin seem similarly effective at clearing lesions and maintaining remission, but both can cause serious adverse effects.
- Oral retinoids may improve clearance of lesions, alone or with ultraviolet light, but may be less effective than ciclosporin.
- Cytokine inhibitors (etanercept, infliximab, and adalimumab) and T cell-targeted therapies (alefacept, efalizumab) may improve lesions, but long-term effects are unknown.
- We don't know whether leflunomide improves psoriasis.
- The Ingram regimen is considered effective, but we don't know whether Goeckerman treatment or other combined treatments are beneficial.

Clinical context

DEFINITION Chronic plaque psoriasis, or psoriasis vulgaris, is a chronic inflammatory skin disease characterised by well demarcated, erythematous, scaly plaques on the extensor surfaces of the body and scalp. The lesions may occasionally itch or sting, and may bleed when injured. Dystrophic nail changes or nail pitting are found in more than one third of people with chronic plaque psoriasis, and psoriatic arthropathy occurs in 1% to more than 10%. The condition waxes and wanes, with wide variations in course and severity among individuals. Other varieties of psoriasis include guttate, inverse, pustular, and erythrodermic psoriasis. This review deals only with treatments for chronic plaque psoriasis and does not cover nail involvement or scalp psoriasis.

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INCIDENCE/ PREVALENCE

Psoriasis affects 1% to 3% of the general population. It is believed to be less frequent in people from Africa and Asia, but we found no reliable epidemiological data to support this. [1]

AETIOLOGY/ RISK FACTORS

About one third of people with psoriasis have a family history of the disease, but physical trauma, acute infection, and some medications (e.g., lithium and beta-blockers) are believed to trigger the condition. A few observational studies have linked the onset or relapse of psoriasis with stressful life events, and with personal habits including cigarette smoking and, less consistently, alcohol consumption. [2] Others have found an association between psoriasis and body mass index (BMI), and with a diet low in fruit and vegetables.

PROGNOSIS

We found no long-term prognostic studies. With the exceptions of erythrodermic and acute generalised pustular psoriasis (severe conditions that affect less than 1% of people with psoriasis, and require intensive hospital care), psoriasis is not known to affect mortality. Psoriasis may substantially affect quality of life, by influencing a negative body image and self-image, and by limiting daily activities, social contacts, and work. One systematic review (search date 2000, 17 cohort studies) suggested that severe psoriasis may be associated with lower levels of quality of life than mild psoriasis. [3] At present, there is no cure for psoriasis. However, in many people it can be well controlled with treatment, at least in the short term.

AIMS OF INTERVENTION

To achieve short-term suppression of symptoms, and long-term modulation of disease severity; to improve quality of life, with minimal adverse effects of treatment.

OUTCOMES

Symptom improvement: Clearance or improvement of lesions over time, often measured by Psoriasis Area and Severity Index (PASI) score; use of routine treatments; **maintenance of remission** in people with psoriasis clearance or previous response: duration of remission, relapse; **quality of life**: patient satisfaction and autonomy; disease-related quality of life; **adverse effects** of treatment on clinical outcomes of interest. Although PASI scores are used to measure outcome in most of the included RCTs, we found no documented evidence that such clinical activity scores are reliable proxies for these symptom improvements. Some trials attempt to overcome score limitations by converting PASI scores into categories of response deemed to be clinically important: for example, at least a 75% reduction in score from baseline (PASI 75) or at least a 90% reduction in score from baseline (PASI 90). Many trials provide no explicit criteria for severity. [4] The effects of placebo treatment have been found to vary across studies in an unpredictable way. [5] Improvements with standardisation of study designs, entry criteria, and outcome measures are needed.

METHODS

Clinical Evidence search and appraisal August 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to August 2007, Embase 1980 to August 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 3. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single-blinded, and containing more than 20 people of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. Short-term, placebo-controlled randomised trials of topical corticosteroids and vitamin D derivatives are still currently performed in psoriasis, mainly for regulatory purposes. We therefore add only longer-term trials, or trials that compare the effectiveness of these treatments versus other psoriasis treatments. We also searched for cohort, case control, RCT, and meta-analysis studies on specific harms of interventions. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. The contributors identified supplementary references through additional electronic literature searches, contact with other experts in the field, and hand searches of several dermatological and medical journals for the years 1976–2004 as a project of the European Dermatoepidemiology Network. The journals searched were the *Journal of Investigative Dermatology*, *British Journal of Dermatology*, *Dermatology*, *Acta Dermo-Venereologica*, *Archives of Dermatology*, *Journal of the American Academy of Dermatology*, *Annales de Dermatologie et de Vénéréologie*, *Giornale Italiano di Dermatologia e Venereologia*, *Hautarzt*, *BMJ*, *Lancet*, *Journal of the American Medical Association*, and *New England Journal of Medicine*. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review

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(see table, p 104). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of non-drug treatments (other than ultraviolet light) for chronic plaque psoriasis?**

OPTION **ACUPUNCTURE**

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We don't know whether treatments that might affect possible triggers, such as acupuncture, improve symptoms of psoriasis, as we found few trials.

Benefits and harms

Acupuncture versus sham acupuncture:

We found one RCT comparing classic acupuncture versus sham (placebo) acupuncture. [6]

Symptom improvement

Acupuncture compared with sham acupuncture We don't know whether acupuncture is more effective than sham acupuncture at reducing psoriasis severity scores at 3 months in people with mild to moderate chronic plaque psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[6] RCT	56 people with mild to moderate chronic plaque psoriasis	**Mean reduction in Psoriasis Area and Severity Index (PASI) score , 3 months** 1.3 with classic acupuncture 2.3 with sham acupuncture	P >0.05	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [6]

Quality of life

No data from the following reference on this outcome. [6]

Adverse effects

No data from the following reference on this outcome. [6]

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Further information on studies

Comment: **Clinical guide:**
Because several trigger and perpetuating factors for psoriasis have been recognised, including physical trauma, acute infections, smoking, diet, and stress, disease severity might be modulated by non-drug treatments. However, we found no good evidence on the effects of acupuncture.

OPTION BALNEOTHERAPY

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We don't know whether treatments that might affect possible triggers, such as balneotherapy, improve symptoms of psoriasis, as we found few trials.

Benefits and harms

Balneotherapy versus placebo:

We found one RCT. [7]

Symptom improvement

Balneotherapy compared with placebo Balneotherapy (thermal baths with bicarbonate, calcium, and magnesium-rich water) may be more effective than placebo at improving psoriasis symptoms severity scores at 3 months in people with chronic plaque psoriasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[7] RCT	50 people with chronic plaque psoriasis, severity not reported	**Proportion of people with improvement in Psoriasis Area and Severity Index (PASI) score , 3 months** 64% with thermal bath (bicarbonate, calcium, and magnesium-rich water) 11% with tap water bath Absolute numbers not reported	P <0.001	○○○	thermal bath

Maintenance of remission

No data from the following reference on this outcome. [7]

Quality of life

No data from the following reference on this outcome. [7]

Adverse effects

No data from the following reference on this outcome. [7]

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Balneotherapy plus phototherapy versus either intervention alone:
See option on phototherapy plus balneotherapy, p 50 .

Further information on studies

Comment: **Clinical guide:**
Because several trigger and perpetuating factors for psoriasis have been recognised, including physical trauma, acute infections, smoking, diet, and stress, disease severity might be modulated by non-drug treatments. However, we found no good evidence on the effects of balneotherapy.

OPTION FISH OIL SUPPLEMENTATION

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We don't know whether treatments that might affect possible triggers, such as fish oil supplementation, improve symptoms of psoriasis, as we found few trials.

Benefits and harms

Fish oil versus placebo:
We found five RCTs, which reported inconclusive results. [8] [9] [10] [11] [12]

Symptom improvement

Fish oil compared with placebo Fish oil supplements may be no more effective than placebo at improving psoriasis severity scores at 2 weeks to 12 months in people with chronic plaque psoriasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[8] RCT	83 people hospitalised for severe psoriasis	**Reduction in Psoriasis Area and Severity Index (PASI) score by at least 50% from baseline , 14 days** 16/43 (37%) with infusion of omega-3 fatty acid 9/40 (23%) with placebo (conventional omega-6)	OR 0.4 95% CI 0.1 to 1.2	⟷	Not significant
[9] RCT	38 people with psoriasis and psoriatic arthritis	**Skin and joint disease activity , 12 months** with evening primrose oil plus fish oil capsule with placebo (empty capsule)	Reported similar disease activity in both groups		
[10] RCT	145 people with moderate to severe psoriasis	**Psoriasis Area and Severity Index (PASI) and total subjective score , 4 months** with fish oil capsule with placebo (corn oil)	Reported similar disease activity in both groups		
[12] RCT	41 people, psoriasis severity not reported	**Clinical activity , 8 weeks** with fish oil with olive oil	Reported similar disease activity in both groups		

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No data from the following reference on this outcome. [11]

Maintenance of remission

Fish oil compared with placebo We don't know whether fish oil or olive oil capsules are more effective than placebo at reducing relapse rate on withdrawal of topical corticosteroids, in people with stable plaque psoriasis using topical corticosteroids (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maintenance of remission					
[11] RCT	25 people with stable plaque psoriasis using topical corticosteroids	**Rate of relapse on withdrawal of topical corticosteroids , 9 weeks** with fish oil capsule with olive oil capsule	Reported similar relapse rates in both groups		

No data from the following reference on this outcome. [8] [9] [10] [12]

Quality of life

No data from the following reference on this outcome. [8] [9] [10] [11] [12]

Adverse effects

No data from the following reference on this outcome. [8] [9] [10] [11] [12]

Further information on studies

Comment: **Clinical guide:**
Because several trigger and perpetuating factors for psoriasis have been recognised, including physical trauma, acute infections, smoking, diet, and stress, disease severity might be modulated by non-drug treatments. However, we found no good evidence on the effects of fish oil supplementation.

OPTION PSYCHOTHERAPY

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We don't know whether treatments that might affect possible triggers, such as psychotherapy, improve symptoms of psoriasis, as we found few trials.

Benefits and harms

Psychotherapy versus no treatment:

We found one small RCT, which did not meet *Clinical Evidence* inclusion criteria because of weak methods. [13]

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Further information on studies

Comment: **Clinical guide:**
Because several trigger and perpetuating factors for psoriasis have been recognised, including physical trauma, acute infections, smoking, diet, and stress, disease severity might be modulated by non-drug treatments. However, we found no good evidence on the effects of psychotherapy.

QUESTION **What are the effects of topical drug treatments for chronic plaque psoriasis?**

OPTION **TAZAROTENE**

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Tazarotene, a topical retinoid, may be effective in the short term at improving symptoms of mild to moderate chronic plaque psoriasis.
- CAUTION: Tazarotene is potentially teratogenic and is contraindicated in women who may be pregnant.

Benefits and harms

Tazarotene versus placebo :

We found one systematic review [14] (search date 1999, 1 RCT) [15] and three additional RCTs (published in 2 papers, one paper including study A and study B) comparing tazarotene versus placebo. [16] [17]

Symptom improvement

Tazarotene compared with placebo Tazarotene, a topical retinoid, may be more effective than placebo in the short term (6–12 weeks) at improving symptoms of mild to moderate chronic plaque psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[16] RCT	1303 people with plaque psoriasis covering at least 2% of body surface, mean coverage of 10%–11% in participants	**Global response, reduction in plaque elevation and scaling , 12 weeks** with tazarotene 0.05% or 0.1% once daily with placebo Absolute results not reported	Reported as significantly more effective than placebo P value not reported	○○○	tazarotene
[17] RCT Study A	45 people with mild to moderate plaque psoriasis Within-participant control, 2 bilateral target plaques	**Treatment success (defined as >75% improvement from baseline) , 6 weeks** 45% with tazarotene 0.05% or 0.1% twice daily 13% with placebo Absolute numbers not reported	P <0.05	○○○	tazarotene
[17] RCT Study A	45 people with mild to moderate plaque psoriasis Within-participant control, 2 bilateral target plaques	**Plaque elevation, scaling, and erythema , 8 weeks** with tazarotene 0.05% or 0.1% twice daily with placebo Absolute results not reported	Reported as significantly more effective than placebo P value not reported	○○○	tazarotene

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[17] RCT Study B	108 people with mild to moderate plaque psoriasis Within-participant control, 2 bilateral target plaques	**Treatment success (defined as >75% improvement from baseline) , 8 weeks** with tazarotene 0.05% or 0.1% once or twice daily with placebo ARs ranged from 48%–63% depending on the various tazarotene treatment regimens; between-group differences not reported	Significance not assessed		
[17] RCT Study B	108 people with mild to moderate plaque psoriasis Within-participant control, 2 bilateral target plaques	**Plaque elevation, scaling, and erythema , 8 weeks** with tazarotene 0.05% or 0.1% once or twice daily with placebo Absolute results not reported	Reported as significantly more effective than placebo P value not reported	○○○	tazarotene
[15] RCT **3-armed trial**	324 people with plaque psoriasis covering at least 20% of body surface and at least moderate-severity plaque elevation The RCT evaluated tazarotene 0.1% and 0.05% versus placebo, but reported results for the two tazoretene arms together	**Composite score (0–12) for plaque elevation, scaling, and erythema , 12 weeks** <4 with tazarotene 0.05% or 0.1% once daily >5 with placebo Absolute results reported graphically Plaque elevation, scaling, and erythema individually measured on a scale of 0–4: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe	P for tazarotene *v* placebo <0.05	○○○	tazarotene
[15] RCT **3-armed trial**	324 people with plaque psoriasis covering at least 20% of body surface and at least moderate-severity plaque elevation	**Proportion of people with treatment success (clinical improvement >50%) , 12 weeks** >60% with tazarotene 0.1% 50% with tazarotene 0.05% 30% with placebo Absolute results reported graphically	P for tazarotene *v* placebo <0.05	○○○	tazarotene

Maintenance of remission

No data from the following reference on this outcome. [15] [16] [17]

Quality of life

No data from the following reference on this outcome. [15] [16] [17]

Adverse effects

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No data from the following reference on this outcome. [15] [16] [17]

Tazarotene plus topical corticosteroids versus tazarotene plus placebo:

We found four RCTs (published in 3 papers) comparing adding topical corticosteroids to tazarotene treatment versus tazarotene plus placebo. [18] [19] [20]

Symptom improvement

Tazarotene plus topical corticosteroids compared with tazarotene plus placebo Adding mid- or high-potency topical corticosteroids to tazarotene treatment seems more effective than tazarotene plus placebo at improving symptoms of mild to moderate chronic plaque psoriasis at 12 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[18] RCT	200 people with plaque psoriasis affecting 5%–20% of body surface	**Global clinical improvement , 12 weeks** with tazarotene 0.1% plus high- or mid-potency corticosteroid with tazarotene alone Absolute results not reported	Combination reported as significantly better than tazarotene alone P value not reported	○○○	tazarotene plus mid-potency corticosteroids
[19] RCT **4-armed trial** Study 1: single-blind RCT	300 people with plaque psoriasis covering at least 20% of body surface The remaining arms evaluated tazarotene plus low-potency corticosteroid and tazarotene plus medium-potency corticosteroid	**Treatment success (at least 50% global improvement in appearance of lesions) , at 12 weeks** 95% with tazarotene plus high-potency corticosteroid 80% with tazarotene plus placebo Number of people in this analysis unclear	P <0.05 for tazarotene plus high-potency corticosteroid *v* tazarotene plus placebo	○○○	tazarotene plus high-potency corticosteroid
[19] RCT **4-armed trial** Study 1: single-blind RCT	300 people with plaque psoriasis covering at least 20% of body surface The remaining arms evaluated tazarotene plus low-potency corticosteroid and tazarotene plus high-potency corticosteroid	**Treatment success (at least 50% global improvement in appearance of lesions) , at 12 weeks** 91% with tazarotene plus medium-potency corticosteroid 80% with tazarotene plus placebo Number of people in this analysis unclear	P <0.05 for tazarotene plus medium-potency corticosteroid *v* tazarotene plus placebo	○○○	tazarotene plus medium-potency corticosteroid
[19] RCT **4-armed trial** Study 1: single-blind RCT	300 people with plaque psoriasis covering at least 20% of body surface The remaining arms evaluated tazarotene plus high-potency corticosteroid and tazarotene plus medium-potency corticosteroid	**Treatment success (at least 50% global improvement in appearance of lesions) , at 12 weeks** with tazarotene plus low-potency corticosteroid 80% with tazarotene plus placebo Absolute results not reported Data for tazarotene plus low-potency group presented graphically Number of people in this analysis unclear	Reported as no significant difference between tazarotene plus low-potency corticosteroid *v* tazarotene plus placebo	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] RCT **4-armed trial** Study 2: double-blind RCT	398 people with plaque psoriasis covering at least 20% of body surface The remaining arms evaluated tazarotene plus low-potency corticosteroid and tazarotene plus mid-potency corticosteroid	**Treatment success (at least 50% global improvement in appearance of lesions) , at 12 weeks** 75% with tazarotene plus high-potency corticosteroid 54% with tazarotene plus placebo Number of people in this analysis unclear	P <0.05 for tazarotene plus high-potency corticosteroid *v* tazarotene plus placebo	○○○	tazarotene plus high-potency corticosteroid
[19] RCT **4-armed trial** Study 2: double-blind RCT	398 people with plaque psoriasis covering at least 20% of body surface The remaining arms evaluated tazarotene plus low-potency corticosteroid and tazarotene plus high-potency corticosteroid	**Treatment success (at least 50% global improvement in appearance of lesions) , at 12 weeks** 55% with tazarotene plus medium-potency corticosteroids 54% with tazarotene plus placebo Number of people in this analysis unclear			
[19] RCT **4-armed trial** Study 2: double-blind RCT	398 people with plaque psoriasis covering at least 20% of body surface The remaining arms evaluated tazarotene plus high-potency corticosteroids and tazarotene plus medium-potency corticosteroids	**Treatment success (at least 50% global improvement in appearance of lesions) , at 12 weeks** with tazarotene plus low-potency corticosteroids 54% with tazarotene plus placebo Data for tazarotene plus low-potency group presented graphically Number of people in this analysis unclear	Reported as not significant for tazarotene plus low-potency corticosteroids *v* tazarotene plus placebo	⟷	Not significant
[20] RCT **4-armed trial**	300 people with stable mild to moderate plaque psoriasis	**Plaque elevation (graded in a 9-point scale, from 0 = none to 8 = very severe) , after 2–12 weeks' treatment** with tazarotene 0.1% gel plus placebo cream with tazarotene 0.1% gel plus low-potency corticosteroid cream with tazarotene 0.1% gel plus medium-potency corticosteroid cream with tazarotene 0.1% gel plus high-potency corticosteroid cream Absolute results reported graphically	Reported as no significant difference between groups P value not reported	⟷	Not significant
[20] RCT **4-armed trial**	300 people with stable mild to moderate plaque psoriasis	**Plaque elevation (graded in a 9-point scale, from 0 = none to 8 = very severe) , 4 weeks after treatment finished** with tazarotene 0.1% gel plus placebo cream with tazarotene 0.1% gel plus low-potency corticosteroid cream	Reported as no significant difference between groups P value not reported	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with tazarotene 0.1% gel plus medium-potency corticosteroid cream with tazarotene 0.1% gel plus high-potency corticosteroid cream Absolute results reported graphically			
[20] RCT **4-armed trial**	300 people with stable mild to moderate plaque psoriasis The remaining arms evaluated tazarotene 0.1% gel plus medium-potency corticosteroid cream and tazarotene 0.1% gel plus high-potency corticosteroid cream	**Percentage of people with global treatment response score between 0 and 3 , 2 weeks** 42% with tazarotene 0.1% gel plus placebo cream 49% with tazarotene 0.1% gel plus low-potency corticosteroid cream Absolute numbers not reported Number of people in this analysis unclear	P reported as not significant for tazarotene plus low-potency corticosteroids *v* tazarotene plus placebo	⟷	Not significant
[20] RCT **4-armed trial**	300 people with stable mild to moderate plaque psoriasis The remaining arms evaluated tazarotene 0.1% gel plus low-potency corticosteroid cream and tazarotene 0.1% gel plus high-potency corticosteroid cream	**Percentage of people with global treatment response score between 0 and 3 , 2 weeks** 42% with tazarotene 0.1% gel plus placebo cream 73% with tazarotene 0.1% gel plus medium-potency corticosteroid cream Absolute numbers not reported Number of people in this analysis unclear	P <0.05 for tazarotene plus medium-potency corticosteroid *v* tazarotene plus placebo	○○○	tazarotene plus medium-potency corticosteroid
[20] RCT **4-armed trial**	300 people with stable mild to moderate plaque psoriasis The remaining arms evaluated tazarotene 0.1% gel plus low-potency corticosteroid cream and tazarotene 0.1% gel plus medium-potency corticosteroid cream	**Percentage of people with global treatment response score between 0 and 3 , 2 weeks** 42% with tazarotene 0.1% gel plus placebo cream 58% with tazarotene 0.1% gel plus high-potency corticosteroid cream Absolute numbers not reported Number of people in this analysis unclear	P <0.05 for tazarotene plus high-potency corticosteroid *v* tazarotene plus placebo	○○○	tazarotene plus high-potency corticosteroids
[20] RCT **4-armed trial**	300 people with stable mild to moderate plaque psoriasis The remaining arms evaluated tazarotene 0.1% gel plus medium-potency corticosteroid cream and tazarotene 0.1% gel plus high-potency corticosteroid cream	**Percentage of people with global treatment response score between 0 and 3* , 12 weeks** 80% with tazarotene 0.1% gel plus placebo cream 79% with tazarotene 0.1% gel plus low-potency corticosteroid cream Absolute numbers not reported Number of people in this analysis unclear	Reported as no significant difference between tazarotene plus low-potency corticosteroid *v* tazarotene plus placebo	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] RCT **4-armed trial**	300 people with stable mild to moderate plaque psoriasis The remaining arms evaluated tazarotene 0.1% gel plus low-potency corticosteroid cream and tazarotene 0.1% gel plus high-potency corticosteroid cream	**Percentage of people with global treatment response score between 0 and 3* , 12 weeks** 80% with tazarotene 0.1% gel plus placebo cream 91% with tazarotene 0.1% gel plus medium-potency corticosteroid cream Absolute numbers not reported Number of people in this analysis unclear	P <0.05 for tazarotene plus medium-potency corticosteroid *v* tazarotene plus placebo	○○○	tazarotene plus medium-potency corticosteroid
[20] RCT **4-armed trial**	300 people with stable mild to moderate plaque psoriasis The remaining arms evaluated tazarotene 0.1% gel plus low-potency corticosteroid cream and tazarotene 0.1% gel plus medium-potency corticosteroid cream	**Percentage of people with global treatment response score between 0 and 3* , 12 weeks** 80% with tazarotene 0.1% gel plus placebo cream 95% with tazarotene 0.1% gel plus high-potency corticosteroid cream Absolute numbers not reported Number of people in this analysis unclear	P <0.05 for tazarotene plus high-potency corticosteroid *v* tazarotene plus placebo	○○○	tazarotene plus high-potency corticosteroid
[20] RCT **4-armed trial**	300 people with stable mild to moderate plaque psoriasis	**Percentage of people with global treatment response score between 0 and 3* , 4 weeks after end of treatment** with tazarotene 0.1% gel plus placebo cream with tazarotene 0.1% gel plus low-potency corticosteroid cream with tazarotene 0.1% gel plus medium-potency corticosteroid cream with tazarotene 0.1% gel plus high-potency corticosteroid cream Absolute results reported graphically	Reported as no significant difference among groups P value not reported	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [18] [19] [20]

Quality of life

No data from the following reference on this outcome. [18] [19] [20]

Adverse effects

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No data from the following reference on this outcome. [18] [19] [20]

Tazarotene plus topical corticosteroids versus vitamin D derivatives:

We found one RCT (120 people with mild to moderate psoriasis) comparing once-daily treatment with tazarotene 0.1% plus topical mometasone furoate 0.1%. [21]

Symptom improvement

Tazarotene plus topical corticosteroids compared with vitamin D derivatives Tazarotene plus topical mometasone may be more effective than calcipotriol at increasing the proportion of people with mild to moderate psoriasis who have a marked improvement of symptoms at 2 weeks. However, combination treatment is no more effective at clearing lesions completely or almost completely (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[21] RCT	120 people (106 evaluable) with plaque psoriasis covering 20% or less of body surface	**Marked improvement (>75% global improvement) , 8 weeks** 45% with tazarotene 0.1% plus mometasone furoate once daily 26% with calcipotriol twice daily Absolute results not reported	P <0.05	○○○	tazarotene plus mometasone furoate
[21] RCT	120 people (106 evaluable) with plaque psoriasis covering 20% or less of body surface	**Clearance (>90% global improvement) , 8 weeks** with tazarotene 0.1% plus mometasone furoate once daily with calcipotriol twice daily Absolute results not reported	Reported as not significant	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [21]

Quality of life

No data from the following reference on this outcome. [21]

Adverse effects

No data from the following reference on this outcome. [21]

Further information on studies

[17] Two multi-centre, double-blind RCTs (study A and study B) reported in one publication.

[19] Two multicentre RCTs, one single-blind and one double-blind (study 1 and study 2), reported in one publication.

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Comment: The RCTs found that some skin irritation was reported in most people using tazarotene.

Clinical guide:
Tazarotene is potentially teratogenic and is contraindicated in women who are, or intend to become, pregnant.

OPTION VITAMIN D DERIVATIVES (TOPICAL)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Vitamin D derivatives may be more effective at improving psoriasis severity scores than placebo, corticosteroids, or short-contact dithranol.
- CAUTION: Vitamin D derivatives are potentially teratogenic and are contraindicated in women who may be pregnant.

Benefits and harms

Vitamin D derivatives versus placebo:

We found one systematic review (search date 1999, 14 RCTs, 1537 people, severity of psoriasis not reported) and two subsequent RCTs comparing vitamin D derivatives versus placebo for clearance of psoriasis, [14] [22] [23] and one further RCT, which assessed calcipotriol versus placebo for maintenance treatment. [24]

Symptom improvement

Vitamin D derivatives compared with placebo Vitamin D derivatives may be more effective at improving psoriasis severity scores at 3 to 8 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[14] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported 10 RCTs in this analysis	**Improvement in psoriasis severity scores , 3–8 weeks** with calcipotriol with placebo Absolute results not reported RCTs scored psoriasis severity using either the Total Severity Score, Psoriasis Area and Severity Index (PASI) score, or the Investigator Assessment of Global Improvement	SMD –0.74 95% CI –0.55 to –0.93	○○○	calcipotriol
[14] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported 4 RCTs in this analysis	**Improvement in psoriasis severity scores , 3–8 weeks** with tacalcitol with placebo Absolute results not reported RCTs scored psoriasis severity using either the Total Severity Score, Psoriasis Area and Severity Index (PASI) score, or the Investigator Assessment of Global Improvement	SMD –0.89 95% CI –0.59 to –1.18	○○○	tacalcitol
[22] RCT **5-armed trial**	144 people with bilateral plaque psoriasis involving less than 20% of the body surface Bilateral study comparing maxacalcitol, used on	**Psoriasis severity scale from 0–24 , 8 weeks** with maxacalcitol with placebo Absolute results reported graphically	P <0.001	○○○	maxacalcitol

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	either the left or right side of each person, with a control treatment on the other side The remaining arms evaluated various concentrations of maxacalcitol versus one another (3 groups) and maxacalcitol versus calcipotriol (1 group)	Psoriasis severity was measured using a scale from 0–24 (the sum of severity scores for erythema, induration, and scaling, each from 0 = no evidence to 8 = severe) 30 people in this analysis			
[23] RCT **3-armed trial**	1136 people with moderate or severe psoriasis The remaining arm evaluated calcipotriene combined with a corticosteroid	**Mean change in Psoriasis Area and Severity Index (PASI) score , 4 weeks** –45% with calcipotriene –33% with vehicle Number of people in this analysis unclear	Mean difference –12% 95% CI –6% to –18% P <0.001	○○○	calcipotriene

No data from the following reference on this outcome. [24]

Maintenance of remission

Vitamin D derivatives compared with placebo Calcipotriol may be more effective than placebo at prolonging time to relapse in people with stable psoriasis for at least 3 months after prior treatment with methotrexate for 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Remission					
[24] RCT	97 people with psoriasis that was stable for at least 3 months, and who had finished at least 6 months' treatment with methotrexate	**Median time to relapse (defined as doubling of baseline modified psoriasis severity score)** 113 days with maintenance treatment with calcipotriol 35 days with placebo	P <0.001	○○○	calcipotriol

No data from the following reference on this outcome. [14] [22] [23]

Quality of life

No data from the following reference on this outcome. [14] [22] [23] [24]

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported	**Local adverse effects** with vitamin D derivatives with placebo	ARR 0% 95% CI –2% to +2%	⟷	Not significant
[23] RCT **3-armed trial**	1136 people with moderate or severe psoriasis The remaining arm evaluated calcipotriene combined with a corticosteroid	**Skin problems (mainly itch, worsening psoriasis, and skin irritation)** 15% with calcipotriene 11% with placebo Absolute numbers not reported Number of people in this analysis unclear	Significance not assessed		
[23] RCT **3-armed trial**	1136 people with moderate or severe psoriasis The remaining arm evaluated calcipotriene combined with a corticosteroid	**Adverse effects , at 8 weeks** 40% with calcipotriene 37% with placebo Absolute numbers not reported Number of people in this analysis unclear	OR 1.17 95% CI 0.87 to 1.56 P = 0.31	⟷	Not significant
[24] RCT	97 people with psoriasis that was stable for at least 3 months, and who had finished at least 6 months' treatment with methotrexate	**Adverse effect** 77% with maintenance treatment with calcipotriol 78% with placebo Absolute numbers not reported The most commonly reported adverse effects were skin irritation, itch, and erythema Number of people in this analysis unclear	P = 0.009	⟷	Not significant
[22] RCT **5-armed trial**	144 people with bilateral plaque psoriasis involving less than 20% of the body surface Bilateral study comparing maxacalcitol, used on either the left or right side of each person, with a control treatment on the other side The remaining arms evaluated various concentrations of maxacalcitol versus one another (3 groups [90 people]) and maxacalcitol versus calcipotriol (1 group [30 people])	**Withdrawal owing to adverse effects** 12/144 (8%) with maxacalcitol at any dose not reported with placebo Absolute results reported graphically Most commonly reported adverse skin effect with maxacalcitol was burning sensation, which caused 3 people to leave the trial			

No data from the following reference on this outcome. [22]

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Different vitamin D derivatives versus each other:

We found one systematic review ((search date 1999) and two subsequent RCTs comparing calcipotriol versus another vitamin D derivative. [14] [22] [25] The systematic review identified one RCT that fulfilled our inclusion criteria. [20]

Symptom improvement

Different vitamin D derivatives compared with each other Calcipotriol may be more effective than tacalcitol at reducing psoriasis severity scores at 8 weeks, but we don't know whether calcipotriol is more effective than maxacalcitol or calcitriol at improving symptom scores at 8 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[20] RCT	287 people with mild to moderate psoriasis In review [14]	**Mean reduction in symptom severity score , 8 weeks** 5 with calcipotriol twice daily 4 with tacalcitol once daily Symptom severity was assessed using a 16-point scale (including severity of itch, erythema, infiltration and scaling, from 0 = least severe to 16 = most severe)	P = 0.0003	○○○	calcipotriol
[22] RCT	144 people with bilateral plaque psoriasis involving less than 20% of the body surface Bilateral study comparing maxacalcitol, used on either the left or right side of each person, with a control treatment on the other side The remaining arms evaluated various concentrations of maxacalcitol versus one another (3 groups [90 people]) and maxacalcitol versus placebo (1 group [30 people])	**Psoriasis severity scale from 0–24 , 8 weeks** with calcipotriol with maxacalcitol Absolute results reported graphically Psoriasis severity was measure using a scale from 0–24 (the sum of severity scores for erythema, induration, and scaling, each from 0 = no evidence to 8 = severe)	Reported as not significant P value not reported	⟷	Not significant
[25] RCT	250 people with mild to moderate chronic plaque psoriasis	**Mean global improvement score , 12 weeks** 2.3 with calcitriol 2.2 with calcipotriol Absolute results reported graphically Global improvement was scored by blinded investigators using a 4-point scale (from 0 = no change or worse to 3 = clear or almost clear)	Reported as not significant P value not reported	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [22] [25] [20]

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Quality of life

No data from the following reference on this outcome. [22] [25] [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] RCT	287 people with mild to moderate psoriasis In review [14]	**Adverse effects** 17/145 (12%) with calcipotriol twice daily 18/142 (13%) with tacalcitol once daily The most commonly reported adverse effects were itch and rash	Significance not assessed		
[25] RCT	250 people with mild to moderate chronic plaque psoriasis	**Mean severity of skin reaction (using a 5-point scale from 0 = none to 4 = very severe)** 0.1 with calcitriol 0.3 with calcipotriol	Significance not assessed		
[25] RCT	250 people with mild to moderate chronic plaque psoriasis	**Moderate and severe skin reactions , 12 weeks** 1% with calcitriol 9% with calcipotriol Absolute numbers not reported	P = 0.004	○○○	calcitriol

No data from the following reference on this outcome. [22]

Vitamin D derivatives versus topical corticosteroids:

We found one systematic review (search date 1999, 9 RCTs, 1875 people, severity of psoriasis not reported). [14] One further systematic review (search date 1999) gave information on adverse effects. [26]

Symptom improvement

Vitamin D derivatives compared with topical corticosteroids We don't know whether vitamin D derivatives are more effective than topical corticosteroids at improving psoriasis severity scores, but they may cause more perilesional and lesional irritation (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[14] Systematic review	Number of people in analysis not reported, psoriasis severity not reported 9 RCTs in this analysis	**Psoriasis severity scores , 3–8 weeks** with vitamin D derivatives with potent topical corticosteroids	SMD +0.06 95% CI –0.12 to +0.24 Significant statistical heterogeneity reported among trials (P <0.01)	⟷	Not significant

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Maintenance of remission

No data from the following reference on this outcome. [14]

Quality of life

No data from the following reference on this outcome. [14]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported 9 RCTs in this analysis	**Local adverse effects , 3–8 weeks** with vitamin D derivatives with potent topical corticosteroids	ARI +10% 95% CI –2% to +21%	⟷	Not significant
[26] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported	**Lesional or perilesional irriation** with calcipotriol with potent topical corticosteroids	Significantly greater rate with calcipotriol NNH 10 95% CI 6 to 34	○○○	potent topical corticosteroids

Vitamin D derivatives versus dithranol:

We found one systematic review (4 RCTs of calcipotriol, 1 RCT of tacalcitol, search date 1999, 972 people) [14] and one additional RCT. [27]

Symptom improvement

Vitamin D derivatives compared with dithranol Vitamin D derivatives may be more effective than dithranol short-contact therapy at improving psoriasis severity scores at 4–12 weeks, and are associated with fewer adverse effects (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[14] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported 5 RCTs in this analysis	**Psoriasis severity scores , 4–12 weeks** with vitamin D derivatives with dithranol short-contact therapy	SMD –0.44 95% CI –0.72 to –0.16	○○○	vitamin D derivatives
[27] RCT	171 people with chronic plaque psoriasis covering 10% of body surface or less (base-	**ESI score (9-point scale) , 8 weeks** 2.6 with calcipotriol 3.8 with dithranol	P = 0.0001 for comparison of change in score	○○○	calcipotriol

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	line severity scores: 6.3 with calcipotriol group *v* 6.2 with dithranol group)				

Maintenance of remission

No data from the following reference on this outcome. [14] [27]

Quality of life

No data from the following reference on this outcome. [14] [27]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported 9 RCTs in this analysis	**Local adverse effects** with vitamin D derivatives with dithranol short-contact therapy	ARI 27% 95% CI 17% to 36%	○○○	vitamin D derivatives

No data from the following reference on this outcome. [27]

Vitamin D derivatives versus dithranol plus coal tar:

We found one RCT comparing calcipotriol ointment (80–100 g/week) plus scalp solution (30–50 mL/week) versus combination treatment with dithranol and coal tar. [28]

Symptom improvement

Vitamin D derivatives compared with dithranol plus coal tar Vitamin D derivatives may be more effective than dithranol plus coal tar at reducing psoriasis severity scores at 4 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[28] RCT	88 people with mild to moderate chronic plaque psoriasis	**Change in PASI score from baseline , 4 weeks** –58% with calcipotriol –36% with dithranol plus coal tar Absolute numbers not reported	P = 0.004	○○○	calcipotriol

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Maintenance of remission

No data from the following reference on this outcome. [28]

Quality of life

No data from the following reference on this outcome. [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] RCT	88 people with mild to moderate chronic plaque psoriasis	**Overall adverse effects** 54% with calcipotriol 34% with dithranol plus coal tar Absolute numbers not reported Most of the reported adverse events were skin problems	P = 0.09	⟷	Not significant

No data from the following reference on this outcome. [27]

Vitamin D derivatives versus coal tar:

We found one systematic review (search date 1999, 2 RCTs, number of people and psoriasis severity not reported). [14]

Symptom improvement

Vitamin D derivatives compared with coal tar Calcipotriol may be more effective than coal tar alone or coal tar combined with allantoin and hydrocortisone at improving psoriasis severity scores at 6–8 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[14] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported 2 RCTs in this analysis	**Psoriasis severity scores , 6–8 weeks** with calcipotriol with coal tar Absolute results not reported	SMD –0.91 95% CI –1.36 to –0.46	◌◌◌	calcipotriol

Maintenance of remission

No data from the following reference on this outcome. [14]

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Quality of life

No data from the following reference on this outcome. [14]

Adverse effects

No data from the following reference on this outcome. [14]

Vitamin D derivatives plus dithranol versus dithranol alone:

We found one RCT comparing the combination of calcipotriol plus short-contact dithranol versus dithranol alone. [29]

Symptom improvement

Vitamin D derivatives plus dithranol compared with dithranol alone Calcipotriol plus short-contact dithranol therapy may be more effective than dithranol alone at improving symptom severity scores in people with mild to moderate chronic plaque psoriasis at 6 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[29] RCT	46 people with mild to moderate chronic plaque psoriasis	**Mean PASI scores , 6 weeks** 0.0 with calcipotriol plus short-contact dithranol 1.2 with dithranol alone	P = 0.0001	○○○	calcipotriol plus dithranol

Maintenance of remission

No data from the following reference on this outcome. [29]

Quality of life

No data from the following reference on this outcome. [29]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] RCT	46 people with mild to moderate chronic plaque psoriasis	**Irritation, burning, and discoloration of the perilesional skin** with calcipotriol plus short-contact dithranol with dithranol alone Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

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Vitamin D derivatives plus fumaric acid esters versus fumaric acid esters alone:

We found one RCT. [30]

Symptom improvement

Vitamin D derivatives plus fumaric acid esters compared with fumaric acid alone Calcipotriol plus oral fumaric acid may be more effective than fumaric acid alone at improving symptom severity scores at 13 weeks in people with severe chronic plaque psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[30] RCT	143 people with severe psoriasis	**Change in PASI score , 13 weeks** –76% with calcipotriol plus fumaric acid –52% with fumaric acid alone Absolute numbers not reported	Mean difference –24% 95% CI –34% to –14%	○○○	calcipotriol plus fumaric acid

Maintenance of remission

No data from the following reference on this outcome. [30]

Quality of life

No data from the following reference on this outcome. [30]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] RCT	143 people with severe psoriasis	**Proportion of people who reported adverse effects** 82% with calcipotriol plus fumaric acid 79% with fumaric acid alone Absolute numbers not reported Adverse effects included diarrhoea, flushing, abdominal pain, and pruritus	OR 1.26 95% CI 0.53 to 2.96	⟷	Not significant

Vitamin D derivatives versus UVB or PUVA:

See option on PUVA, p 37 .

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Vitamin D derivatives versus topical corticosteroids plus topical retinoids:
See option on tazarotene, p 8 .

Vitamin D derivatives plus PUVA or plus UVB:
See option on adding calcipotriol (topical) to PUVA or UVB, p 92 .

Vitamin D derivatives plus systemic drugs:
See option on systemic drug treatment plus topical vitamin D derivatives, p 97 .

Further information on studies

Comment: **Clinical guide:**
Vitamin D derivatives are an option for the treatment of psoriasis of limited extension. There is consensus that the dosage of calcipotriol cream 0.005% should be limited to 100 g weekly.

OPTION DITHRANOL

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Dithranol may improve lesions compared with placebo. It may be less effective than topical vitamin D derivatives such as calcipotriol.
- Staining and burning are the main reported adverse effects of dithranol.

Benefits and harms

Dithranol versus placebo:
We found one systematic review of topical preparations for the treatment of psoriasis (search date 1999, 3 small RCTs, number of people, and severity of psoriasis not reported). [14]

Symptom improvement

Dithranol compared with placebo Dithranol may be more effective than placebo at improving psoriasis severity scores at 4–8 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[14] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported 3 RCTs in this analysis	**Improvement in psoriasis severity scores , 4–8 weeks** with dithranol with placebo Absolute results not reported RCTs scored psoriasis severity using either the Total Severity Score, Psoriasis Area and Severity Index (PASI) score, or the Investigator Assessment of Global Improvement	SMD –1.04 95% CI –1.65 to –0.42	○○○	dithranol

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Maintenance of remission

No data from the following reference on this outcome. [14]

Quality of life

No data from the following reference on this outcome. [14]

Adverse effects

No data from the following reference on this outcome. [14]

Dithranol versus vitamin D derivatives:
See option on vitamin D derivatives (topical), p 15 .

Dithranol combined with vitamin D derivatives:
See option on vitamin D derivatives (topical), p 15 .

Dithranol versus UVB or PUVA:
See option on PUVA, p 37 .

Ingram regimen (which contains dithranol:
See option on Ingram regimen, p 89 .

Further information on studies

Comment: Staining and burning are the main reported adverse effects of dithranol.

Conventional versus short-contact treatment with dithranol:
We found one systematic review, which assessed the quality of methods of published studies (search date 1989, 22 small RCTs) comparing conventional dithranol treatment versus dithranol short-contact treatment (shorter contact time at higher concentrations). [31] It reported no significant difference in outcomes between groups, but stated that the trials were too small to detect clinically important differences (data not reported in the review because its focus was assessing study methods). Few trials examined participant satisfaction, so it remains unclear whether short-contact treatment is easier and more convenient for people at home compared with conventional dithranol treatment.

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OPTION EMOLLIENTS

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- There is consensus that topical emollients are effective as initial and adjunctive treatment for people with chronic plaque psoriasis.
- Local irritation and contact dermatitis have been reported with emollients.

Benefits and harms

Emollients versus placebo:

We found no RCTs.

Emollients plus UVB radiation:

See option on UVB plus emollients, p 95 .

Further information on studies

Comment: Local irritation and contact dermatitis have been reported with emollients.

Clinical guide:
Emollients are usually used as adjuncts to other treatments. They include ointments (containing paraffin or lanolin) as well as aqueous cream and other substances used as vehicles in topical treatments. Although we found no RCTs of emollients, there is consensus that they are effective, and they are the initial treatment for most people with chronic plaque psoriasis.

OPTION KERATOLYTICS (SALICYLIC ACID, UREA)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- There is consensus that salicylic acid is effective as initial and adjunctive treatment for people with chronic plaque psoriasis.

Benefits and harms

Salicylic acid versus placebo:

We found one systematic review (search date 1999), which identified one small RCT (number of people and severity of psoriasis not reported). [14]

Symptom improvement

Salicylic acid compared with placebo Salicylic acid may be no more effective than placebo at improving psoriasis severity scores at 3 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[14] Systematic review	People with psoriasis (severity not reported), number of people in analysis not reported Data from 1 RCT	**Psoriasis severity scores between groups , 3 weeks** with salicylic acid with placebo Absolute results not reported	SMD –0.80 95% CI –1.71 to +0.11	⟷	Not significant

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Maintenance of remission

No data from the following reference on this outcome. [14]

Quality of life

No data from the following reference on this outcome. [14]

Adverse effects

No data from the following reference on this outcome. [14]

Urea versus placebo:
We found no systematic reviews or RCTs.

Further information on studies

Comment: **Clinical guide:**
Keratolytics are usually used as adjuncts to other treatments. Although we found limited RCT evidence, there is consensus that keratolytics are a useful adjunctive treatment for psoriasis. Local irritation and contact dermatitis have been reported with keratolytics such as salicylic acid.

OPTION CORTICOSTEROIDS (TOPICAL)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Potent topical corticosteroids may improve psoriasis compared with placebo, and efficacy may be increased by adding tazarotene, oral retinoids, or vitamin D and derivatives, or by wrapping in occlusive dressings.
- Short-term, placebo-controlled randomised trials of topical corticosteroids and vitamin D derivatives are still currently performed in psoriasis, mainly for regulatory purposes. From a clinical point of view, there is no need for further trials of this sort; however, there is still a need for additional long-term or comparative trials.
- Topical corticosteroids may cause striae and atrophy, which increase with potency and use of occlusive dressings. Continuous use may lead to adrenocortical suppression, and case reports suggest that severe flares of the disease may occur on withdrawal.

Benefits and harms

Topical corticosteroids versus placebo:
We found one systematic review of topical corticosteroid preparations versus placebo (search date 1999, 17 RCTs, 1686 people, psoriasis severity not reported) [14] and six subsequent RCTs examining the use of corticosteroids versus placebo for psoriasis clearance. [32] [33] [34] [35] [36] [37] However, the subsequent RCTs offered no substantial new evidence about the role of topical corticosteroids in people with psoriasis. Consequently, we are not providing data on these additional RCTs: only RCTs presenting evidence on maintenance, comparative RCTs, and studies providing data on adverse effects will be considered for inclusion further to the systematic review. One of

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the RCTs identified by the systematic review (90 people with psoriasis covering <10% of body surface) compared maintenance treatment with weekly application of betamethasone dipropionate versus placebo. [38]

Symptom improvement

Topical corticosteroids compared with placebo Potent and very potent topical corticosteroids may be more effective than placebo in the short term (4 weeks) at improving psoriasis severity scores (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[14] Systematic review	1040 people, psoriasis severity not reported 12 RCTs in this analysis	**Psoriasis severity scores , 3–12 weeks** with potent corticosteroids with placebo Absolute results not reported	SMD –0.84 95% CI –0.99 to –0.68	○○○	potent corticosteroids
[14] Systematic review	646 people, psoriasis severity not reported 5 RCTs in this analysis	**Psoriasis severity scores , 2–4 weeks** with very potent corticosteroids with placebo Absolute results not reported	SMD –1.51 95% CI –1.76 to –1.25	○○○	very potent corticosteroids

No data from the following reference on this outcome. [38]

Maintenance of remission

Topical corticosteroids compared with placebo Topical corticosteroids applied less frequently may be more effective than placebo at maintaining clear or nearly cleared areas at 6 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maintenance of remission					
[38] RCT	90 people with psoriasis covering less than 10% of body surface, whose psoriasis had already cleared, or almost cleared, with the use of betamethasone dipropionate In review [14]	**Proportion of people whose psoriasis remained clear, or nearly clear , 6 months** 27/46 (59%) with weekly application of betamethasone dipropionate 7/44 (16%) with placebo	P <0.001	○○○	betamethasone

No data from the following reference on this outcome. [14]

Quality of life

No data from the following reference on this outcome. [14] [38]

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] Systematic review	People with psoriasis (psoriasis severity not reported), number of people in analysis not reported	**Adverse effects , 2–4 weeks** with topical corticosteroids with placebo Absolute results not reported	ARI 0.00 95% CI –0.05 to 0.00	⟷	Not significant
[38] RCT	90 people with psoriasis covering less than 10% of body surface, whose psoriasis had already cleared, or almost cleared, with the use of betamethasone dipropionate In review [14]	**Adverse effects , 6 months** with weekly application of betamethasone dipropionate with placebo No adverse effects associated with weekly maintenance topical corticosteroids were found, and no signs of atrophy	May have been underpowered to detect clinically important adverse effects The RCT assessed the effects of treatment on lesions rather than on people	○○○	
[35] RCT	40 people with mild to moderate plaque-type psoriasis Split body study: people used betamethasone foam on one side of the body and placebo foam on the other side	**Adverse effects** with betamethasone valerate foam with placebo foam Several people reported itching, stinging, or burning, which caused 3 out of 40 people to withdraw from the RCT			

Topical corticosteroids plus occlusive dressings versus topical corticosteroids alone:
We found two small RCTs. [39] [40]

Symptom improvement

Topical corticosteroids plus occlusive dressings compared with topical corticosteroids alone Topical corticosteroids applied under occlusion may be more effective than topical corticosteroids alone at increasing clearance in people with chronic plaque psoriasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[39] RCT **4-armed trial**	70 people with chronic plaque psoriasis (symmetrical localized) Data from 1 RCT Bilateral study: each person applied corticosteroid plus occlusive dressing on one lesion and the same topical corticosteroid alone on another lesion The remaining arms evaluated clobetasol plus occlusion versus clo-	**Clearance , 3 weeks** 79% with betamethasone plus occlusion for 3 weeks 15% with betamethasone alone for 3 weeks Absolute numbers not reported Erythema, induration, and scaling each scored from 0 = none to 3 = severe; clearance defined as scores of 0 or 1 in each area	P <0.0001 for betamethasone plus occlusion *v* betamethasone alone	○○○	betamethasone plus occlusion

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	betasol alone for 2 weeks				
[39] RCT **4-armed trial**	70 people with chronic plaque psoriasis (symmetrical localized) Data from 1 RCT Bilateral study: each person applied corticosteroid plus occlusive dressing on one lesion and the same topical corticosteroid alone on another lesion The remaining arms evaluated betamethasone plus occlusion versus betamethasone alone for 3 weeks	**Clearance , 2 weeks** 86% with clobetasol plus occlusion for 2 weeks 14% with clobetasol alone for 2 weeks Absolute numbers not reported Erythema, induration, and scaling each scored from 0 = none to 3 = severe; clearance defined as scores of 0 or 1 in each area	P < 0.0001 for clobetasol plus occlusion *v* clobetasol alone		clobetasol plus occlusion
[40] RCT	61 people	**Clearance , 6 weeks** 97% with clobetasol plus occlusion 69% with clobetasol alone Absolute numbers not reported	P = 0.005		clobetasol plus occlusion

Maintenance of remission

No data from the following reference on this outcome. [39] [40]

Quality of life

No data from the following reference on this outcome. [39] [40]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39] RCT **4-armed trial**	70 people with chronic plaque psoriasis Data from 1 RCT	**Local skin reactions** with betamethasone plus occlusion with betamethasone alone with clobetasol plus occlusion with clobetasol alone 1 person withdrew due to erythema and itch. 1 person developed worse psoriasis around the	Significance not assessed		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		dressing edge. 3 people developed folliculitis			
[40] RCT	61 people	**Pruritus, stinging, discomfort, and secondary infection** 13% with clobetasol plus occlusion 7% with clobetasol alone Absolute numbers not reported	Significance not assessed		

Topical corticosteroids versus vitamin D derivatives:

See option on vitamin D derivatives (topical), p 15 .

Topical corticosteroids plus vitamin D derivatives versus vitamin D derivatives alone:

We found one systematic review (search date 1999) [14] and three subsequent RCTs. [41] [42] [43] We found additional RCTs that offered no substantial new evidence about the role of fixed combinations of topical corticosteroids and topical vitamin D derivatives in psoriasis. As a consequence, we are not providing data on these additional RCTs. Only RCTs presenting evidence on maintenance, comparative RCTs, and studies assessing adverse effects will be further considered for inclusion.

Symptom improvement

Topical corticosteroids plus vitamin D derivatives compared with vitamin D derivatives alone Potent topical corticosteroids plus calcipotriol may be more effective than calcipotriol alone at improving psoriasis symptoms at 4 weeks, and in the short term decrease irritation (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[14] Systematic review	671 people; psoriasis severity not reported 3 RCTs in this analysis	**Psoriasis severity scores , 6–8 weeks** with calcipotriol plus potent topical corticosteroids with calcipotriol alone Absolute results not reported	SMD 0.42 95% CI 0.12 to 0.72	○○○	calcipotriol plus potent topical corticosteroids
[14] Systematic review	218 people. psoriasis severity not reported 2 RCTs in this analysis	**Psoriasis severity scores , 6–8 weeks** with calcipotriol plus very potent topical corticosteroids with calcipotriol alone Absolute results not reported	SMD +0.37 95% CI –0.08 to +0.81	⟷	Not significant
[41] RCT **4-armed trial**	1603 people with chronic plaque psoriasis involving at least 10% of body surface The remaining arms evaluated betamethasone alone and placebo	**Mean change in Psoriasis Area and Severity Index (PASI) score , 4 weeks** –71% with combined calcipotriol plus betamethasone –46% with calcipotriol alone Number of people in this analysis unclear	Significance for combination treatment *v* calcipotriol alone not reported		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[42] RCT **4-armed trial**	1043 people with mild to moderate chronic plaque psoriasis involving at least 10% of body surface The remaining arms evaluated betamethasone alone and placebo	**Proportion of people with marked improvement in lesion severity , 4 weeks** 229/301 (76%) with calcipotriol plus betamethasone 103/308 (33%) with calcipotriol alone	OR 0.14 for combination *v* calcipotriol alone 95% CI 0.10 to 0.20	●●●	calcipotriol plus betamethasone
[43] RCT **3-armed trial**	972 people with psoriasis affecting at least 10% of body surface The remaining arm evaluated an alternating regimen: calcipotriol and betamethasone once daily for 4 weeks, then calcipotriol alone on week days and the combined product on weekends	**Mean reduction in PASI score** 73% with calcipotriol and betamethasone once daily for 8 weeks 64% with calcipotriol alone twice daily Absolute numbers not reported Number of people in this analysis unclear	P <0.001 for combined treatment *v* calcipotriol alone	○○○	calcipotriol plus betamethasone
[43] RCT **3-armed trial**	972 people with psoriasis affecting at least 10% of body surface The remainng arm evaluated calcipotriol and betamethasone once daily for 8 weeks	**Mean reduction in PASI score** 68% with alternating regimen: calcipotriol and betamethasone once daily for 4 weeks, then calcipotriol alone on week days and the combined product on weekends 64% with calcipotriol alone twice daily Absolute numbers not reported Number of people in this analysis unclear	P = 0.03 for alternating regimen *v* calcipotriol alone	○○○	calcipotriol plus betamethasone

Maintenance of remission

No data from the following reference on this outcome. [14] [41] [42] [43]

Quality of life

No data from the following reference on this outcome. [14] [41] [42] [43]

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Skin reactions					
[41] RCT **4-armed trial**	1603 people with chronic plaque psoriasis involving at least 10% of body surface The remaining arms evaluated betamethasone alone and placebo	**Local skin reactions** 6% with calcipotriol plus betamethasone 11% with calcipotriol alone Absolute numbers not reported The most commonly reported adverse effect was itch	OR 0.49 95% CI 0.31 to 0.70 P = 0.003	●●○	calcipotriol plus betamethasone
[42] RCT **4-armed trial**	1043 people with mild to moderate chronic plaque psoriasis involving at least 10% of body surface The remaining arms evaluated betamethasone alone and placebo	**Local skin reactions** 30/304 (10%) with calcipotriol plus betamethasone 53/308 (17%) with calcipotriol alone The most commonly reported adverse effect was itch	OR 0.53 95% CI 0.33 to 0.85 P = 0.008	●○○	calcipotriol plus betamethasone
[43] RCT **3-armed trial**	972 people with psoriasis affecting at least 10% of body surface The remaining arm evaluated an alternating regimen: combined calcipotriol and betamethasone for 4 weeks only, then calcipotriol alone on week days and the combined product on weekends	**Skin reactions** 35/322 (11%) with combined treatment (calcipotriol and betamethasone) 73/327 (22%) with calcipotriol alone Most common skin reactions included itch, burning, and erythema	P <0.001	○○○	calcipotriol plus betamethasone

Topical corticosteroids plus topical retinoids :
See option on tazarotene, p 8 .

Topical corticosteroids versus UVB or PUVA:
See option on PUVA, p 37 .

Topical corticosteroids plus oral retinoids:
See option on retinoids (oral) plus topical corticosteroids, p 96 .

Further information on studies

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Comment: **Clinical guide:**
Topical corticosteroids are a treatment option for psoriasis of limited extension.

OPTION TARS

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Tars are often used as adjuncts to other treatments; however, we don't know whether they are effective.

Benefits and harms

Tars versus placebo:

We found no systematic reviews or RCTs.

Coal tar plus fatty acids versus coal tar alone:

We found one small RCT. [44]

Adverse effects

Coal tar alone compared with coal tar plus fatty acids Coal tar plus fatty acids is no more effective than coal tar alone at 8 weeks at improving composite scores for erythema, desquamation, and infiltration in people with mild to moderate chronic plaque psoriasis (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[44] RCT	20 people in hospital with mild to moderate chronic plaque psoriasis One treatment applied to the right side of the body and the other treatment to the left, the sides determined randomly.	**Mean % improvement in composite score for erythema, desquamation, and infiltration , 8 weeks** 54% with coal tar plus esterified essential fatty acids 56% with coal tar alone	P = 0.52 The RCT was probably too small to detect a clinically important difference between treatments The RCT found that both coal tar plus fatty acids and coal tar alone were graded as "very satisfactory or satisfactory" by 15/20 (75%) people and "very unsatisfactory or unsatisfactory" by 4/20 (20%) people when assessing ease of application, messiness, odour, and comfort	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [44]

Quality of life

No data from the following reference on this outcome. [44]

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Study group name					
[44] RCT	20 people in hospital with mild to moderate chronic plaque psoriasis One treatment applied to the right side of the body and the other treatment to the left, the sides determined randomly	**Patient rating for ease of application, messiness, odour, and comfort** with coal tar plus esterified essential fatty acids with coal tar alone The RCT found that both coal tar plus fatty acids and coal tar alone were graded as "very satisfactory or satisfactory" by 15/20 (75%) people and "very unsatisfactory or unsatisfactory" by 4/20 (20%) people		⟷	Not significant

Tars versus vitamin D and derivatives:
See option on vitamin D derivatives (topical), p 15 .

Goeckerman treatment (which contains coal tar):
See option on Goeckerman treatment, p 94 .

Ingram regimen (contains coal tar):
See option on Ingram regimen, p 89 .

Tars versus PUVA or UVB:
See option on PUVA, p 37 .

Further information on studies

Comment: **Clinical guide:**
Tars are often used as adjuncts to other treatments. Smell, staining, and burning are the main adverse effects of coal tar.

QUESTION **What are the effects of ultraviolet light treatments for chronic plaque psoriasis?**

OPTION **HELIOTHERAPY**

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- There is consensus that heliotherapy is beneficial.
- Heliotherapy may improve lesions and reduce relapse, but increase the risks of photo-ageing and skin cancer.

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Benefits and harms

Heliotherapy versus no intervention:

We found one RCT. [45]

Symptom improvement

Heliotherapy compared with no intervention Heliotherapy may be more effective than no intervention at improving symptom severity scores at 1 year in people with all forms of chronic plaque psoriasis severity (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[45] RCT **Crossover design**	95 people with mild, moderate, or severe psoriasis	**Psoriasis Area and Severity Index score (taking into consideration scaling, infiltration) , 1 year** 4.2 with 4 weeks of supervised heliotherapy 6.2 with no intervention Pre-crossover results reported	P <0.05	○○○	heliotherapy

Maintenance of remission

No data from the following reference on this outcome. [45]

Quality of life

No data from the following reference on this outcome. [45]

Adverse effects

No data from the following reference on this outcome. [45]

Further information on studies

Comment: **Clinical guide:**
Although we found limited evidence, there is consensus that heliotherapy is an effective option for most people with chronic plaque psoriasis.

OPTION PUVA

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- PUVA may improve lesions and reduce relapse, but increases the risks of photo-ageing and skin cancer.

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Benefits and harms

PUVA versus no treatment:

We found one RCT, which compared PUVA versus no treatment as a maintenance treatment. [46]

Symptom improvement

No data from the following reference on this outcome. [46]

Maintenance of remission

Maintenance with PUVA compared with no maintenance Maintenance treatment with PUVA is more effective than no maintenance at reducing relapses at 18 months in people whose psoriasis has been cleared with prior PUVA treatment (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maintenance of remission					
[46] RCT **Crossover design** **4-armed trial**	1005 people with psoriasis that had been cleared by PUVA, 831 people with plaque psoriasis, 122 people with guttate psoriasis, 25 people with erythrodermic psoriasis	**Proportion of people who relapsed , 18 months** 27% with treatment once weekly 30% with treatment every 2 weeks 34% with treatment every 3 weeks 62% with no treatment Absolute numbers not reported Pre-crossover results reported	P <0.05 for all PUVA regimens combined versus no treatment	○○○	PUVA

Quality of life

No data from the following reference on this outcome. [46]

Adverse effects

No data from the following reference on this outcome. [46]

High-dose psoralen in PUVA versus low-dose psoralen in PUVA:

We found one systematic review (search date 1999, 51 RCTs, total number of people not reported), which identified two RCTs (162 people), and we found one subsequent RCT comparing higher-dose psoralen in PUVA versus lower-dose psoralen in PUVA. [47] [48]

Symptom improvement

Different doses of psoralen in PUVA regimens compared with each other Higher doses of psoralen are more effective than lower doses at increasing clearance of lesions in people with severe psoriasis (low-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	56 people with extensive chronic plaque psoriasis of trunk and limbs Data from 1 RCT	**Proportion of people with major improvement or full remission after 12 treatments , time of assessment not reported** 24/26 (92%) with 8-methoxsalen 40 mg in PUVA 6/30 (20%) with 8-methoxsalen 10 mg in PUVA	ARI 72% 95% CI 54% to 90%	○○○	8-methoxsalen 40 mg
[47] Systematic review	106 people with plaque, guttate, and seborrhoeic psoriasis, proportion of people with each not reported Data from 1 RCT	**Proportion of people with complete clearance , time of assessment not reported** 63/63 (100%) with 5-methoxsalen in PUVA 1.2 mg/kg 48/48 (100%) with 5-methoxsalen 0.6 mg/kg in PUVA	ARI 0 95% CI 0 to 0	⟷	Not significant
[48] RCT	46 people with moderate to severe plaque psoriasis	**Psoriasis Area and Severity Index (PASI) , time of assessment not reported** 3.3 with low-dose bath methoxsalen (1 mg/L) plus UVA 1.4 with high-dose bath methoxsalen (5 mg/L) plus UVA Treatment was given four times a week, but participants had a variable number of weeks' treatment dependent on clinical response	P <0.01 The trial was small and may not have detected small differences between regimens	○○○	high-dose bath methoxsalen

Maintenance of remission

No data from the following reference on this outcome. [47] [48]

Quality of life

No data from the following reference on this outcome. [47] [48]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[48] RCT	46 people with moderate to severe plaque psoriasis	**Moderate phototoxic erythema** 4/20 (20%) with low-dose bath methoxsalen (1 mg/L) plus UVA 4/21 (19%) with high-dose bath methoxsalen (5 mg/L) plus UVA Other adverse effects, reported with high-dose methoxsalen PUVA only, included polymorphic light eruption and pruritus	Significance not assessed		

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Comparison of different oral psoralens in PUVA regimens:

We found no systematic reviews or RCTs that reported clinical outcomes.

Comparison of different topical psoralens in PUVA regimens:

We found no systematic reviews or RCTs that reported clinical outcomes.

Comparison of different formulations of the same oral psoralen in PUVA regimens:

We found one systematic review (search date 1999, 51 RCTs, total number of people not reported) which identified one RCT comparing different formulations of the same oral psoralen in PUVA regimens. [47]

Symptom improvement

Different formulations of the same oral psoralen in PUVA regimens compared with each other Liquid and crystalline forms of oral 8-methoxsalen are equally effective at increasing the proportion of people with severe psoriasis who have a marked improvement or clearance of lesions (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	47 people with plaque, pustular, or erythrodermic psoriasis affecting more than 20% of body surface; proportion of people with chronic plaque psoriasis not reported Data from 1 RCT	**Proportion of people with marked improvement or clearance , time of assessment not reported** 20/25 (80%) with liquid oral 8-methoxsalen in PUVA 12/22 (55%) with crystalline oral 8-methoxsalen in PUVA	ARI +25% 95% CI –1% to +51%	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

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Oral versus bath psoralen formulations in PUVA:

We found one systematic review (search date 1999, 51 RCTs, total number of people not reported) which identified 2 RCTs (137 people) comparing oral versus bath psoralen formulations in PUVA. [47]

Symptom improvement

Oral compared with bath psoralen formulations in PUVA regimens We don't know how oral psoralens and bath psoralen formulations in PUVA regimens compare at improving or clearing lesions or at reducing the need for mean cumulative UVA dose in people with severe psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	44 people with at least 10% of body surface affected by psoriasis Data from 1 RCT	**Proportion of people with psoriasis clearance , time of assessment not reported** with oral 8-methoxsalen in PUVA with bath 8-methoxsalen in PUVA Absolute results not reported	ARI 0.0 95% CI –0.28 to +0.28	⟷	Not significant
[47] Systematic review	93 people, severity of psoriasis not reported Data from 1 RCT	**Proportion of people whose psoriasis was rated as "excellent" or "good" , time of assessment not reported** with oral 8-methoxsalen with bath trioxsalen Absolute results not reported	ARI –0.02 for oral 8-methoxsalen *v* bath trioxsalen 95% CI –0.17 to +0.1	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

High-dose versus low-dose PUVA:

We found one systematic review (search date 1999, 51 RCTs, total number of people not reported), which identified two RCTs (157 people) comparing the routine use of the minimal phototoxic dose of UVA versus a strategy of setting the UVA dose according to skin type. [47]

Symptom improvement

Different dose-setting strategies in PUVA regimens compared with each other We don't know whether routine use of minimal phototoxic dose of UVA at each treatment is more effective than a strategy of setting the UVA dose ac-

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cording to skin type at improving clearance of lesions, or at reducing the need for mean cumulative UVA dose, in people with severe psoriasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	74 people with chronic plaque psoriasis covering at least 8% of body surface Data from 1 RCT	**Proportion of people with psoriasis clearance , time of assessment not reported** with minimal phototoxic dose with skin type-adjusted dose Absolute results not reported	ARI +0.03 with minimal phototoxic dose *v* skin type-adjusted dose 95% CI –0.14 to 0.20	⟷	Not significant
[47] Systematic review	83 people with psoriasis affecting at least 10% of body surface Data from 1 RCT	**Proportion of people with psoriasis clearance , 6 weeks** with minimal phototoxic dose with skin type-adjusted dose Absolute results not reported	ARI –0.03 for minimal phototoxic dose *v* skin type-adjusted dose 95% CI –0.18 to +0.12	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

PUVA versus PUVB:

We found one systematic review (search date 1999, 51 RCTs, total number of people not reported), which identified one RCT comparing PUVA versus psoralen plus narrowband UVB (PNBUVB). [47]

Symptom improvement

PUVA compared with PUVB We don't know how PUVA and PUVB compare at clearing lesions in people with severe psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[47] Systematic review	100 people with plaque psoriasis, severity not reported Data from 1 RCT	**Clearance of exposed lesions** with PUVA with PNBUVB Absolute results not reported	ARI –12% 95% CI –28% to +4%	⟷	Not significant

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Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

PUVA versus other topical or systemic treatments (dithranol, tar, vitamin D analogues, corticosteroids, and fish oil):

We found one systematic review (search date 1999, 51 RCTs, total number of people not reported), which identified 1 RCT (224 people), comparing PUVA versus dithranol treatment. [47]

Symptom improvement

PUVA compared with dithranol PUVA may be modestly more effective than dithranol at clearing lesions in people with severe psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[47] Systematic review	224 people Data from 1 RCT	**Proportion of people not cleared of psoriasis , time of assessment not reported** 9% with PUVA 18% with dithranol Absolute results not reported	P >0.05	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

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No data from the following reference on this outcome. [47]

PUVA versus UVB:
See option on UVB, p 44 .

PUVA plus vitamin D analogues versus PUVA alone:
See option on adding calcipotriol (topical) to PUVA or UVB, p 92 .

PUVA plus oral retinoids versus PUVA alone:
See option on adding oral retinoids to PUVA, p 90 .

Further information on studies

Comment:

Chronic toxicity:
The best evidence on chronic toxicity comes from an ongoing study of more than 1300 people who first received PUVA treatment in 1975. [49] The study found a dose-dependent increased risk of squamous cell carcinoma, basal cell carcinoma, and possibly malignant melanoma compared with the risk in the general population. After less than 15 years, about one quarter of people exposed to 300 or more treatments of PUVA had at least one squamous cell carcinoma of the skin, with particularly high risk in people with skin types I and II. A systematic review (search date 1998) of eight additional studies has confirmed the findings concerning squamous cell carcinoma. [50] A combined analysis of two cohort studies (944 people treated with bath PUVA) found no increase in the risk of squamous cell carcinoma after a mean follow-up of 14.7 years (standardised incidence ratio 1.1, 95% CI 0.2 to 3.2), suggesting that bath PUVA is possibly safer than conventional PUVA. [51] Premature photo-ageing is another expected adverse effect. In people who wear UVA-opaque glasses for 24 hours after psoralen ingestion, the risk of cataract development seems negligible.

Clinical guide:
There is consensus that PUVA is effective for clearance of psoriasis. People receiving PUVA should be closely monitored for acute toxicity and long-term cutaneous carcinogenic effects. We have considered PUVA as a single treatment because psoralens are used to increase sensitivity to ultraviolet light, and because, without ultraviolet light, they are not effective as a treatment. This is in comparison with other listed combination treatments, where either intervention used in combination is effective alone.

OPTION ULTRAVIOLET B (UVB)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Ultraviolet B (UVB) may improve lesions and reduce relapse, but increases the risks of photo-ageing and skin cancer.

Benefits and harms

UVB versus no UVB:
We found no RCTs comparing UVB versus no treatment for psoriasis clearance. We found two RCTs that evaluated UVB versus no treatment for maintenance treatment. [52] [53] For further comment and information from observational studies on harms, see comment.

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Symptom improvement

No data from the following reference on this outcome. [52] [53]

Maintenance of remission

Maintenance with UVB compared with no maintenance We don't know whether maintenance treatment with UVB is more effective than no maintenance at reducing relapses at 6–12 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maintenance of remission					
[52] RCT	104 people with initial clearance of symptoms	**Proportion of people still clear of symptoms , 181 days** >50% with weekly UVB 28% with no UVB Absolute numbers not reported	RR 0.67 for relapse 95% CI 0.41 to 0.92	●○○	UVB
[53] RCT	46 people with 75% reduction in initial Psoriasis Area and Severity Index [PASI] score for plaque psoriasis (complete trial included 42 people with guttate or plaque psoriasis) Subgroup analysis	**Proportion of people with <50% of severity of pre-treatment state , 12 months** 8/14 (57%) with 12 sessions of narrowband UVB over 2 months 3/18 (17%) with no maintenance treatment	P = 0.31 The RCT was small, and randomised using toss of a coin. It is likely to have been underpowered to detect clinically important differences between groups	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [52] [53]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] RCT	46 people with 75% reduction in initial Psoriasis Area and Severity Index [PASI] score for plaque psoriasis (complete trial included 42 people with guttate or plaque psoriasis) Subgroup analysis	**Adverse effects** with 12 sessions of narrowband UVB over 2 months with no maintenance treatment Absolute results not reported The RCT reported that erythema and pruritus were the most common adverse effects, but did not report differences between groups	The RCT was small, and randomised using toss of a coin. It is likely to have been underpowered to detect clinically important differences between groups		

No data from the following reference on this outcome. [52]

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Narrowband UVB versus broadband UVB:

We found one systematic review of people with severe psoriasis [47] (search date 1999, 3 small crossover RCTs, 146 people) comparing narrowband versus broadband UVB, and one subsequent RCT. [54] The review reported that it was unable to extract data from the trials about response rates.

Symptom improvement

Narrowband UVB compared with broadband UVB Narrowband UVB and broadband UVB may be equally effective at increasing clearance rates (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[54] RCT	100 people	**Proportion of people clear of psoriasis at the end of treatment , time of assessment not reported** 28/50 (56%) with narrowband UVB 20/50 (40%) with selective broadband UVB	OR 2.00 95% CI 0.87 to 4.62	⟷	Not significant

No data from the following reference on this outcome. [47]

Maintenance of remission

No data from the following reference on this outcome. [47] [54]

Quality of life

No data from the following reference on this outcome. [47] [54]

Adverse effects

No data from the following reference on this outcome. [47] [54]

Twice-weekly versus three times-weekly narrowband UVB:

We found no systematic review but found one RCT. [55]

Symptom improvement

Narrowband UVB twice weekly compared with three times weekly Twice-weekly and three times-weekly administration of ultraviolet light are equally effective at increasing clearance rates, but twice-weekly treatment prolongs the time to reach clearance in people with mild to moderate psoriasis (moderate-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[55] RCT	113 people with mild to moderate psoriasis	**Clearance rates** 40/58 (69%) with twice-weekly UVB 44/55 (80%) with 3 times-weekly UVB	P = 0.21	⟷	Not significant
[55] RCT	113 people with mild to moderate psoriasis	**Mean time to clearance** 88 days with twice-weekly UVB 58 days with 3 times-weekly UVB	P <0.0001	○○○	3 times-weekly UVB

Maintenance of remission

No data from the following reference on this outcome. [55]

Quality of life

No data from the following reference on this outcome. [55]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[55] RCT	113 people with mild to moderate psoriasis	**Proportion of people with grade 2 erythema** 56% with twice-weekly UVB 31% with 3 times-weekly UVB Absolute numbers not reported	P = 0.007	○○○	twice-weekly UVB

UVB (broadband or narrowband) versus PUVA:

We found no systematic review but found three RCTs comparing UVB versus PUVA. [56] [57] [58]

Symptom improvement

UVB (broadband or narrowband) compared with PUVA We don't know how UVB (broadband or narrowband) and PUVA compare at clearing lesions in people with moderate to severe psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[56] RCT	183 people with moderate to severe psoriasis	**Clearance rates , time of assessment not reported** 88% with PUVA 80% with broadband UVB	RR 0.62 95% CI 0.29 to 1.22	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported			
[57] RCT	100 people	**Clearance rates , time of assessment not reported** 84% with PUVA 63% with narrowband UVB Absolute numbers not reported	OR 3.0 95% CI 1.2 to 7.8	●●○	PUVA
[58] RCT	88 people with chronic plaque psoriasis with skin types from I to IV Subgroup analysis	**Proportion clear of psoriasis at the end of the treatment period , time of assessment not reported** 31/37 (84%) with PUVA 22/34 (65%) with UVB People continued to have treatments until their psoriasis had cleared, up to a maximum of 30 sessions. Clearance of psoriasis reported for one subgroup only; no overall results were reported	P = 0.02	○○○	PUVA

Maintenance of remission

No data from the following reference on this outcome. [56] [57] [58]

Quality of life

No data from the following reference on this outcome. [56] [57] [58]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Erythema					
[56] RCT	183 people with moderate to severe psoriasis	**Erythema during clearance treatment** 84 with UVB 48 with PUVA	Significance not assessed		
[57] RCT	100 people	**Erythema , time of assessment not reported** 73% with UVB 35% with PUVA	Significance not assessed		
[58] RCT	88 people with chronic plaque psoriasis with skin types from I to IV Subgroup analysis	**Erythema** 21/43 (43%) with PUVA 10/45 (22%) with UVB	Significance not assessed		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blistering					
[56] RCT	183 people with moderate to severe psoriasis	**Blistering during clearance treatment** 6 with UVB 15 with PUVA	Significance not assessed		
Itching					
[56] RCT	183 people with moderate to severe psoriasis	**Itching during clearance treatment** 25 with UVB 53 with PUVA	Significance not assessed		
Nausea					
[56] RCT	183 people with moderate to severe psoriasis	**Nausea during clearance treatment** 0 with UVB 7 with PUVA	Significance not assessed		

UVB or PUVA versus topical or systemic treatments:
See option on PUVA, p 37 .

UVB phototherapy plus balneotherapy:
See option on phototherapy plus balneotherapy, p 50 .

UVB phototherapy plus balneotherapy versus balneotherapy alone:
See option on phototherapy plus balneotherapy, p 50 .

UVB plus emollients:
See option on UVB plus emollients, p 95 .

UVB plus vitamin D analogues:
See option on adding calcipotriol (topical) to PUVA or UVB, p 92 .

UVB plus oral retinoids:
See option on adding oral retinoids to PUVA, p 90 .

Goeckerman treatment (which uses UVB):
See option on Goeckerman treatment, p 94 .

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Ingram regimen (which uses UVB):

See option on Ingram regimen, p 89 .

Further information on studies

Comment: UVB radiation may increase photo-ageing and the risk of skin cancer. One systematic review (search date 1996) estimated that the excess annual risk of non-melanoma skin cancer associated with UVB radiation was likely to be less than 2%. [59] Another systematic review (search date 2002, 11 prospective and retrospective cohort or case control studies, 3400 people, most with psoriasis) also found limited evidence (by comparing skin cancer rates in people who had received UVB with expected rates in people who had not) that UVB treatment did not increase the risk of skin cancer over about 25 years' follow-up (significance not reported for most studies). [60]

Broadband UVB covers the UVB spectrum from 280 nm to 320 nm in wavelength, whereas narrow-band UVB covers only a part of the UVB spectrum, with a peak at about 311 nm.

Clinical guide:
We found insufficient evidence from RCTs on the effects of UVB. However, consensus regards the treatment as effective.

OPTION PHOTOTHERAPY PLUS BALNEOTHERAPY

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We found no RCT evidence on the effects of phototherapy plus balneotherapy.

Benefits and harms

Phototherapy plus balneotherapy versus either intervention alone:

We found one systematic review (search date 2000) [61] and one subsequent RCT [62] assessing phototherapy plus salt water baths. The systematic review identified three small RCTs, [61] none of which met our inclusion criteria, owing to lack of either blinding or allocation concealment.

Symptom improvement

Phototherapy plus balneotherapy compared with phototherapy alone We don't know how phototherapy plus balneotherapy (saline spa water) and phototherapy alone compare at improving psoriasis severity scores at 21 days in people with chronic plaque psoriasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[62] RCT **3-armed trial**	71 people with Psoriasis Area and Severity Index (PASI) score >10 The remaining arm evaluated saline spa water balneotherapy alone	**Change in PASI score , 21 days** –55% with phototherapy plus saline spa water balneotherapy –64% with phototherapy alone	P value not reported for combination treatment *v* phototherapy alone		
[62] RCT **3-armed trial**	71 people with Psoriasis Area and Severity Index (PASI) score >10	**Change in PASI score , 21 days** –55% with phototherapy plus saline spa water balneotherapy –29% with saline spa water balneotherapy alone	P <0.001 for combination *v* balneotherapy alone	○○○	phototherapy plus balneotherapy

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated phototherapy alone				

Maintenance of remission

No data from the following reference on this outcome. [62]

Quality of life

No data from the following reference on this outcome. [62]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[62] RCT **3-armed trial**	71 people with Psoriasis Area and Severity Index (PASI) score >10	**Adverse effects** with phototherapy plus saline spa water balneotherapy with saline spa water balneotherapy alone with phototherapy alone Adverse effects not reported separately for each group. Four people withdrew because of adverse effects: three had skin irritation, and one a chest infection	Not reported		

Further information on studies

Comment: **Clinical guide:**
Because several trigger and perpetuating factors for psoriasis have been recognised (including physical trauma, acute infections, smoking, diet, and stress), disease severity might be modulated by non-drug treatments. However, we found no good evidence on the effects of phototherapy plus balneotherapy.

OPTION UVA

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We don't know whether UVA is effective at improving psoriasis as few studies were found.
- Exposure to ultraviolet light has been associated with adverse effects.

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Benefits and harms

UVA versus placebo or no treatment:

We found one small RCT comparing UVA sun bed treatment versus placebo (visible light). [63]

Symptom improvement

UVA compared with placebo UVA sun bed treatment may be more effective than visible light at improving psoriasis severity scores in people with mild to moderate chronic stable plaque psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[63] RCT **3-armed trial**	38 people with mild to moderate chronic stable plaque psoriasis	**Median modified Psoriasis Area and Severity Index (PASI) score** 3.9 with UVA 4.2 with placebo (visible light) In each person, one side of the body was exposed to UVA light and the other to placebo	P = 0.04	○○○	UVA

Maintenance of remission

No data from the following reference on this outcome. [63]

Quality of life

No data from the following reference on this outcome. [63]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[63] RCT **3-armed trial**	38 people with mild to moderate chronic stable plaque psoriasis	**Skin irritation** with UVA with placebo (visible light) One person receiving placebo (visible light) treatment felt a burning sensation on the side of the body during treatment In each person, one side of the body was exposed to UVA light and the other to placebo			

Further information on studies

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Comment: Exposure to ultraviolet light has been associated with adverse effects (see UVB, p 44 and PUVA, p 37).

QUESTION What are the effects of systemic drug treatments for chronic plaque psoriasis?

OPTION T CELL-TARGETED THERAPIES (ALEFACEPT)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Alefacept may improve lesions, but long-term effects are unknown.
- Alefacept is a relatively new drug for the treatment of psoriasis, and there is limited evidence regarding the possibility of long-term or rare severe adverse effects.

Benefits and harms

Alefacept versus placebo:

We found three RCTs, described in at least six publications. [64] [65] [66] [67] [68] [69] For further information on harms, see comment.

Symptom improvement

Alefacept compared with placebo Alefacept is more effective than placebo at increasing the proportion of people with a reduction in psoriasis severity scores at 12 weeks (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[64] RCT **4-armed trial**	229 people with plaque psoriasis involving at least 10% of body surface	**Proportion of people with at least a 75% decrease in baseline Psoriasis Area and Severity Index (PASI) score , 12 weeks after the end of treatment** 33% with alefacept 0.025 mg/kg 31% with alefacept 0.075 mg/kg 19% with alefacept 0.150 mg/kg 11% with placebo Absolute results reported graphically	P = 0.02 for any dose *v* placebo	○○○	alefacept
[66] RCT	553 people with plaque psoriasis involving at least 10% of body surface area	**Proportion of people with at least a 75% decrease in baseline PASI score , 2 weeks after treatment** 53/367 (14%) with intravenous alefacept 7.5 mg once weekly for 12 weeks 7/186 (4%) with placebo for 12 weeks	P <0.001	○○○	alefacept
[68] RCT **3-armed trial**	507 people with chronic plaque psoriasis involving a mean 21% of body surface area	**Proportion of people with at least a 75% decrease in baseline PASI score , 12 weeks after the end of treatment** 28% with intramuscular alefacept 10 mg once weekly 33% with intramuscular alefacept 15 mg once weekly 13% with placebo once weekly Absolute numbers not reported	Reported as significant P <0.001 for alefacept at either dose *v* placebo	○○○	alefacept

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Maintenance of remission

No data from the following reference on this outcome. [64] [65] [66] [67] [68] [69]

Quality of life

Alefacept compared with placebo Alefacept may be more effective at improving quality-of-life scores (Dermatology Life Quality Index) at 12 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[65] RCT **4-armed trial**	229 people with plaque psoriasis involving at least 10% of body surface area Further report of reference [64]	**Mean improvement from baseline on Dermatology Life Quality Index (DLQI) scale (from 0 to 30) , 12 weeks after the end of treatment** 4.0 with alefacept 0.025 mg/kg 4.4 with alefacept 0.075 mg/kg 3.2 with alefacept 0.150 mg/kg 1.7 with placebo Absolute results reported graphically	P = 0.04 for alefacept at any dose *v* placebo However, the clinical importance of these results is difficult to assess (see further information on studies)	○○○	alefacept at any dose
[67] RCT	553 people with plaque psoriasis involving at least 10% of body surface area Further report of reference [66]	**Mean improvement from baseline on DLQI scale (from 0 to 30) , 2 weeks after treatment** 4.4 with intravenous alefacept 7.5 mg once weekly for 12 weeks 1.8 with placebo for 12 weeks	P <0.0001 However, the clinical importance of these results is difficult to assess	○○○	alefacept
[69] RCT **3-armed trial**	507 people with chronic plaque psoriasis involving a mean 21% of body surface area Further report of reference [68] The remaining arm evaluated intramuscular alefacept 10 mg once weekly	**Mean improvement in DLQI score from baseline (scale from 0 to 30) , 2 weeks after end of treatment** 4.9 with intramuscular alefacept 15 mg once weekly 2.7 with placebo once weekly Absolute numbers not reported	P <0.001 for alefacept (15 mg) *v* placebo However, the clinical importance of these results is difficult to assess	○○○	alefacept 15 mg
[69] RCT **3-armed trial**	507 people with chronic plaque psoriasis involving a mean 21% of body surface area Further report of reference [68] The remaining arm evaluated intramuscular alefacept 15 mg once weekly	**Mean improvement in DLQI score from baseline (scale from 0 to 30) , 2 weeks after end of treatment** 3.8 with intramuscular alefacept 10 mg once weekly 2.7 with placebo once weekly	P reported as not significant for alefacept 10 mg *v* placebo However, the clinical importance of these results is difficult to assess	⟷	Not significant

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[64] RCT **4-armed trial**	229 people with plaque psoriasis involving at least 10% of body surface	**Accidental injury** 13% with alefacept (0.025 mg/kg, 0.075 mg/kg, and 0.0150 mg/kg) 5% with placebo Absolute numbers not reported	Significance not assessed		
[64] RCT **4-armed trial**	229 people with plaque psoriasis involving at least 10% of body surface	**Dizziness** 9% with alefacept (0.025 mg/kg, 0.075 mg/kg, and 0.0150 mg/kg) 2% with placebo Absolute numbers not reported	Significance not assessed		
[64] RCT **4-armed trial**	229 people with plaque psoriasis involving at least 10% of body surface	**Nausea** 6% with alefacept (0.025 mg/kg, 0.075 mg/kg, and 0.0150 mg/kg) 0% with placebo Absolute numbers not reported	Significance not assessed		
[64] RCT **4-armed trial**	229 people with plaque psoriasis involving at least 10% of body surface area	**Cough** 5% with alefacept (0.025 mg/kg, 0.075 mg/kg, and 0.0150 mg/kg) 0% with placebo	Significance not assessed		
[68] RCT **3-armed trial**	507 people with chronic plaque psoriasis involving a mean 21% of body surface area	**Headache** 19% with alefacept (10 mg and 15 mg) 15% with placebo Absolute numbers not reported	Significance not assessed		
[68] RCT **3-armed trial**	507 people with chronic plaque psoriasis involving a mean 21% of body surface area	**Pruritus** 16% with alefacept (10 mg and 15 mg) 10% with placebo Absolute numbers not reported	Significance not assessed		
[68] RCT **3-armed trial**	507 people with chronic plaque psoriasis involving a mean 21% of body surface area	**Infection** 16% with alefacept (10 mg and 15 mg) 11% with placebo Absolute numbers not reported	Significance not assessed		

Further information on studies

[65] The clinical importance of these results is difficult to assess. People who achieved a 50% or greater and 75% or greater reduction in PASI reported similar improvements in quality of life, which were significantly greater than improvements reported by people with higher PASI scores.

Comment: One integrated analysis of 13 clinical trials (including 6 double-blind RCTs and 5 open label studies) found that the most commonly reported adverse events during alefacept treatment were headache (at least 14%), nasopharyngitis (7%–25%), influenza (up to 8%), upper respiratory tract infection

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(at least 12%), and pruritus. Less than 1% of people developed serious infections, and the analysis found no clear relation with CD4+ T lymphocyte counts. [70] The rate of discontinuation due to adverse effects ranged from 0%–4.8% among studies, and did not increase with repeated exposure. [70]

Harms alerts:
The FDA issued a Medical Product Safety Alert to inform people that alefacept reduces CD4+ T lymphocyte counts and should not be given to people with HIV. [71]

Clinical guide:
Alefacept is a recombinant protein that binds to CD2 receptors on memory effector T lymphocytes. Like efalizumab, it is a new drug for the treatment of psoriasis. The evidence on the effects of T cell-targeted treatments in people with plaque psoriasis is still limited. Further comparative studies are needed to predict precisely how these drugs will fit into current psoriasis management.

OPTION T CELL-TARGETED THERAPIES (EFALIZUMAB)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Efalizumab may improve lesions, but long-term effects are unknown.
- Efalizumab is a relatively new drug for the treatment of psoriasis, and there is limited evidence regarding the possibility of long-term or rare severe adverse effects.

Benefits and harms

Efalizumab versus placebo:

We found five RCTs, published in seven papers. [72] [73] [74] [75] [76] [77] [78]

Symptom improvement

Efalizumab compared with placebo Efalizumab is more effective than placebo at increasing the proportion of people who achieve an improvement in psoriasis severity scores at 12 weeks in moderate to severe psoriasis (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[72] RCT **3-armed trial**	597 people with moderate to severe psoriasis	**Proportion of people with at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score , 12 weeks** 28% with efalizumab 2 mg/kg 22% with efalizumab 1 mg/kg 5% with placebo Absolute numbers not reported	P <0.001 for efalizumab at either dose *v* placebo	○○○	efalizumab
[73] RCT	556 people with moderate to severe psoriasis	**Proportion of people who achieved at least a 75% improvement in PASI score , 12 weeks** 98/369 (27%) with efalizumab 8/187 (4%) with placebo	ARI 22.3% 95% CI 15.8% to 29.5% NNT 4 95% CI 3 to 6	○○○	efalizumab
[73] RCT	556 people with moderate to severe psoriasis	**Mean improvement in itching** +38% with efalizumab –0.2% with placebo	P <0.001	○○○	efalizumab
[73] RCT	556 people with moderate to severe psoriasis	**Mean improvement in Psoriasis Symptom Assessment frequency subscale** 48% with efalizumab 18% with placebo	ARI 22.3% 95% CI 15.8% to 29.5% NNT 4 95% CI 3 to 6	○○○	efalizumab

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[73] RCT	556 people with moderate to severe psoriasis	**Mean improvement in Psoriasis Symptom Assessment severity subscale , 12 weeks** 47% with efalizumab 17% with placebo	P <0.001	○○○	efalizumab
[74] RCT **3-armed trial**	498 people	**Proportion of people who achieved at least a 75% improvement in PASI score , 12 weeks** 39% with efalizumab 1 mg/kg 27% with efalizumab 2 mg/kg 2% with placebo Absolute numbers not reported	P <0.001 for efalizumab at either dose *v* placebo	○○○	efalizumab
[74] RCT	183 people who did not respond to initial treatment regimen Subgroup analysis	**Proportion of people who achieved at least a 75% improvement in PASI score , at 24 weeks** 20% with efalizumab 7% with placebo Absolute numbers not reported	P = 0.018	○○○	efalizumab
[75] RCT	793 people with moderate to severe plaque psoriasis affecting up to 10% of body area	**Proportion of people with 75% or greater improvement in PASI scores , week 12** 31% with efalizumab 4% with placebo Absolute numbers not reported People randomised in a 2:1 ratio to efalizumab:placebo	P <0.0001 OR 10.5 95% CI 5.6 to 19.8	○○○	efalizumab
[75] RCT	526 high-need people — defined as people for whom at least two systemic treatments were unsuitable because of lack of efficacy, intolerance, or contraindication Subgroup analysis	**Proportion of high-need people with 75% or greater improvement in PASI scores , week 12** 29% with efalizumab 3% with placebo Absolute numbers not reported People randomised in a 2:1 ratio to efalizumab:placebo in original study	P <0.0001 OR 14.9 95% CI 5.9 to 37.4	○○○	efalizumab
[78] RCT	686 people with moderate to severe psoriasis	**Proportion of people with at least a 75% improvement in PASI score , 12 weeks** 24% with efalizumab 3% with placebo	P <0.001	○○○	efalizumab

Maintenance of remission

No data from the following reference on this outcome. [72] [73] [74] [75] [76] [77] [78]

Quality of life

Efalizumab compared with placebo Efalizumab is more effective than placebo at improving quality-of-life scores (Dermatology Life Quality Index) at 12 weeks (moderate-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[73] RCT	556 people with moderate to severe psoriasis	**Mean improvement in Dermatology Life Quality Index (DLQI) score , 12 weeks** 47% with efalizumab 14% with placebo Absolute numbers not reported	P <0.001	○○○	efalizumab
[77] RCT	793 people with moderate to severe plaque psoriasis affecting up to 10% of body area Further report of reference [75]	**DLQI score improvement from baseline (scale from 0–30) , 12 weeks** 5.7 with efalizumab 2.3 with placebo People randomised in a 2:1 ratio to efalizumab:placebo	P <0.01	○○○	efalizumab
[77] RCT	526 high-need people (defined as people for whom at least two systemic treatments were unsuitable because of lack of efficacy, intolerance, or contraindication) Further report of reference [75] Subgroup analysis	**DLQI score improvement from baseline (scale from 0–30) , 12 weeks** 5.4 with efalizumab 2.3 with placebo People randomised in a 2:1 ratio to efalizumab:placebo in original study	P <0.01	○○○	efalizumab

No data from the following reference on this outcome. [72] [74] [75] [76]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Skin adverse events					
[75] RCT	793 people with moderate to severe plaque psoriasis affecting up to 10% of body area	**Psoriatic erythroderma** 9/529 (1.7%) with efalizumab 1/264 (0.4%) with placebo	Reported as significant		
[75] RCT	793 people with moderate to severe plaque psoriasis affecting up to 10% of body area	**Diagnosed erythema multiforme** 1/529 (0.2%) with efalizumab 0/264 (0%) with placebo	Reported as significant	○○○	efalizumab
Adverse effects (other than skin adverse effects)					
[75] RCT	793 people with moderate to severe plaque psoriasis affecting up to 10% of body area	**Proportion reporting at least one adverse event** 72% with efalizumab 60% with placebo The most common adverse events with efalizumab were headache, rigor, pyrexia, and myalgia	Significance not assessed		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[72] RCT **3-armed trial**	597 people with moderate to severe psoriasis	**Headache** 38% with efalizumab 2 mg/kg 31% with efalizumab 1 mg/kg 5% with placebo Absolute numbers not reported	P <0.05 for both efalizumab groups *v* placebo	○○○	placebo
[78] RCT	686 people with moderate to severe psoriasis	**Headache** 31% with efalizumab 17% with placebo Absolute numbers not reported	Significance not assessed		
[72] RCT **3-armed trial**	597 people with moderate to severe psoriasis	**Pain** 12% with efalizumab 2 mg/kg 15% with efalizumab 1 mg/kg 3% with placebo Absolute numbers not reported	P <0.001 for both efalizumab groups *v* placebo	○○○	placebo
[72] RCT **3-armed trial**	597 people with moderate to severe psoriasis	**Back pain** 16% with efalizumab 2 mg/kg 4% with efalizumab 1 mg/kg 1% with placebo Absolute numbers not reported	P <0.05 for both efalizumab groups *v* placebo	○○○	placebo
[78] RCT	686 people with moderate to severe psoriasis	**Generalised pain** 7% with efalizumab 4% with placebo Absolute numbers not reported	Signficance not assessed		
[72] RCT **3-armed trial**	597 people with moderate to severe psoriasis	**Chills** 13% with efalizumab 2 mg/kg 16% with efalizumab 1 mg/kg 2% with placebo Absolute numbers not reported	P <0.05 for both efalizumab groups *v* placebo	○○○	placebo
[78] RCT	686 people with moderate to severe psoriasis	**Chills** 12% with efalizumab 4% with placebo Absolute numbers not reported	Significance not assessed		
[72] RCT **3-armed trial**	597 people with moderate to severe psoriasis	**Fever** 12% with efalizumab 2 mg/kg 11% with efalizumab 1 mg/kg 5% with placebo Absolute results not reported	P <0.05 for both efalizumab groups *v* placebo	○○○	placebo
[78] RCT	686 people with moderate to severe psoriasis	**Influenza syndrome** 10% with efalizumab 6% with placebo Absolute numbers not reported	Significance not assessed		
[78] RCT	686 people with moderate to severe psoriasis	**Nausea** 9% with efalizumab 5% with placebo	Significance not assessed		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported			
[78] RCT	686 people with moderate to severe psoriasis	**Asthenia** 6% with efalizumab 2% with placebo Absolute numbers not reported	Significance not assessed		

Further information on studies

[72] The RCT performed a 12-week open extension phase in 516 people who had achieved a less than 75% improvement in PASI over the initial 12-week treatment.

[76] All participants received efalizumab. After 24 weeks, 44% of people had at least a 75% improvement in PASI score. However, only a subset completed the 24-week treatment period.

Comment: Rebound flares of psoriasis have been reported in people taking efalizumab. [79]

Harms alerts:
The FDA issued a warning about Raptiva (efalizumab) to healthcare professionals and patients due to reports of immune-mediated haemolytic anaemia, and warnings regarding post-marketing reports of thrombocytopenia and serious infections including necrotising fasciitis, tuberculous pneumonia, bacterial sepsis with seeding of distant sites, severe pneumonia with neutropenia, and worsening of infection (e.g., cellulitis, pneumonia) despite antimicrobial treatment. [80]

Raptiva (efalizumab) is to be withdrawn from the US market by June 2009, owing to a potential risk of developing progressive multifocal leukoencephalopathy (http://www.fda.gov).

Clinical guide:
Efalizumab is a humanised monoclonal antibody that targets the CD11a component of lymphocyte function-associated antigen-1. It is a relatively new drug for the treatment of psoriasis. The evidence on the effects of T cell-targeted treatments is still limited. Further comparative studies are needed to predict precisely how these drugs will fit into current psoriasis management.

OPTION CYTOKINE BLOCKING AGENTS (ETANERCEPT)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Etanercept may improve lesions, but long-term effects are unknown.
- Etanercept is a relatively new drug for the treatment of psoriasis, and there is limited evidence regarding the possibility of long-term or rare but severe adverse events.

Benefits and harms

Etanercept versus placebo:

We found no systematic review. We found four RCTs, reported in six publications. [81] [82] [83] [84] [85] [86]

Symptom improvement

Etanercept compared with placebo Etanercept is more effective than placebo at increasing the proportion of people with improved psoriasis severity scores at 12 to 24 weeks in people with moderate to severe psoriasis (moderate-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[81] RCT	112 people with plaque psoriasis involving at least 10% of body surface area	**Proportion of people with at least a 75% improvement in Psoriasis Area and Severity Index (PASI) score , at 24 weeks** 32/57 (56%) with subcutaneous etanercept (25 mg twice weekly) 3/55 (5%) with placebo	P <0.001	○○○	etanercept
[82] RCT **4-armed trial**	652 people with plaque psoriasis involving at least 10% of body surface area	**Proportion of people who achieved at least a 75% improvement in PASI score , 12 weeks** 81/164 (49%) with high-dose etanercept (50 mg twice weekly) 55/162 (34%) with medium-dose etanercept (25 mg twice weekly) 23/160 (14%) with low-dose etanercept (25 mg once weekly) 6/166 (4%) with placebo	P reported as <0.001 for each dose of etanercept *v* placebo	○○○	etanercept
[84] RCT **3-armed trial**	583 people with moderate to severe plaque psoriasis	**Proportion of people with at least a 75% improvement in PASI score , 12 weeks** 49% with etanercept 50 mg 34% with etanercept 25 mg 3% with placebo Absolute numbers not reported	P <0.001 for comparison of each dose of etanercept *v* placebo	○○○	etanercept
[86] RCT	618 people with moderate to severe psoriasis	**Proportion of people with at least 75% improvement in PASI score , 12 weeks** 147/311 (47%) with etanercept 15/306 (5%) with placebo	Difference: 42 95% CI 36% to 48% P <0.0001	○○○	etanercept

No data from the following reference on this outcome. [83] [85]

Maintenance of remission

No data from the following reference on this outcome. [81] [82] [83] [84] [85] [86]

Quality of life

Etanercept compared with placebo Etanercept is more effective than placebo at improving quality-of-life scores (Dermatology Life Quality Index) at 12 weeks (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[83] RCT **4-armed trial**	652 people with plaque psoriasis involving at least 10% of body surface area	**Mean improvement in Dermatology Life Quality Index (DLQI) score , 12 weeks** 61% with high-dose etanercept (50 mg twice weekly)	P reported as <0.001 for each dose of etanercept *v* placebo	○○○	etanercept

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Further report of reference [82]	51% with medium-dose etanercept (25 mg twice weekly) 47% with low-dose etanercept (25 mg once weekly) 11% with placebo			
[85] RCT **3-armed trial**	583 people with moderate to severe plaque psoriasis Further report of reference [84]	**Proportion with clinically meaningful improvement in quality of life (defined as reduction of at least 5 points or a score of 0 in DLQI) , 12 weeks** 150/194 (77%) with etanercept 50 mg 140/194 (72%) with etanercept 25 mg 50/193 (26%) with placebo Absolute numbers not reported	P <0.0001 for comparison of either dose of etanercept *v* placebo	○○○	etanercept
Depression scores					
[86] RCT	618 people with moderate to severe psoriasis	**Beck Depression Inventory (BDI) score improvement mean difference , 12 weeks** with etanercept with placebo Absolute results reported graphically	Mean difference 1.8 95% CI 0.6 to 2.9 P = 0.0001	○○○	etanercept
[86] RCT	618 people with moderate to severe psoriasis	**Hamilton Depression Rating Scale (HAM-D) score improvement , 12 weeks** 1.5 with etanercept 0.4 with placebo	Mean difference 1.2 95% CI 0.4 to 1.9 P = 0.0012	○○○	etanercept
[86] RCT	618 people with moderate to severe psoriasis	**Functional Assessment of Chronic Illness Therapy-Fatigue (FACITF) score improvement , 12 weeks** 5.0 with etanercept 1.9 with placebo Absolute results reported graphically	Mean difference 3.0 95% CI 1.6 to 4.5 P <0.0001	○○○	etanercept

No data from the following reference on this outcome. [81] [83] [84]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Injection site reactions					
[81] RCT	112 people with plaque psoriasis involving at least 10% of body surface area	**Mild injection-site reactions** 9% with etanercept 0% with placebo For full details see also further information about studies	Significance not assessed		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[82] RCT **4-armed trial**	652 people with plaque psoriasis involving at least 10% of body surface area	**Injection-site reactions** 13% with high-dose etanercept (50 mg twice weekly) 17% with medium-dose etanercept (25 mg twice weekly) 11% with low-dose etanercept (25 mg once weekly) 7% with placebo	Signficance not assessed		
[86] RCT	618 people with moderate to severe psoriasis	**At least 1 injection-site reaction** 34/312 (11%) with etanercept 2/306 (1%) with placebo	Significance not assessed		
Adverse effects (other than injection site reactions)					
[81] RCT	112 people with plaque psoriasis involving at least 10% of body surface area	**Adverse effects** with etanercept with placebo The RCT reported a similar frequency and rate of occurrence of adverse effects with etanercept and placebo			
[81] RCT	112 people with plaque psoriasis involving at least 10% of body surface area	**Peripheral oedema** 0.04 events/person-year with etanercept 0.41 events/person-year with placebo	P <0.05	○○○	etanercept
[84] RCT **3-armed trial**	583 people with moderate to severe plaque psoriasis	**Adverse effects** with etanercept 50 mg with etanercept 25 mg with placebo The RCT reported a similar frequency and rate of occurrence of adverse effects between different dosages of etanercept and placebo			
[86] RCT	618 people with moderate to severe psoriasis	**At least 1 serious adverse event** 6/312 (2%) with etanercept 3/306 (1%) with placebo	Significance not assessed		
[86] RCT	618 people with moderate to severe psoriasis	**Fatigue** 13/312 (4%) with etanercept 4/306 (1%) with placebo	Significance not assessed		
[86] RCT	618 people with moderate to severe psoriasis	**Nasopharyngitis** 22/312 (7%) with etanercept 4/306 (1%) with placebo	Significance not assessed		
[86] RCT	618 people with moderate to severe psoriasis	**Sinusitis** 11/312 (4%) with etanercept 4/306 (1%) with placebo	Significance not assessed		

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Further information on studies

[84] After 12 weeks, all groups were given open label etanercept 25 mg twice weekly for an additional 12 weeks, and the RCT reported no apparent decrease in efficacy after dose reduction, although the significance of this outcome was not reported (>75% improvement in PASI score at 24 weeks: 54% in 50 mg plus 25 mg group *v* 45% in continuous 25 mg group *v* 28% in placebo plus 25 mg group; significance assessment not reported).

Comment:

Most evidence on the safety of etanercept is from studies in people with rheumatoid arthritis or Crohn's disease. Cutaneous reactions to etanercept have been reported with a frequency of up to 5%, including reactions at the injection site and urticarial manifestations. [87] Upper respiratory tract infections have been reported with etanercept.

Harms alerts:

A drug safety alert has been issued on the risk of opportunistic fungal infections associated with TNF-alpha blockers (tumour necrosis factor alpha-blockers), which could be fatal (http://www.fda.gov). A drug safety alert has been issued on the increased risk of lymphoma and other malignancies in children and adolescents, and the risks of leukaemia and new-onset psoriasis, associated with TNF blockers (http://www.fda.gov).

Clinical guide:

Etanercept is a recombinant molecule consisting of the human tumour necrosis factor-alpha p75 receptor fused to the Fc portion of the human immunoglobulin G1 molecule. Good-quality evidence on the long-term effects of cytokine blocking agents in people with plaque psoriasis is still scarce. Further comparative studies are needed to predict precisely how these drugs will fit into current psoriasis management.

OPTION CYTOKINE BLOCKING AGENTS (INFLIXIMAB)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Infliximab may improve lesions, but long-term effects are unknown.

Benefits and harms

Infliximab versus placebo:

We found four RCTs comparing infliximab versus placebo in people with psoriais, reported in six publications. [88] [89] [90] [91] [92] [93] For further information on adverse events of infliximab, anti-tumour necrosis factor antibodies, and adalimumab from studies in people with rheumatoid arthritis, see comments. [94]

Symptom improvement

Infliximab compared with placebo Infliximab is more effective than placebo at increasing the proportion of people who achieve an improvement in psoriasis severity scores at 10 weeks in people with moderate to severe psoriasis (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis severity					
[88] RCT **3-armed trial**	33 people with moderate to severe psoriasis The remaining arm evaluated inflix-imab 5 mg/kg	**Physician's Global Assess-ment rating of good, excellent, or clear** 10/11 (91%) with infliximab 10 mg/kg 2/11 (18%) with placebo	ARI 73% for infliximab10 mg/kg 95% CI 30% to 94%	○○○	infliximab
[88] RCT **3-armed trial**	33 people with moderate to severe psoriasis The remaining arm evaluated inflix-imab 10 mg/kg	**Physician's Global Assess-ment rating of good, excellent, or clear** 9/11 (82%) with infliximab 5 mg/kg 2/11 (18%) with placebo	ARI 64% for infliximab 5 mg/kg 95% CI 20% to 89%	○○○	infliximab

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[89] RCT **3-armed trial**	249 people with severe psoriasis	**Proportion of people with at least a 75% improvement in the Psoriasis Area and Severity Index (PASI) score , 10 weeks** 71/99 (72%) with infliximab 3 mg/kg 87/99 (88%) with infliximab 5 mg/kg 3/51 (6%) with placebo	P <0.001 for either dose *v* placebo	○○○	infliximab
[91] RCT	378 people with moderate to severe psoriasis	**Response rates (at least 75% improvement in PASI score) , 10 weeks** 242/301 (80%) with infliximab 5 mg/kg at 0, 2, and 6 weeks followed by maintenance treatment every 8 weeks up to 24 weeks 2/77 (3%) with placebo People allocated to infliximab:placebo in a 4:1 allocation	P <0.001 Method of randomisation not reported	○○○	infliximab
[93] RCT **3-armed trial**	835 people with moderate to severe psorias The remaining arm evaluated infliximab 5 mg/kg given at weeks 0, 2, and 6	**Proportion of people with at least a 75% reduction in PASI score , 10 weeks** 70% with infliximab 3 mg/kg given at weeks 0, 2, and 6 2% with placebo given at weeks 0, 2, and 6	P <0.001 for infliximab 3 mg/kg *v* placebo	○○○	infliximab
[93] RCT **3-armed trial**	835 people with moderate to severe psorias The remaining arm evaluated infliximab 3 mg/kg given at weeks 0, 2, and 6	**Proportion of people with at least a 75% reduction in PASI score , 10 weeks** 76% with infliximab 5 mg/kg given at weeks 0, 2, and 6 2% with placebo given at weeks 0, 2, and 6	P <0.001 for infliximab 5 mg/kg *v* placebo	○○○	infliximab

No data from the following reference on this outcome. [94]

Maintenance of remission

No data from the following reference on this outcome. [88] [89] [90] [91] [92] [93]

Quality of life

Infliximab compared with placebo Infliximab is more effective than placebo at improving quality-of-life scores (Dermatology Life Quality Index) at 10 weeks (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[90] RCT **3-armed trial**	249 people with severe psoriasis Further report of reference [89]	**Median improvement in the Dermatology Life Quality Index (DLQI) , 10 weeks** 91% with infliximab 5 mg/kg 84% with infliximab 3 mg/kg	P <0.001 for either dose *v* placebo	○○○	infliximab

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		0% with placebo Absolute numbers not reported			
[92] RCT	378 people with moderate to severe psoriasis Further report of reference [91]	**DLQI score improvement from baseline (range: 11.8–12.7) , 10 weeks** 10.3 with infliximab 0.4 with placebo People allocated to infliximab:placebo in a 4:1 allocation	P <0.001 for improvement from baseline at 10 weeks Method of randomisation not reported	○○○	infliximab
[92] RCT	378 people with moderate to severe psoriasis Further report of reference [91]	**SF-36 bodily pain score** 8.1 with infliximab –0.6 with placebo People allocated to infliximab:placebo in a 4:1 allocation	P <0.001 Method of randomisation not reported	○○○	infliximab
[92] RCT	378 people with moderate to severe psoriasis Further report of reference [91]	**SF-36 mental health score** 11.0 with infliximab –1.7 with placebo People allocated to infliximab:placebo in a 4:1 allocation	P <0.001 Method of randomisation not reported	○○○	infliximab
[92] RCT	378 people with moderate to severe psoriasis Further report of reference [91]	**SF-36 social functioning score** 19.4 with infliximab –1.6 with placebo People allocated to infliximab:placebo in a 4:1 allocation	P <0.001 Method of randomisation not reported	○○○	infliximab

No data from the following reference on this outcome. [88] [89] [91] [93]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[88] RCT **3-armed trial**	33 people with moderate to severe psoriasis	**Headache** 7/11 (64%) with infliximab 10 mg/kg 1/11 (9%) with infliximab 5 mg/kg 2/11 (18%) with placebo	Significance not reported		
[89] RCT **3-armed trial**	249 people with severe psoriasis	**Proportion of people with one or more adverse effects** 78% with infliximab 3 mg/kg 79% with infliximab 5 mg/kg 63% with placebo	Significance not reported		
[89] RCT **3-armed trial**	249 people with severe psoriasis	**Serious adverse effects** with infliximab 3 mg/kg with infliximab 5 mg/kg with placebo	Significance not reported		

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Four people receiving infliximab had serious adverse effects (squamous cell carcinoma, cholecystitis, cholelithiasis, diverticulitis, sepsis, and pyelonephritis)			
[91] RCT	378 people with moderate to severe psoriasis	**Proportion of people with at least one adverse effect , at 24 weeks** 82% with infliximab 71% with placebo Adverse effects included serious infections (3 people taking infliximab); delayed hypersensitivity reaction with fever, myalgia, arthralgia, and skin rash (3 people taking infliximab); lupus-like syndrome with arthralgia and antidouble-stranded DNA antibodies (2 people taking infliximab); and markedly transitory increases in liver enzymes (6% of people with infliximab *v* 0% with placebo) People allocated to infliximab:placebo in a 4:1 allocation			
[93] RCT **3-armed trial**	835 people with moderate to severe psorias	**Tuberculosis** 2/627 (0.3%) with infliximab 3 mg/kg or 5 mg/kg given at weeks 0, 2, and 6 0/207 (0%) with placebo given at weeks 0, 2, and 6			
[93] RCT **3-armed trial**	835 people with moderate to severe psorias	**Malignancies** with infliximab 3 mg/kg or 5 mg/kg given at weeks 0, 2, and 6 with placebo given at weeks 0, 2, and 6 12 people who received infliximab were diagnosed with various malignancies (1 breast cancer, 1 salpingeal cancer, 1 squamous cell carcinoma, 9 basal cell carcinomas); there were no reported malignancies in the placebo group			

Further information on studies

[93] People in the infliximab groups were further randomised to receive maintenance treatment at the same dose either regularly (every 8 weeks), or when required. The RCT found that regular maintenance treatments increased the proportion of people with a 75% improvement in PASI score compared with maintenance given as needed for both doses at week 50, though the significance was not reported (3 mg/kg: 56/128 [44%] with regular *v* 32/126 [25%] with as needed; 5 mg/kg: 73/134 [54%] with regular *v* 51/134 [38%] with as needed; P values not reported). By 50 weeks, however, 162 people (28%) had withdrawn from the study, and were not analysed.

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Comment: Most of the evidence on the safety of infliximab is from studies in people with rheumatoid arthritis or Crohn's disease. Upper respiratory tract infections have been reported with infliximab. A few cases of lupus-like syndrome, as well as severe infections, have been reported with infliximab treatment. [95] We found one systematic review (search date 2005; 9 RCTs, 3493 people receiving active treatment; 1512 people receiving placebo) on adverse events with infliximab, anti-tumour necrosis factor antibodies, and adalimumab in people with rheumatoid arthritis. [94] Pooled analysis for infliximab and adalimumab suggested increased malignancies and severe infections (increased malignancies: OR 3.3, 95% CI 1.2 to 9.1; NNH 154, 95% CI 91 to 500 for 1 additional malignancy with a treatment period of 6–12 months; absolute data not reported; severe infections: OR 2.0, 95% CI 1.3 to 3.1; NNH 59, 95% CI 39 to 125 for 1 additional severe infection over a treatment period of 3–12 months; absolute data not reported).

Harms alerts:
A drug safety alert has been issued on the risk of opportunistic fungal infections associated with TNF-alpha blockers (tumour necrosis factor alpha-blockers), which could be fatal (http://www.fda.gov). A drug safety alert has been issued on the increased risk of lymphoma and other malignancies in children and adolescents, and the risks of leukaemia and new-onset psoriasis, associated with TNF blockers (http://www.fda.gov).

Clinical guide:
Infliximab is a monoclonal antibody that binds to and inhibits the activity of tumour necrosis factor-alpha. Good-quality evidence on the effects of cytokine blocking agents in people with plaque psoriasis is still scarce. Further comparative studies are needed to predict precisely how these drugs will fit into current psoriasis management.

OPTION CYTOKINE BLOCKING AGENTS (ADALIMUMAB)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Adalimumab may improve lesions, but long-term effects are unknown.
- Adalimumab is a relatively new drug for the treatment of psoriasis, and there is limited evidence regarding the possibility of long-term or rare but severe adverse events.

Benefits and harms

Adalimumab versus placebo:

We found no systematic reviews, but found one RCT. [96] The RCT compared adalimumab given weekly, and adalimumab given every 2 weeks, versus placebo, all for 12 weeks. A second paper reported quality-of-life outcomes from the same RCT. [97]

Symptom improvement

Adalimumab compared with placebo Adalimumab is more effective at increasing the proportion of people with moderate to severe psoriasis who achieve an improvement in severity scores at 12 weeks (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[96] RCT **3-armed trial**	148 people with moderate to severe psoriasis The remaining arm evaluated adalimumab every 2 weeks	**Proportion of people with at least 75% improvement in Psoriasis Area and Severity Index (PASI) score , 12 weeks** 40/50 (80%) with adalimumab weekly 2/52 (4%) with placebo	Adalimumab weekly *v* placebo: P <0.001	○○○	adalimumab
[96] RCT **3-armed trial**	148 people with moderate to severe psoriasis The remaining arm evaluated adalimumab weekly	**Proportion of people with at least 75% improvement in PASI score , 12 weeks** 24/45 (53%) with adalimumab every 2 weeks 2/52 (4%) with placebo	Adalimumab every 2 weeks *v* placebo: P <0.001	○○○	adalimumab

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Maintenance of remission

No data from the following reference on this outcome. [96]

Quality of life

Adalimumab compared with placebo Adalimumab is more effective than placebo at improving quality-of-life scores (Dermatology Life Quality Index) at 12 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[97] RCT **3-armed trial**	148 people with moderate to severe psoriasis Further report of reference [96]	**Change in Dermatology Life Quality Index (DLQI) score (from 0 to 30) , from baseline to week 12** –11.5 with adalimumab weekly –1.3 with placebo	Adalimumab weekly *v* placebo: P <0.001 The RCT found similarly larger improvements in EQ-5D and SF-36 scores with adalimumab, both weekly and every 2 weeks, compared with placebo	○○○	adalimumab
[97] RCT **3-armed trial**	148 people with moderate to severe psoriasis Further report of reference [96] The remaining arm evaluated adalimumab weekly	**Change in DLQI score (from 0 to 30) , from baseline to week 12** –10.8 with adalimumab every 2 weeks –1.3 with placebo	Adalimumab every 2 weeks *v* placebo: P <0.001 The RCT found similarly larger improvements in EQ-5D and SF-36 scores with adalimumab, both weekly and every 2 weeks, compared with placebo	○○○	adalimumab

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[96] RCT **3-armed trial**	148 people with moderate to severe psoriasis The remaining arm evaluated adalimumab every 2 weeks	**Serious adverse effects , 12 weeks** 4/50 (8%) with adalimumab weekly 1/45 (2%) with adalimumab every 2 weeks 0/52 (0%) with placebo	Significance not reported (P value not reported)		
[96] RCT **3-armed trial**	148 people with moderate to severe psoriasis	**Serious adverse effects , 60 weeks** with adalimumab Over the whole trial period of 60 weeks, the last 48 weeks of which had no placebo group, 14 people who received adalimumab suffered a serious adverse event, including malignancies (2 melanomas, 1 squamous cell carcinoma with cervical lymphadenopathy, 1 gastric adenocarcinoma, 1 breast cancer)			

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Further information on studies

[96] [97] From week 12 to week 60 the RCT compared various dosage regimens of adalimumab without a placebo group: we have not reported these results here.

Comment:

Adverse effects from studies in people with rheumatoid arthritis or Crohn's disease:
Most of the evidence on the safety of adalimumab is from studies in people with rheumatoid arthritis or Crohn's disease. We found one systematic review (search date 2005; 9 RCTs, 3493 people receiving active treatment; 1512 people receiving placebo) evaluating adverse events with the anti-tumour necrosis factor antibodies infliximab and adalimumab, in people with rheumatoid arthritis. [94] Meta-analysis for infliximab and adalimumab suggested increased malignancies and severe infections (increased malignancies: OR 3.3, 95% CI 1.2 to 9.1; NNH 154, 95% CI 91 to 500 for 1 additional malignancy with a treatment period of 6–12 months; absolute data not reported; severe infections: OR 2.0, 95% CI 1.3 to 3.1; NNH 59, 95% CI 39 to 125 for 1 additional severe infection over a treatment period of 3–12 months; absolute data not reported).

Harms alerts:
Drug safety alerts have been issued on the risk of hepatosplenic T-cell lymphoma associated with adalimumab (http://www.mhra.gov.uk), and on the risk of opportunistic fungal infections associated with TNF-alpha blockers (tumour necrosis factor alpha-blockers), which could be fatal (http://www.fda.gov). A drug safety alert has been issued on the increased risk of lymphoma and other malignancies in children and adolescents, and the risks of leukaemia and new-onset psoriasis, associated with TNF blockers (http://www.fda.gov).

Clinical guide:
There is still insufficient evidence to say how adalimumab might fit into the management of psoriasis.

OPTION CICLOSPORIN

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Ciclosporin has been associated with hypertension and renal dysfunction.

Benefits and harms

Ciclosporin versus placebo :

We found one systematic review of people with severe psoriasis (search date 1999, 18 RCTs; 13 on induction of remission, 5 on maintenance of remission). [47] Success was defined mostly as a reduction in Psoriasis Area and Severity Index (PASI) score, or in clinical criteria such as "clearance". Dosages of ciclosporin (cyclosporin) ranged from 1.25 to 14 mg/kg daily. Duration of treatment ranged from 4 to 12 weeks. The data could not be pooled. For additional information on adverse effects of ciclosporin from observational studies, see comment.

Symptom improvement

Ciclosporin compared with placebo Ciclosporin may be more effective than placebo at 10 weeks at increasing lesion clearance and at reducing psoriasis severity scores in people with severe psoriasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	289 people 6 RCTs in this analysis	**Treatment success** with ciclosporin with placebo Absolute results not reported Treatment success defined as at least 50% decrease in Psoriasis Area and Severity Index (PASI), at least 75% decrease in PASI, PASI <8, or clinically "clear or almost clear"	ARI for success 38% 95% CI 32% to 44% These results should be interpreted with caution, as there was heterogeneity in the results of the individual RCTs potentially because of differing definitions of success, and differing doses of ciclosporin used	○○○	ciclosporin

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[47] Systematic review	People with psoriasis Data from 1 RCT Largest RCT included in the review	**AR for a at least 75% reduction of PASI , 10 weeks** with ciclosporin with placebo Absolute results not reported	ARI for a at least 75% reduction of PASI 22% 95% CI 7% to 37%	○○○	ciclosporin

Maintenance of remission

Ciclosporin compared with placebo Ciclosporin may be more effective than placebo at increasing the proportion of people who remain in remission (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maintenance of remission					
[98] RCT **3-armed trial**	People with psoriasis In review [47]	**AR for "good response" (defined as <50% of baseline body surface area affected) , 24 weeks** 58% with ciclosporin (3.0 mg/kg daily) 0% with ciclosporin (1.5 mg/kg daily) 16% with placebo Absolute numbers not reported			
[99] RCT **3-armed trial**	People with psoriasis In review [47]	**AR for "positive response" (defined as increase of no more than 2 points on a 7-point severity scale where 1 = complete clearance and 7 = most severe) , 16 weeks** 57% with ciclosporin 3.0 mg/kg daily 21% with ciclosporin 1.5 mg/kg daily 5% with placebo Absolute results not reported			

Quality of life

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] Systematic review	400 people with psoriasis Data from 1 RCT	**Adverse effects** with intermittent treatment with a microemulsion formulation with placebo Intermittent treatment with a microemulsion formulation for 1 year (maximum treatment periods of 12 weeks as 1–4 courses) was well tolerated and produced no			

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		clinically significant change in blood pressure or creatinine concentration. With this regimen, only 10 (2.5%) people withdrew because of adverse events. Long-term follow-up studies are needed to confirm this finding			

Different ciclosporin formulations versus each other:

The review identified two RCTs (345 people, 12 weeks, 1 with a crossover design). [47]

Symptom improvement

Different ciclosporin formulations compared with each other Conventional oil-based ciclosporin and microemulsion preconcentrate are equally effective at increasing the proportion of people achieving a marked response (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	345 people, 12 weeks, 1 study with a crossover design 2 RCTs in this analysis	**Proportion of people achieving a marked response (at least 75% decrease in Psoriasis Area and Severity Index [PASI] score)** with conventional oil-based ciclosporin formulation with microemulsion preconcentrate ciclosporin formulation Absolute results not reported No significant difference between groups		⟷	Not significant
[47] Systematic review	People with psoriasis Data from 1 RCT Larger, parallel group RCT identified by the systematic review	**Proportion of people achieving a marked response (at least 75% decrease in PASI)** 78% with conventional oil-based ciclosporin formulation 80% with microemulsion preconcentrate ciclosporin formulation Absolute numbers not reported	ARI +2% 95% CI –7% to +11%	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

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Adverse effects

No data from the following reference on this outcome. [47]

Different ciclosporin doses versus each other:

We found one review, which identified two non-blinded RCTs (468 people) comparing different dosages of ciclosporin. [47]

Symptom improvement

Different ciclosporin doses compared with each other A ciclosporin dose of 5.0 mg/kg daily may be more effective than a ciclosporin dose of 2.5 mg/kg daily at increasing the proportion of people achieving a decrease in psoriasis severity scores (very low-quality evidence). Any advantage of higher doses may be offset by an increase in dose-related adverse effects, particularly increased renal toxicity and hypertension.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	People with psoriasis Data from 1 RCT	**Proportion of people achieving a 75% decrease in Psoriasis Area and Severity Index (PASI) score** with ciclosporin 5 mg/kg daily with ciclosporin 2.5 mg/kg daily Absolute results not reported	ARI 19% 95% CI 4% to 34%	○○○	ciclosporin 5 mg/kg daily
[47] Systematic review	People with psoriasis Data from 1 RCT	**Proportion of people achieving a 75% decrease in PASI** with ciclosporin 5 mg/kg daily with ciclosporin 2.5 mg/kg daily Absolute results not reported	ARI 41% 95% CI 31% to 51%	○○○	ciclosporin 5 mg/kg daily

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47]	People with psoriasis	**Hypertension (diastolic blood pressure >90 mmHg) , 12 weeks**			

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Systematic review		4/36 (11%) with ciclosporin 1.25 mg/kg daily 25/121 (21%) with ciclosporin 2.5 mg/kg daily 16/60 (26%) with ciclosporin 5 mg/kg daily			
[47] Systematic review	People with psoriasis	**Renal impairment, creatinine at least 130% of baseline value** 1% with ciclosporin 1.25 mg/kg daily 5% with ciclosporin 2.5 mg/kg daily 13% with ciclosporin 5 mg/kg daily			

Ciclosporin versus etretinate:

See option on retinoids (oral etretinate, acitretin), p 80 .

Ciclosporin versus methotrexate:

See option on methotrexate versus ciclosporin, p 77 .

Ciclosporin plus calcipotriol versus ciclosporin alone:

See option on systemic drug treatment plus topical vitamin D derivatives, p 97 .

Further information on studies

Comment:

Observational evidence suggests that the incidence of adverse events increases over time. In a case series follow-up study of 122 consecutive people treated continuously with ciclosporin for 3 to 76 months at a dose not exceeding 5 mg/kg daily, 104 people discontinued treatment. [100] The mean percentage of people who discontinued treatment because of adverse effects (mostly renal dysfunction and hypertension) rose from 14% at 12 months to 41% at 48 months.

One prospective cohort study documented an increased risk of malignancies in 152 people with psoriasis treated with ciclosporin for up to 5 years. Malignancies were diagnosed in 3.8% of people, with a standardised incidence ratio of 2:1 as compared with the general population. There was a sixfold increase in the incidence of skin cancer as compared with the general population, whereas non-skin malignancies did not show a significant increased risk. [101]

Clinical guide:

Ciclosporin is an established treatment option for moderate to severe psoriasis. Relapses are often seen on withdrawal, and long-term treatment is limited by adverse effects (mainly renal dysfunction and hypertension).

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OPTION FUMARIC ACID DERIVATIVES

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We found no direct information from RCTs about the effects of fumaric acid derivatives as maintenance treatment. Fumaric acid esters have been associated with flushing and with gastrointestinal symptoms.

Benefits and harms

Fumaric acid derivatives versus placebo:

We found one systematic review of people with severe psoriasis (search date 1999, 4 placebo-controlled RCTs, 203 people). [47] Two of the RCTs (123 people) compared a mixture of dimethylfumaric and monoethylfumaric acid esters versus placebo. The remaining RCTs in the review were reported in a single article [102] and compared either monoethylfumaric acid ester or dimethylfumaric acid ester versus placebo. We found no RCTs examining the use of fumaric acid as a maintenance treatment.

Symptom improvement

Fumaric acid derivatives compared with placebo Dimethylfumaric acid alone or mixed with monoethyl fumaric acid may be more effective than placebo at 16 weeks at reducing psoriasis severity scores in people with severe psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	123 people with severe psoriasis 2 RCTs in this analysis	**AR for at least 70% reduction in Psoriasis Area and Severity Index (PASI) score , 16 weeks** with mixture of dimethylfumaric and monoethylfumaric acid esters with placebo Absolute results not reported	Pooled ARR 0.47 95% CI 0.33 to 0.61	○○○	mixture of dimethylfumaric and monoethylfumaric acid esters
[102] RCT 2 RCTs reported in a single article	People with severe psoriasis In review [47]	**AR for at least 50% reduction in PASI score** 27% with dimethylfumaric acid ester 0% with placebo Absolute numbers not reported	ARR 27% 95% CI 6% to 45%	○○○	dimethylfumaric acid ester
[102] RCT 2 RCTs reported in a single article	People with severe psoriasis In review [47]	**AR at least 50% improvement in PASI score , 16 weeks** with monoethylfumaric acid ester with placebo Absolute results not reported	ARR –5% 95% CI –22% to +12%	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

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Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] Systematic review	People with psoriasis 4 RCTs in this analysis	**Adverse effects** with fumaric acid esters with placebo Absolute results not reported All RCTs of fumaric acid esters found high withdrawal rates — 39% of the drug group of one RCT stopped treatment prematurely, mostly because of gastrointestinal adverse effects. Acute adverse effects, including flushing and gastrointestinal symptoms, were reported in up to 75% of people. Eosinophilia was often reported. There have been case reports of renal failure, but one recent systematic review found no evidence of significant renal impairment			
[47] Systematic review	50 people with psoriasis Data from 1 RCT	**Adverse effects , 16 weeks** with fumaric acid esters with placebo Absolute results not reported Diarrhoea was reported 27 times, stomach ache or stomach cramps 35 times, flushing 21 times, and skin burning twice			
[47] Systematic review	101 people with psoriasis, open study Data from 1 RCT	**Adverse effects , 16 weeks** with fumaric acid esters with placebo Absolute results not reported Adverse effects reported in 69% of people (mainly gastrointestinal [56%] and flushing [31%])			

Fumaric acid esters plus vitamin D derivatives (calcipotriol) :
See option on vitamin D derivatives (topical), p 15 .

Further information on studies

Comment: **Clinical guide:**
Additional evidence is needed on predictive factors for treatment failure, safety, and long-term efficacy of fumaric acid esters. Fumaric acid derivatives are not available in many European countries or in the USA.

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OPTION METHOTREXATE

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Methotrexate and ciclosporin seem similarly effective at clearing lesions and maintaining remission, but both can cause serious adverse effects.
- Methotrexate has been associated with acute myelosuppression. Long-term methotrexate carries the risk of hepatic fibrosis and cirrhosis, which is related to the dose regimen employed.

Benefits and harms

Methotrexate versus placebo:

We found one systematic review (search date 2000), [103] which identified one small RCT. [104] For further information on harms of methotrexate, see comment.

Symptom improvement

Methotrexate compared with placebo Methotrexate may be more effective than placebo at reducing the surface area of psoriasis at 12 weeks in people with psoriatic arthritis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[104] RCT	37 people with psoriatic arthritis In review [103]	**Reduction in surface area of lesions , 12 weeks** 114 cm^2 with oral methotrexate 7.5–15 mg weekly 0 cm^2 with placebo	P = 0.04 Randomisation method and concealment not reported	○○○	methotrexate

Maintenance of remission

No data from the following reference on this outcome. [103]

Quality of life

No data from the following reference on this outcome. [103]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[104] RCT	37 people with psoriatic arthritis In review [103]	**Adverse effects , 12 weeks** with oral methotrexate 7.5–15 mg weekly with placebo A significant increase in serum bilirubin was reported with methotrexate compared with placebo (P = 0.043). Three people taking methotrexate had gastrointestinal distress or stomatitis; there were no withdrawals due to adverse effects	Randomisation method and concealment not reported	○○○	placebo

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Methotrexate versus ciclosporin:

We found one single-blinded RCT. [105]

Symptom improvement

Methotrexate compared with ciclosporin We don't know how methotrexate and ciclosporin compare at increasing complete or partial remission rates as measured by a decrease in psoriasis severity scores (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[105] RCT	88 people	**Complete remission (at least 90% reduction in Psoriasis Area and Severity Index [PASI] score) , 16 weeks' treatment** 17/43 (40%) with oral methotrexate (up to 22.5 mg weekly) 14/42 (33%) with ciclosporin (up to 5 mg/kg daily)	P = 0.55 The RCT is likely to have been underpowered to detect clinically important differences between groups	⟷	Not significant
[105] RCT	88 people	**Partial remission (at least 75% reduction in PASI score) , 16 weeks' treatment** 26/43 (60%) with oral methotrexate (up to 22.5 mg weekly) 30/42 (71%) with ciclosporin (up to 5 mg/kg daily)	P = 0.29 The RCT is likely to have been underpowered to detect clinically important differences between groups	⟷	Not significant

Maintenance of remission

Methotrexate compared with ciclosporin We don't know how methotrexate and ciclosporin compare at increasing complete or partial remission rates as measured by a decrease in psoriasis severity scores or the duration of remission of psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maintenance of remission					
[105] RCT	88 people	**Duration of complete remission , after 16 weeks' treatment stopped** with oral methotrexate (up to 22.5 mg weekly) with ciclosporin (up to 5 mg/kg daily) Absolute results not reported	P = 0.34 The RCT is likely to have been underpowered to detect clinically important differences between groups	⟷	Not significant
[105] RCT	88 people	**Duration of partial remission , after 16 weeks' treatment stopped** with oral methotrexate (up to 22.5 mg weekly) with ciclosporin (up to 5 mg/kg daily) Absolute results not reported	P = 0.43 The RCT is likely to have been underpowered to detect clinically important differences between groups	⟷	Not significant

Quality of life

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No data from the following reference on this outcome. [105]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[105] RCT	88 people	**Treatment discontinuations due to elevated liver enzymes** 12 people (29%) with oral methotrexate (up to 22.5 mg weekly) 1 person (2%) with ciclosporin (up to 5 mg/kg daily)	Significance not reported		
[105] RCT	88 people	**Proportion of people with nausea** 19/43 (44%) with oral methotrexate (up to 22.5 mg weekly) 4/42 (10%) with ciclosporin (up to 5 mg/kg daily)	P <0.001	○○○	ciclosporin
[105] RCT	88 people	**Proportion of people with headaches** 7/43 (16%) with oral methotrexate (up to 22.5 mg weekly) 18/42 (43%) with ciclosporin (up to 5 mg/kg daily)	P = 0.009	○○○	methotrexate
[105] RCT	88 people	**Proportion of people with muscle ache** 3/43 (7%) with oral methotrexate (up to 22.5 mg weekly) 12/42 (29%) with ciclosporin (up to 5 mg/kg daily)	P = 0.007	○○○	methotrexate
[105] RCT	88 people	**Proportion of people with paraesthesias in the fingertips and toes** 1/43 (2%) with oral methotrexate (up to 22.5 mg weekly) 14/42 (33%) with ciclosporin (up to 5 mg/kg daily)	P <0.001	○○○	methotrexate

Methotrexate plus narrowband UVB treatment:

We found one small RCT (24 people) that reported a median time to clear of 4 weeks with methotrexate 15 mg plus narrowband UVB. As more than half of people treated with placebo plus narrowband UVB did not clear after 24 weeks, no median time could be calculated for the comparison group. [106]

Further information on studies

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Comment: The most serious acute reaction, particularly in older people taking methotrexate, was dose-related myelosuppression. In the long term, major adverse events included liver fibrosis and pulmonary toxicity. One systematic review (search date not reported) found that about 28% (95% CI 24% to 32%) of people taking long-term methotrexate for psoriasis and rheumatoid arthritis developed liver fibrosis of histological grade I or higher on liver biopsy, whereas 5% developed advanced liver disease (histological grade IIIB or IV). [107] The risk was dose-related and was higher with increased alcohol consumption. A limitation of the systematic review was the lack of untreated control groups. Pulmonary disease associated with methotrexate has been described as an acute or chronic interstitial pneumonitis. [108] Adverse pulmonary effects of treatment are considered much rarer in psoriasis than in rheumatoid arthritis, but we found no published evidence to support this claim. Several drug interactions that increase methotrexate toxicity have been described (e.g., with sulphonamides). Methotrexate seems to double the risk of developing squamous cell carcinoma in people exposed to PUVA, and may be an independent risk factor for this cancer in people with psoriatic arthritis. [49] A higher risk of lymphoproliferative diseases in long-term users has been suggested by a few case reports. On the basis of data from a large case series (248 people), the cumulative incidence of lymphoma is not expected to be much higher than 1%. [109]

Clinical guide:
People using methotrexate are closely monitored for liver toxicity [47] and are advised to limit their consumption of alcohol. The most reliable test of liver damage remains needle biopsy of the liver. It is rare for life-threatening liver disease to develop with the first 1.0–1.5 g of methotrexate. In one uncontrolled case series (113 people with severe psoriasis), maintenance treatment with low-dose methotrexate (weekly dose up to 15 mg) provided satisfactory control of skin lesions in 81% of people (mean treatment duration: 8 years). [110] When treatment was stopped, 45% of people experienced a full relapse within 6 months.

OPTION RETINOIDS (ORAL ETRETINATE, ACITRETIN)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Retiniods seem to improve symptoms in people with psoriasis.
- Teratogenicity renders oral retinoids less acceptable. Etretinate is no longer available in many countries.

Benefits and harms

Etretinate versus placebo:

We found one systematic review (search date 1999, 11 RCTs, 455 people comparing any oral retinoids versus placebo). [47] Heterogeneity among trials often prevented meta-analysis. Four of the included RCTs (197 people) compared etretinate versus placebo for clearance of psoriasis. The review identified one additional RCT comparing etretinate versus placebo for maintenance of remission.

Symptom improvement

Etretinate compared with placebo Etretinate may be more effective than placebo at increasing response rates in people with severe psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	40 people with severe psoriasis Data from 1 RCT	**Response rates (almost-complete or complete clearance) , 16 weeks** 7/20 (35%) with etretinate 1 mg/kg 1/20 (5%) with placebo	ARR 30% 95% CI 7% to 53% Heterogeneity prevented meta-analysis	◌◌◌	etretinate 1 mg/kg
[47] Systematic review	30 people with psoriasis Data from 1 RCT	**Response rates (almost-complete or complete remission) , 16 weeks** 7/15 (47%) with etretinate 1 mg/kg 0/15 (0%) with placebo	ARR 47% 95% CI 0% to 72% Heterogeneity prevented meta-analysis	◌◌◌	etretinate 1 mg/kg

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[47] Systematic review	30 people with psoriasis Data from 1 RCT	**Response rates (complete remission) , 10 weeks** 13/15 (87%) with etretinate 1 mg/kg 0/15 (0%) with placebo	ARR 87% 95% CI 7% to 104% Heterogeneity prevented meta-analysis	○○○	etretinate 1 mg/kg
[47] Systematic review **Crossover design**	97 people with psoriasis Data from 1 RCT	**Complete remission** 8/48 (17%) with etretinate 50 mg 3/49 (6%) with placebo	ARR +11% 95% CI –2% to +24% The RCT is likely to have been underpowered to detect a clinically important difference between groups Heterogeneity prevented meta-analysis	⟷	Not significant

Maintenance of remission

Etretinate compared with placebo Low doses of etretinate may be more effective than placebo at reducing relapse rates at 1 year in people with severe psoriasis who have achieved clearance with PUVA plus etretinate (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maintenance of remission					
[47] Systematic review	36 people with psoriasis affecting 40% or more of body, who achieved clearance with PUVA plus etretinate prior to the trial Data from 1 RCT	**Absence of relapse , 1 year** 9/16 (56%) with low-dose etretinate (half of the maximum dose tolerated to achieve clearance) 3/20 (15%) with placebo Both groups also received PUVA once a week for the first two months of maintenance treatment phase	ARR 41% 95% CI 12% to 70%	○○○	low-dose etretinate

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] Systematic review	People with psoriasis	**Adverse effects** with oral retinoids with placebo Between 10% and 20% of people in the included RCTs discontinued treatment as a result of adverse effects. Most people experienced mucocutaneous adverse effects, such as dry skin, cheilitis, and conjunctivitis. Oral retinoids are also potentially teratogenic.			

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		For further information on adverse effects, see comment			

Acitretin versus placebo:

We found one systematic review (search date 1999, 11 RCTs, 455 people, comparing any oral retinoids *v* placebo), which identified only two RCTs comparing acitretin with placebo with extractable results. [47] Heterogeneity among trials prevented meta-analysis. One of the RCTs included an initial treatment phase and a maintenance phase.

Symptom improvement

Acitretin compared with placebo Acitretin may be more effective than placebo at increasing the proportion of people who achieve a decrease in psoriasis severity scores (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review **5-armed trial**	38 people Data from 1 RCT	**Response rate** with acitretin (10 mg, 25 mg, 50 mg, or 75 mg) with placebo	Reported no significant difference between acitretin (any dose) and placebo RCT was underpowered	⟷	Not significant
[47] Systematic review **4-armed trial**	80 people with severe psoriasis Data from 1 RCT The remaining arms evaluated acitretin 50 mg and acitretin 10 mg	**Proportion of people who achieved a 75% or greater decrease in Psoriasis Area and Severity Index (PASI) score, or a PASI score of <8 , 8 weeks** 12/20 (60%) with acitretin 25 mg 5/20 (25%) with placebo	ARI 35% 95% CI 6% to 64%	○○○	acitretin 25 mg
[47] Systematic review **4-armed trial**	80 people with severe psoriasis Data from 1 RCT The remaining arm evaluated acitretin 25 mg and acitretin 10 mg	**Proportion of people who achieved a 75% or greater decrease in PASI, or a PASI score of <8 , 8 weeks** 14/20 (70%) with acitretin 50 mg 5/20 (25%) with placebo	ARI 45% 95% CI 17% to 73%	○○○	acitretin 50 mg
[47] Systematic review **4-armed trial**	80 people with severe psoriasis Data from 1 RCT The remaining arm evaluated acitretin 25 mg and acitretin 50 mg	**Proportion of people achieving a 75% or greater decrease in PASI score, or a PASI score of <8 , 8 weeks** 8/20 (40%) with acitretin 10 mg 5/20 (25%) with placebo	ARI +15% 95% CI –14% to +44%	⟷	Not significant

Maintenance of remission

Acitretin compared with placebo Actitretin may be more effective than placebo at reducing relapse rates at 1 year in people with severe psoriasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maintenance of remission					
[47] Systematic review	80 people with severe psoriasis Data from 1 RCT	**Percentage changes to Psoriasis Area and Severity Index (PASI) scores , 6 months**	Reported no significant different between placebo and acitretin (any dose)	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial	Maintenance phase of trial following 8-week treatment phase with the same treatment dose	with acitretin (10, 25, and 50 mg/day) with placebo Absolute results not reported	People were also allowed to use 0.1% difluacortolone valerate ointment		

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] Systematic review	People with psoriasis	**Adverse effects** with oral retinoids with placebo Between 10% and 20% of people in the included RCTs discontinued treatment as a result of adverse effects. Most people experienced mucocutaneous adverse effects, such as dry skin, cheilitis, and conjunctivitis. Oral retinoids are also potentially teratogenic. For further information on adverse effects, see comment			

Acitretin versus etretinate:

We found one systematic review of people with severe psoriasis (search date 1999). [47] The main outcome was treatment success, as indicated by a specific decrease in the Psoriasis Area and Severity Index (PASI) score, or the extent of body surface area involved, or by a global improvement. Heterogeneity among trials often prevented meta-analysis.

Symptom improvement

Acitretin compared with etretinate Acitretin and etretinate are equally effective at increasing the proportion of people who achieve a marked improvement as measured by a reduction in psoriasis severity scores (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	508 people 4 RCTs in this analysis	**Proportion of people achieving a marked improvement (at least 75% decrease in PASI or Psoriasis Severity Index [a modified PASI], or a marked or total clearance for the largest study** with acitretin 40 mg with etretinate 40 mg	Risk difference (pooled analysis): –0.05 95% CI –0.13 to +0.02 For largest study: ARR +2% 95% CI –17% to +13%	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported For the largest study: 74% of people achieved clearance with acitretin 40 mg *v* 76% with etretinate 40 mg			

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] Systematic review	People with psoriasis	**Adverse effects** with oral retinoids Absolute results not reported Between 10% and 20% of people in the included RCTs discontinued treatment as a result of adverse effects. Most people experienced mucocutaneous adverse effects, such as dry skin, cheilitis, and conjunctivitis. Oral retinoids are also potentially teratogenic. For further information on adverse effects, see comment			

Etretinate versus ciclosporin:

We found one systematic review of people with severe psoriasis (search date 1999). [47] The review included two RCTs (286 people) comparing higher or lower doses of etretinate versus ciclosporin (cyclosporin), and the results could not be pooled. [47]

Symptom improvement

Etretinate compared with ciclosporin Etretinate is less effective than ciclosporin at increasing response rates as measured by a reduction in psoriasis severity scores (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	76 people with psoriasis Data from 1 RCT	**People with at least 75% decrease in Psoriasis Area and Severity Index (PASI) score**	ARR 24% 95% CI 9% to 39%	○○○	ciclosporin

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		97% with ciclosporin 5 mg/kg 73% with etretinate 0.7 mg/kg Absolute numbers not reported			
[47] Systematic review **4-armed trial**	210 people with psoriasis Data from 1 RCT The remaining arms evaluated ciclosporin 5 mg/kg and etretinate 0.75 mg/kg	**Proportion of people with at least 70% decrease in PASI** 62% with ciclosporin 2.5 mg/kg 16% with etretinate 0.5 mg/kg Absolute numbers not reported	ARI 46% 95% CI 34% to 58%	○○○	ciclosporin

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] RCT	People with psoriasis	**Adverse effects** with ciclosporin with etretinate 7/140 (0.05%) people taking ciclosporin developed hypertension (diastolic blood pressure >90 mmHg) Oral retinoids are also potentially teratogenic. For further information on adverse effects, see comment			

Oral retinoids plus topical corticosteroids:
See option on retinoids (oral) plus topical corticosteroids, p 96 .

Oral retinoids plus vitamin D and derivatives :
See option on systemic drug treatment plus topical vitamin D derivatives, p 97 .

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Further information on studies

Comment: Low-grade hepatotoxicity was observed in about 1% of people treated with etretinate in a prospective cohort study (956 patients with psoriasis treated with etretinate). [111] Two people who also received liarozole (an inhibitor of retinoic acid metabolism) were withdrawn because of liver enzyme abnormalities. Occasionally, acute hepatitis occurred, possibly as an idiosyncratic hypersensitivity reaction. Radiographic evidence of extraspinal tendon and ligament calcifications has been documented. In the cohort study, one quarter of 956 people treated with etretinate attributed a joint problem or its worsening to the drug. [111] Etretinate is a known teratogen and may be detected in the plasma for 2 to 3 years after treatment stops. Acitretin can undergo esterification to etretinate.

Clinical guide:
Women of child-bearing age are given effective contraception for 1 month before starting etretinate or acitretin, throughout treatment, and for 2 years after stopping acitretin treatment and 3 years after stopping etretinate treatment, because these drugs are potentially teratogenic. Etretinate is no longer available in many countries.

OPTION LEFLUNOMIDE

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Leflunomide is currently primarily used in people with psoriatic arthritis; the effects of treatment in people with psoriasis remain unclear.

Benefits and harms

Leflunomide versus placebo:

We found one RCT comparing oral leflunomide (100 mg/day loading dose followed by 20 mg/day) versus placebo for 24 weeks. [112]

Symptom improvement

Leflunomide compared with placebo Leflunomide may be more effective than placebo in people with psoriatic arthritis at increasing the proportion of people with a reduction in psoriasis symptom severity scores at 24 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[112] RCT	190 people with active psoriatic arthritis and psoriasis with at least 3% involvement	**Proportion of people with at least a 75% improvement in Psoriasis Area and Severity Index score** 17% with oral leflunomide (100 mg/day loading dose followed by 20 mg/day) 8% with placebo Absolute numbers not reported	P <0.05	○○○	leflunomide

Maintenance of remission

No data from the following reference on this outcome. [112]

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Quality of life

No data from the following reference on this outcome. [112]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[112] RCT	190 people with active psoriatic arthritis and psoriasis with at least 3% involvement	**Proportion of people with diarrhoea** 24% with oral leflunomide (100 mg/day loading dose followed by 20 mg/day) 13% with placebo Absolute numbers not reported			
[112] RCT	190 people with active psoriatic arthritis and psoriasis with at least 3% involvement	**Proportion of people with increased liver enzymes (alanine transaminase increase of at least 2 times the upper limit of normal)** 12% with oral leflunomide (100 mg/day loading dose followed by 20 mg/day) 5% with placebo Absolute numbers not reported			
[112] RCT	190 people with active psoriatic arthritis and psoriasis with at least 3% involvement	**Proportion of people with tiredness/lethargy** 6% with oral leflunomide (100 mg/day loading dose followed by 20 mg/day) 1% with placebo Absolute numbers not reported			

Further information on studies

Comment: **Clinical guide:**
Leflunomide is currently primarily used in people with psoriatic arthritis; the effects of treatment in people with psoriasis remain unclear.

OPTION PIMECROLIMUS

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Pimecrolimus is not an established treatment for psoriasis, and the long-term effects of treatment in people with psoriasis remain unclear.
- Pimecrolimus has been associated with pruritus, gastrointestinal effects, and paraesthesia.

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Benefits and harms

Pimecrolimus versus placebo:

We found one RCT comparing oral pimecrolimus (10, 20, or 30 mg twice daily) versus placebo for 12 weeks. [113]

Symptom improvement

Pimecrolimus compared with placebo Oral pimecrolimus may be more effective than placebo at improving psoriasis symptom severity scores at 12 weeks in people with moderate to severe psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[113] RCT **4-armed trial**	143 people with moderate to severe psoriasis	**Decrease in Psoriasis Area and Severity Index scores from baseline , 12 weeks** 22% with pimecrolimus 10 mg 51% with pimecrolimus 20 mg 54% with pimecrolimus 30 mg 3% with placebo	P <0.01 for pimecrolimus 20 mg or 30 mg *v* placebo	○○○	pimecrolimus

Maintenance of remission

No data from the following reference on this outcome. [113]

Quality of life

No data from the following reference on this outcome. [113]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[113] RCT **4-armed trial**	143 people with moderate to severe psoriasis	**Gastrointestinal disorders , 12 weeks** 13/38 (34%) with pimecrolimus 10 mg 11/32 (34%) with pimecrolimus 20 mg 14/35 (40%) with pimecrolimus 30 mg 5/37 (14%) with placebo			
[113] RCT **4-armed trial**	143 people with moderate to severe psoriasis	**Pruritus , 12 weeks** 3/38 (8%) with pimecrolimus 10 mg 2/32 (6%) with pimecrolimus 20 mg 4/35 (11%) with pimecrolimus 30 mg 1/37 (3%) with placebo			

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[113] RCT **4-armed trial**	143 people with moderate to severe psoriasis	**Paraesthesia , 12 weeks** 6/38 (13%) with pimecrolimus 10 mg 9/32 (28%) with pimecrolimus 20 mg 14/35 (40%) with pimecrolimus 30 mg 5/37 (14%) with placebo			

Further information on studies

Comment: **Clinical guide:**
Pimecrolimus is not an established treatment for psoriasis, and the long-term effects of treatment in people with psoriasis remain unclear.

QUESTION **What are the effects of combined treatment with drugs plus ultraviolet light for chronic plaque psoriasis?**

OPTION **INGRAM REGIMEN**

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- There is consensus that the Ingram regimen is likely to be beneficial for the clearance of psoriasis.

Benefits and harms

Ingram regimen versus dithranol alone:

We found one systematic review (search date 1999) examining treatment for severe psoriasis, which identified one RCT comparing the Ingram regimen versus dithranol plus emulsifying ointment bath. [47]

Symptom improvement

Ingram regimen compared with dithranol alone The Ingram regimen may be no more effective than dithranol alone at improving severity scores or clearance rates in people with severe psoriasis (very low-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	53 people Data from 1 RCT	**Clearance rates** 20/27 (74%) with Ingram regimen 16/26 (62%) with dithranol plus emulsifying ointment	ARR +12% 95% CI –13% to +37% The trial was too small to detect a clinically important difference between groups	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [47]

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Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

Further information on studies

Comment: **Clinical guide:**
There is consensus that the Ingram regimen is likely to be beneficial for clearing psoriasis. Adverse effects vary with the treatments being combined. Local irritation often occurs.

OPTION ADDING RETINOIDS (ORAL) TO PUVA

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Adding oral retinoids to PUVA may increase clinical response, but this should be weighed against possible teratogenicity from retinoids. Oral retinoids are known teratogens.

Benefits and harms

Oral retinoids plus PUVA versus PUVA alone:

We found one systematic review of people with severe psoriasis (search date 1999). [47] The review identified six RCTs (305 people) comparing oral retinoids plus PUVA versus PUVA alone.

Symptom improvement

Oral retinoids plus PUVA compared with PUVA alone Adding oral retinoids to PUVA regimens is more effective than PUVA alone at increasing clearance rates in people with severe psoriasis (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	305 people 6 RCTs in this analysis	**Clearance rates** with oral retinoids plus PUVA with PUVA alone Absolute results not reported	RR 0.14 95% CI 0.04 to 0.23	●●●	oral retinoids plus PUVA

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

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No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

Oral retinoids plus PUVA versus oral retinoids alone:
We found no RCTs.

Further information on studies

Comment: **Clinical guide:**
Adding oral retinoids to PUVA may increase clinical response, but this should be weighed against possible teratogenicity from retinoids. Oral retinoids are known teratogens.

OPTION ADDING RETINOIDS (ORAL) TO PUVB

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Teratogenicity renders oral retinoids less acceptable.

Benefits and harms

Oral retinoids plus UVB (broadband or narrowband) versus oral retinoids alone or UVB alone:
We found one systematic review of people with severe psoriasis (search date 1999). [47] The review identified four RCTs (245 people). [47] The results could not be pooled, and two reviews reported original results of only two RCTs. In these RCTs, the combined treatment was superior to ultraviolet treatment alone or oral retinoids alone.

Symptom improvement

UVB plus oral retinoids compared with either treatment alone UVB (broadband or narrowband) plus oral retinoids may be more effective than either treatment alone at increasing clearance rates and at improving psoriasis severity scores in people with severe psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[47] Systematic review	82 people Data from 1 RCT	**Proportion of people with at least 75% decrease in Psoriasis Area and Severity Index (PASI) score** 24/42 (57%) with UVB plus acitretin 35 mg daily 9/40 (23%) with UVB alone	ARR 34% 95% CI 14% to 54%	○○○	UVB plus acitretin
[47] Systematic review	18 people Data from 1 RCT	**Proportion who had at least 80% clearance** 8/9 (89%) with UVB plus acitretin	ARR 67% 95% CI 33% to 100%	○○○	UVB plus acitretin

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		2/9 (22%) with acitretin alone			

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

Further information on studies

Comment: **Clinical guide:**
The combination of oral retinoids plus UVB may be a treatment option in people who do not respond to the individual agents in a satisfactory way. However, teratogenicity is a limiting factor for retinoid use. Oral retinoids are known teratogens.

OPTION ADDING VITAMIN D OR DERIVATIVES TO PUVA OR UVB

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We found no convincing evidence of a treatment benefit from adding calcipotriol to a combination of PUVA or UVB.

Benefits and harms

PUVA or UVB plus calcipotriol versus either PUVA or UVB alone:
We found one systematic review (search date 1999, 9 RCTs, 552 people) [114] and one subsequent RCT. [115]

Symptom improvement

PUVA/UVB plus calcipotriol compared with PUVA or UVB alone Calcipotriol plus PUVA/UVB may be no more effective than PUVA or UVB alone at improving psoriasis symptoms or at reducing the cumulative exposure to phototherapy (low-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[114] Systematic review	People with psoriasis; number of people not reported	**Rate of marked improvement , 12 weeks** with PUVA plus calcipotriol with PUVA alone	RR 1.2 95% CI 0.9 to 1.6	⟷	Not significant
[114]	People with psoriasis; number of people not reported	**Rate of marked improvement , at 8 weeks** with UVB plus calcipotriol with UVB alone	RR 1.0 95% CI 0.8 to 1.1	⟷	Not significant
[115] RCT	164 people	**Median number of UVB treatments required to achieve clearance** 22 with UVB plus calcipotriol 25 with UVB alone	RR 3.66 95% CI 2.16 to 6.20	●●○	UVB plus calcipotriol

Maintenance of remission

No data from the following reference on this outcome. [114] [115]

Quality of life

No data from the following reference on this outcome. [114] [115]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[114] Systematic review	People with psoriasis; number of people not reported	**Proportion of people who had adverse effects** with PUVA plus calcipotriol with PUVA alone	RR 0.98 95% CI 0.59 to 12.63	⟷	Not significant
[114] Systematic review	People with psoriasis; number of people not reported	**Proportion of people who had adverse effects** with UVB plus calcipotriol with UVB alone	RR 1.0 95% CI 0.16 to 6.42	⟷	Not significant
[115]	164 people	**Rates of adverse effects** 57% with UVB plus calcipotriol 66% with UVB alone Absolute numbers not reported Adverse effects included burns, pruritus, and erythema	P value not reported		

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Further information on studies

[114] The review found no significant difference between groups in cumulative exposure to phototherapy, or in use of systemic treatment.

Comment: **Clinical guide:**
We found no convincing evidence of a treatment benefit from adding calcipotriol to a combination of PUVA or UVB. Adverse effects vary with the treatments being combined. Local irritation often occurs.

OPTION GOECKERMAN TREATMENT

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We don't know whether Goeckerman treatment is effective with people with psoriasis, as we found few trials.

Benefits and harms

Goeckerman treatment versus placebo or no treatment:

We found no systematic review or RCTs.

Goeckerman treatment versus UVB alone or UVB plus emollients:

We found one systematic review (search date 1999, 1 RCT, 49 people with severe psoriasis) [47] and one additional RCT [116] comparing Goeckerman treatment (daily application of coal tar followed by UVB iradiation) versus UVB with no tar. [116]

Symptom improvement

Goeckerman treatment compared with UVB irradiation alone Goeckerman treatment may be no more effective than UVB irradiation alone at improving response rates in people with chronic plaque psoriasis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis improvement					
[47] Systematic review	49 people with severe psoriasis Data from 1 RCT	**Clearance (complete resolution of at least 90% of psoriasis)** 19/30 (63%) with suberythematous UVB + tar oil 14/19 (74%) with maximally erythematous UVB + emollients	ARR –0.11 95% CI –0.37 to +0.1 The RCT was underpowered to detect clinically important differences between groups	⟷	Not significant
[116] RCT	22 people with severe psoriasis, bilateral study (two sides of the body treated differently)	**Response rates** with tar oil plus suberythemogenic doses of ultraviolet B radiation with oil vehicle (an emollient) plus suberythemogenic doses of ultraviolet B radiation	The RCT found no evidence that adding coal tar to UVB improved response rates. However, it was underpowered to detect clinically important differences between groups	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [47]

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Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

Further information on studies

Comment: **Clinical guide:**
We found no good evidence to support the use of Goeckerman treatment for psoriasis. Adverse effects vary with the treatments being combined. Local irritation often occurs.

OPTION UVB LIGHT PLUS EMOLLIENTS

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We found little specific RCT evidence about the effects of UVB light plus emollients; however, it is usual practice to combine emollients with most of the treatment modalities used in psoriasis.

Benefits and harms

UVB radiation plus emollient versus UVB alone :
We found one small RCT. [117]

Symptom improvement

UVB radiation plus emollient compared with UVB alone UVB radiation plus an oil-in-water emollient may temporarily be more effective than UVB alone at improving psoriasis at 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis improvement					
[117] RCT	43 people	**Improvement in psoriasis , 12 weeks** with UVB radiation plus an oil-in-water emollient with UVB radiation alone Absolute results reported graphically Temporarily improved with UVB radiation plus an oil-in-water emollient	P <0.001	○○○	UVB radiation plus an oil-in-water emollient

Maintenance of remission

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No data from the following reference on this outcome. [117]

Quality of life

No data from the following reference on this outcome. [117]

Adverse effects

No data from the following reference on this outcome. [117]

Further information on studies

Comment: **Clinical guide:**
We found little evidence about the effects of UVB light plus emollients. However, it is usual practice to combine emollients with most of the treatment modalities used in psoriasis. Pretreatment with oil-in-water emollient can accelerate clearance in people treated with UVB.

QUESTION What are the effects of combined systemic plus topical drug treatments for chronic plaque psoriasis?

OPTION RETINOIDS (ORAL) PLUS CORTICOSTEROIDS (TOPICAL)

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- Topical potent corticosteroids may improve psoriasis compared with placebo, and efficacy may be increased by adding oral retinoids.
- Topical corticosteroids may cause striae and atrophy, which increase with potency and use of occlusive dressings. Continuous use may lead to adrenocortical suppression, and severe flares of the disease may occur on withdrawal. Teratogenicity renders oral retinoids less acceptable.

Benefits and harms

Retinoids (oral) plus corticosteroids (topical) versus either treatment alone:

We found one systematic review of people with severe psoriasis (search date 1999, 3 RCTs, 296 people). [47] The review could not pool the results of RCTs because of heterogeneity in the outcomes assessed.

Symptom improvement

Oral retinoids plus topical corticosteroids compared with either treatment alone Oral retinoids plus topical corticosteroids may be more effective then either treatment alone at improving psoriasis severity scores in people with severe psoriasis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis improvement					
[47] Systematic review	296 people with severe psoriasis 3 RCTs in this analysis	**Improvement in psoriasis (measured by proportion of people with a 75% or greater decrease in total score on a scale from 1–16, complete or**	ARRs all significant	◌◌◌	topical corticosteroid plus an oral retinoid

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		satisfactory remission, or overall improvement) with topical corticosteroid plus an oral retinoid with topical corticosteroid or oral retinoid alone All of the RCTs found that a topical corticosteroid plus an oral retinoid was significantly better than either as a single treatment in improving psoriasis			

Maintenance of remission

No data from the following reference on this outcome. [47]

Quality of life

No data from the following reference on this outcome. [47]

Adverse effects

No data from the following reference on this outcome. [47]

Further information on studies

Comment: **Clinical guide:**
Adding topical corticosteroids to oral retinoids may speed up psoriasis clearance. However, topical corticosteroids may cause striae and atrophy, which increase with potency and use of occlusive dressings. Continuous use may lead to adrenocortical suppression, and case reports suggest that severe flares of the disease may occur on withdrawal. Oral retinoids are known teratogens.

OPTION SYSTEMIC DRUG TREATMENT PLUS TOPICAL VITAMIN D AND DERIVATIVES

- For GRADE evaluation of interventions for Psoriasis (chronic plaque), see table, p 104 .
- We don’t know whether combining systemic drug treatment plus topical vitamin D and derivatives is effective in the treatment of psoriasis.

Benefits and harms

Oral retinoid plus calcipotriol versus oral retinoid alone:

We found one systematic review (search date 1999), which identified 1 RCT comparing acitretin plus calcipotriol versus acitretin alone. [114]

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Symptom improvement

Oral retinoid plus calcipotriol compared with oral retinoid alone Oral retinoid plus calcipotriol may be no more effective than oral retinoid alone at improving symptoms at 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Psoriasis improvement					
[114] Systematic review	135 people Data from 1 RCT	**Rate of marked improvement , 12 weeks** with acitretin plus calcipotriol with acitretin alone Absolute results not reported	RR 1.4 95% CI 1.0 to 1.9	⟷	Not significant

Maintenance of remission

No data from the following reference on this outcome. [114]

Quality of life

No data from the following reference on this outcome. [114]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[114] Systematic review	135 people Data from 1 RCT	**Adverse effects , 12 weeks** with acitretin plus calcipotriol with acitretin alone Absolute results not reported	RR 1.03 95% CI 0.96 to 1.10	⟷	Not significant

Calcipotriol plus ciclosporin versus ciclosporin alone:

We found one systematic review (search date 1999), which identified 1 RCT comparing acitretin plus calcipotriol versus acitretin alone. [114]

Symptom improvement

Calcipotriol plus ciclosporin compared with ciclosporin alone Calcipotriol plus ciclosporin may be no more effective than ciclosporin alone at improving symptoms at 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[114] Systematic review	69 people Data from 1 RCT	**Rate of marked improvement , 6 weeks** with ciclosporin plus calcipotriol with ciclosporin alone Absolute results not reported	RR 1.2 95% CI 0.9 to 1.6	⟷	Not significant

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Maintenance of remission

No data from the following reference on this outcome. [114]

Quality of life

No data from the following reference on this outcome. [114]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[114] Systematic review	69 people Data from 1 RCT	**Adverse effects , 6 weeks** with ciclosporin plus calcipotriol with ciclosporin alone Absolute results not reported	RR 0.92 95% CI 0.59 to 1.43	⟷	Not significant

Further information on studies

Comment: **Clinical guide:**
We found no good evidence that a clinical advantage could be achieved by adding topical calcipotriol to oral retinoid or ciclosporin.

GLOSSARY

Goeckerman treatment A daily application of coal tar followed by ultraviolet B irradiation.

Hamilton Depression Rating Scale a measure of depressive symptoms using 17 items, with total scores from 0 to 54 (higher scores indicate increased severity of depression).

Ingram regimen A daily application of dithranol (sometimes in combination with coal tar bath) plus ultraviolet B irradiation.

Physician's Global Assessment See Investigator assessment of global improvement.

Beck Depression Inventory Standardised scale to assess depression. This instrument consists of 21 items to assess the intensity of depression. Each item is a list of 4 statements (rated 0, 1, 2, or 3), arranged in increasing severity, about a particular symptom of depression. The range of scores possible are 0 = least severe depression to 63 = most severe depression. It is recommended for people aged 13 to 80 years. Scores of more than 12 or 13 indicate the presence of depression.

Body mass index (BMI) A measure of obesity, defined as the weight (in kg) divided by the square of the height (in metres).

Dermatology Life Quality Index Validated 10-item questionnaire for assessing quality or life in people with various skin conditions, including psoriasis. Overall score ranges from 0 to 30, with a higher score indicating a lower quality of life.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

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Investigator Assessment of Global Improvement A measure of overall change in lesion severity from baseline, scored on a 6- or 7-point scale, where the lowest score indicates worsening and the highest score indicates clearing of lesions. May also be referred to as the Physician's Global Assessment.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Psoriasis Area and Severity Index (PASI) score Composite score grading severity of psoriasis in four body regions according to erythema, scaling, thickness, and the total area of skin affected. Severity of each of erythema, scaling, and thickness is graded from 0–4, and extension in each body region is graded from 1–6. The final composite score ranges from 0–72, with a higher score indicating a greater severity of psoriasis.

SF-36 A scale that assesses health-related quality of life across 8 domains: limitations in physical activities (physical component); limitations in social activities; limitations in usual role activities owing to physical problems; pain; psychological distress and wellbeing (mental health component); limitations in usual role activities because of emotional problems; energy and fatigue; and general health perceptions.

Total Severity Score Assesses signs (redness, scaling, and thickness) and symptoms (itching) of psoriasis on 3- or 4-point scales. The scores for all signs and symptoms are summed to obtain the total severity score, which typically ranges from 0 to 12, where a higher score indicates greater severity.

Ultraviolet A 315 nm to 400 nm ultraviolet radiation.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Corticosteroids (topical) Two RCTs added comparing clobetasol propionate versus placebo. [36] [37] The first RCT found that clobetasol propionate reduced lesion severity compared with placebo at 4 weeks. [36] The second RCT found that clobetasol propionate increased the proportion of people whose psoriasis was clear, or nearly clear, at 4 weeks. [37] Categorisation unchanged (Trade-off between benefits and harms).

Cytokine blocking agents (adalimumab) One RCT added comparing adalimumab versus placebo. [96] It found that adalimumab increased the proportion of people with a 75% improvement in psoriasis severity scores compared with placebo at 12 weeks. Categorisation unchanged (Trade-off between benefits and harms).

Cytokine blocking agents (infliximab) One RCT added comparing both high- and low-dose infliximab versus placebo. [93] It found that both doses of infliximab increased the proportion of people with a 75% improvement in psoriasis severity scores compared with placebo at 10 weeks. Categorisation unchanged (Trade-off between benefits and harms).

PUVA One RCT added comparing PUVA using higher-dose bath psoralen versus PUVA using lower-dose bath psoralen. It found no significant difference in size of improvement of Psoriasis Area and Severity Index (PASI) score between groups at 10 weeks. [48] Categorisation unchanged (Likely to be beneficial).

Ultraviolet B (UVB) One RCT added comparing selective broadband UVB versus narrowband UVB. [54] It found no significant difference in the proportion of people clear of psoriasis at the end of treatment. Another RCT added comparing narrowband UVB versus PUVA. [58] It found that PUVA increased the proportion of people clear of psoriasis compared with UVB at the end of treatment. Categorisation unchanged (Likely to be beneficial).

Vitamin D derivatives (topical) One RCT added comparing calcipotriol versus calcitriol. It found no significant difference in global improvement in psoriasis between groups at 12 weeks. [25] Categorisation unchanged (Beneficial).

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GRADE Evaluation of interventions for Psoriasis (chronic plaque).

Important outcomes	Adverse effects, Maintenance of remission, Quality of life, Symptom improvement								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of non-drug treatments (other than ultraviolet light) for chronic plaque psoriasis?									
1 (56) [6]	Symptom improvement	Acupuncture versus sham acupuncture	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
1 (50) [7]	Symptom improvement	Balneotherapy versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for uncertainty about disease severity and method of assessing improvement
4 (325) [8] [9] [10] [12]	Symptom improvement	Fish oil versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for uncertainty about disease severity and method of assessing improvement
1 (25) [11]	Maintenance of remission	Fish oil versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting. Directness point deducted for unclear assessment of efficacy
What are the effects of topical drug treatments for chronic plaque psoriasis?									
3 (1672) [15] [16] [17]	Symptom improvement	**Tazarotene versus placebo**	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement
3 (1198) [18] [19] [20]	Symptom improvement	Tazarotene plus topical corticosteroids versus tazarotene plus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (106) [21]	Symptom improvement	Tazarotene plus topical corticosteroids versus vitamin D derivatives	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
16 (2817) [14] [22] [23]	Symptom improvement	Vitamin D derivatives versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for method of assessing improvement
1 (97) [24]	Maintenance of remission	Vitamin D derivatives versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
3 (681) [22] [25] [20]	Symptom improvement	Different vitamin D derivatives versus each other	4	0	0	–1	0	Moderate	Directness point deducted for method of assessing improvement
9 (1875) [14]	Symptom improvement	Vitamin D derivatives versus topical corticosteroids	4	–1	0	–2	0	Very low	Quality point deducted for statistical heterogeneity between studies. Directness points deducted for uncertainty about disease severity and method of assessing improvement
6 (1143) [14] [27]	Symptom improvement	Vitamin D derivatives versus dithranol	4	0	0	–2	0	Low	Directness points deducted for uncertainty about disease severity and method of assessing improvement

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Important outcomes	Adverse effects, Maintenance of remission, Quality of life, Symptom improvement								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (80) [28]	Symptom improvement	Vitamin D derivatives versus dithranol plus coal tar	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
2 (not reported) [14]	Symptom improvement	Vitamin D derivatives versus coal tar	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting. Directness points deducted for uncertainty about disease severity and method of assessing improvement
1 (46) [29]	Symptom improvement	Vitamin D derivatives plus dithranol versus dithranol alone	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
1 (143) [30]	Symptom improvement	Vitamin D derivatives plus fumaric acid esters versus fumaric acid esters alone	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
3 (not reported) [14]	Symptom improvement	Dithranol versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement
1 (not reported) [14]	Symptom improvement	Salicylic acid versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting. Directness points deducted for uncertainty about disease severity and method of assessing improvement
17 (1686) [14]	Symptom improvement	Topical corticosteroids versus placebo	4	0	0	–2	0	Low	Directness points deducted for uncertainty about disease severity and method of assessing improvement
1 (90) [38]	Maintenance of remission	Topical corticosteroids versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for uncertainty about disease severity and method of assessing improvement
2 (131) [39] [40]	Symptom improvement	Topical corticosteroids plus occlusive dressings versus topical corticosteroids alone	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and methodological weaknesses. Directness point deducted for uncertainty about method of assessing improvement
8 (less than 4507) [14] [41] [42] [43]	Symptom improvement	Topical corticosteroids plus vitamin D derivatives versus vitamin D derivatives alone	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for method of assessing improvement
1 (20) [44]	Adverse effects	Coal tar plus fatty acids versus coal tar alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of ultraviolet light treatments for chronic plaque psoriasis?									
1 (95) [45]	Symptom improvement	Heliotherapy versus no intervention	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
1 (1005) [46]	Maintenance of remission	PUVA versus no treatment	4	0	0	–1	+1	High	Directness point deducted for mixed population. Effect-size point added for RR 0.2–0.5
3 (208) [47] [48]	Symptom improvement	High-dose psoralen in PUVA versus low-dose psoralen in PUVA	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement

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Important outcomes	Adverse effects, Maintenance of remission, Quality of life, Symptom improvement								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (207) [47]	Symptom improvement	Comparison of different formulations of the same oral psoralen in PUVA regimens	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
2 (137) [47]	Symptom improvement	Oral versus bath psoralen formulations in PUVA	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (157) [47]	Symptom improvement	High-dose versus low-dose PUVA	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement
1 (100) [47]	Symptom improvement	PUVA versus PUVB	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (224) [47]	Symptom improvement	PUVA versus other topical or systemic treatments (dithranol, tar, vitamin D analogues, corticosteroids, and fish oil)	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement
2 (150) [52] [53]	Maintenance of remission	UVB versus no UVB	4	–2	–1	–1	0	Very low	Quality points deducted for sparse data, and for methodological weaknesses in one RCT. Consistency point deducted for conflicting results. Directness point deducted for differences in disease severity between groups
1 (100) [54]	Symptom improvement	Narrowband UVB versus broadband UVB	4	–2	0	0	0	Low	Quality points deducted for sparse data and inconsistent treatment between groups
1 (113) [55]	Symptom improvement	Twice-weekly versus three times-weekly narrowband UVB	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (371) [56] [57] [58]	Symptom improvement	UVB (broadband or narrowband) versus PUVA	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (71) [62]	Symptom improvement	Phototherapy plus balneotherapy versus either intervention alone	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement
1 (38) [63]	Symptom improvement	UVA versus placebo or no treatment	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement.
What are the effects of systemic drug treatments for chronic plaque psoriasis?									
3 (1289) [64] [65] [66] [67] [68] [69]	Symptom improvement	Alefacept versus placebo	4	0	+1	–1	0	High	Consistency point added for dose response. Directness point deducted for uncertainty about method of assessing improvement
3 (1289) [64] [65] [66] [67] [68] [69]	Quality of life	Alefacept versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about clinical significance of results
5 (3130) [72] [73] [74] [75] [76] [77] [78]	Symptom improvement	Efalizumab versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about method of assessing improvement

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Important outcomes	Adverse effects, Maintenance of remission, Quality of life, Symptom improvement								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (1349) [73] [77] [78]	Quality of life	Efalizumab versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about clinical significance of results
4 (1965) [81] [82] [84] [86]	Symptom improvement	Etanercept versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about method of assessing improvement
3 (1853) [83] [85] [86]	Quality of life	Etanercept versus placebo	4	0	0	0	0	High	
4 (1495) [88] [89] [91] [93]	Symptom improvement	Infliximab versus placebo	4	–1	+1	–1	0	Moderate	Quality point deducted for not reporting method of randomisation in large study. Consistency point added for dose response. Directness point deducted for uncertainty about method of assessing improvement
2 (627) [90] [92]	Quality of life	Infliximab versus placebo	4	–1	+1	0	0	High	Quality point deducted for not reporting method of randomisation in large study. Consistency point added for dose response
1 (148) [96] [97]	Symptom improvement	Adalimumab versus placebo	4	0	0	–1	+2	High	Directness point deducted for uncertainty about method of assessing improvement. Effect-size points added for RR >5
1 (148) [97]	Quality of life	Adalimumab versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (289) [47]	Symptom improvement	**Ciclosporin versus placebo**	4	−1	0	−2	0	Very low	Quality point deducted for heterogeneity in results. Directness points deducted for comparing different doses and uncertainty about method of assessing improvement
2 (not clear) [98] [99]	Maintenance of remission	**Ciclosporin versus placebo**	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and no statistical analysis. Directness point deducted for uncertainty about method of assessing improvement
2 (345) [47]	Symptom improvement	Different ciclosporin formulations versus each other	4	0	0	−1	0	Moderate	Directness point deducted for uncertainty about method of assessing improvement
2 (468) [47]	Symptom improvement	Different ciclosporin doses versus each other	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and for lack of blinding. Directness point deducted for uncertainty about method of assessing improvement
4 (203) [47] [102]	Symptom improvement	Fumaric acid derivatives versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement
1 (37) [104]	Symptom improvement	Methotrexate versus placebo	4	−3	0	−2	0	Very low	Quality points deducted for sparse data and methodological weaknesses. Directness points deducted for inclusion of people with non-plaque psoriasis and uncertainty about method of assessing improvement
1 (88) [105]	Symptom improvement	Methotrexate versus ciclosporin	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement

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Important outcomes	Adverse effects, Maintenance of remission, Quality of life, Symptom improvement								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (88) [105]	Maintenance of remission	Methotrexate versus ciclosporin	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
4 (197) [47]	Symptom improvement	Etretinate versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
1 (36) [47]	Maintenance of remission	Etretinate versus placebo	4	−1	0	−2	0	Very low	Quality point deducted for sparse data. Directness points deducted for uncertainty about method of assessing severity and relapse and inclusion of PUVA
2 (118) [47]	Symptom improvement	Acitretin versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results but added back for dose response. Directness point deducted for uncertainty about method of assessing improvement
1 (80) [47]	Maintenance of remission	Acitretin versus placebo	4	–2	0	–2	0	Very low	Quality point deducted for sparse data and incomplete reporting. Directness point deducted for uncertainty about assessing severity and use of corticosteroid allowed
4 (508) [47]	Symptom improvement	Acitretin versus etretinate	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about method of assessing improvement
2 (286) [47]	Symptom improvement	Etretinate versus ciclosporin	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about assessing improvement
1 (190) [112]	Symptom improvement	Leflunomide versus placebo	4	−1	0	−2	0	Very low	Quality point deducted for sparse data. Directness points deducted for inclusion of people with non-plaque psoriasis and for uncertainty about method of assessing improvement
1 (143) [113]	Symptom improvement	Pimecrolimus versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
What are the effects of combined treatment with drugs plus ultraviolet light for chronic plaque psoriasis?									
1 (53) [47]	Symptom improvement	Ingram regimen versus dithranol alone	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement
6 (305) [47]	Symptom improvement	Oral retinoids plus PUVA versus PUVA alone	4	−1	0	0	+2	High	Quality point deducted for incomplete reporting of results. Effect-size points added for RR <0.2
2 (100) [47]	Symptom improvement	Oral retinoids plus UVB (broadband or narrowband) versus oral retinoids alone or UVB alone	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing improvement
9 (552) [114]	Symptom improvement	PUVA or UVB plus calcipotriol versus either PUVA or UVB alone	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about disease severity

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Important outcomes	Adverse effects, Maintenance of remission, Quality of life, Symptom improvement								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (71) [47] [116]	Symptom improvement	Goeckerman treatment versus UVB alone or UVB plus emollients	4	−2	0	−1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement
1 (43) [117]	Symptom improvement	**UVB radiation plus emollient versus UVB alone**	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of combined systemic plus topical drug treatments for chronic plaque psoriasis?									
3 (296) [47]	Symptom improvement	Retinoids (oral) plus corticosteroids (topical) versus either treatment alone	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about method of assessing improvement
1 (135) [114]	Symptom improvement	Oral retinoid plus calcipotriol versus oral retinoid alone	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (69) [114]	Symptom improvement	Calcipotriol plus ciclosporin versus ciclosporin alone	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.

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