The effectiveness of two-compound formulation calcipotriol and betamethasone dipropionate gel in the treatment of moderately severe scalp psoriasis: a systematic review of direct and indirect evidence

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CRD summary
The review found that the two-compound formulation calcipotriol and betamethasone dipropionate gel may be safer and more effective than other topical therapies for treating moderately severe psoriasis of the scalp. In view of limitations in the review, in particular differences between the included trials and the use of indirect comparisons, the reliability of the authors' conclusions is unclear.

Authors' objectives
To assess the effectiveness of two-compound formulation of calcipotriol and betamethasone dipropionate gel for treating moderately severe psoriasis of the scalp.

Searching
MEDLINE, EMBASE, DARE, Cochrane Central Register of Controlled Trials (CENTRAL) and 17 other databases and websites were searched up to June 2008. All published and unpublished RCTs conducted by the pharmaceutical company sponsoring the review were checked. The search was limited to studies published in English or available unpublished in full text.

Study selection
Eligible studies were randomised controlled trials (RCTs) that evaluated at least two of the commonly used topical treatments for scalp psoriasis including medicated shampoo, potent corticosteroid, coal tar preparation, and/or vitamin D analogue. Trials were required to measure response rates using Investigator Global Assessment or Total Sign Score criteria, using definitions reported in the review. Other review outcomes were all adverse events, skin adverse events, and withdrawal due to adverse events. Crossover studies and those with fewer than 50 participants per group were excluded.

The mean age of participants in the included trial ranged from 43 to 51 years; the proportion of men ranged from 42% to 53%. Baseline Total Sign Score ratings ranged from 4.9 to 7.0. Daily two-compound formulation calcipotriol and betamethasone dipropionate gel was directly compared with daily betamethasone dipropionate alone, daily or twice daily calcipotriol, or placebo. Other comparisons were twice daily calcipotriol (with or without polytar), daily capasal, twice daily betamethasone valerate, calcipotriol, polytar, and placebo. The duration of treatment in most trial was eight weeks (range four to 52 weeks). Outcomes were reported at four weeks for effectiveness and at up to eight weeks for adverse effects. All trials were multi-centred; most were international.

One author selected studies for inclusion, checked by a second author.

Assessment of study quality
Published methods were used to evaluate trial quality for: reporting of inclusion criteria, number randomised, baseline characteristics and withdrawals; power calculation; sample size; random sequence generation; allocation concealment; blinding; baseline equality of groups; co-interventions; compliance; use of intention to treat analysis; and follow-up of at least 80%. Trials rated as high quality (criteria not defined) or which were high quality apart from lack of double-blinding were included in the review.

One author assessed the quality of reporting in the included studies, which was independently checked by a second author. Discrepancies were resolved by discussion.

Data extraction
Relative risks and 95% confidence intervals were extracted or calculated by comparing event rates in the two groups. Data were extracted from head-to-head (direct) comparisons of two-compound formulation calcipotriol betamethasone
dipropionate gel versus comparator. Where direct comparisons were not available, interventions were compared by meta-regression on the basis of a common comparator, using a published method of adjusted indirect comparison. This required the assumption that the relative efficacy of the intervention was consistent across trials.

As outcomes were reported at eight weeks in most trials, four week outcome data were calculated if necessary and/or data were requested from primary authors or sponsors.

One author extracted the data, which were independently checked by a second author. Discrepancies were resolved by discussion.

**Methods of synthesis**
Data were pooled using a random-effects model to calculate pooled relative risks and 95% confidence intervals. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$. The absolute response rate for daily two-compound formulation calcipotriol and betamethasone dipropionate gel was calculated by pooling across all relevant trial arms in all direct and indirect comparisons. The absolute response rate per topical comparator treatment was also calculated, using methods described in the review.

There were too few trials to formally test for publication bias.

**Results of the review**
Ten RCTs were included in the review, with 6,341 participants (range 177 to 1,505). Eight RCTs apparently met all quality criteria, while two met all criteria apart from double-blinding.

When all direct and indirect comparisons were pooled, the two-compound formulation calcipotriol and betamethasone dipropionate gel was associated with a significantly higher response rate at four weeks than any other treatment, measured with either the Investigator Global Assessment (risk ratios ranging from 1.16 to 5.18) or Total Sign Score (risk ratios ranging from 1.29 to 13.79).

At up to eight weeks, two-compound formulation calcipotriol and betamethasone dipropionate gel was associated with: significantly lower rates of all adverse events than calcipotriol once or twice daily; fewer skin adverse effects than placebo, calcipotriol (once or twice daily) or calcipotriol with polytar; and fewer withdrawals due to adverse events than calcipotriol once or twice daily. For other adverse events, there was no significant difference between the two-compound gel and comparators.

The absolute response rate for two-compound formulation calcipotriol and betamethasone dipropionate gel using the Investigator Global Assessment was estimated at 60.33% (95% CI 57.9 to 62.7), while rates for comparators ranged from 11.7% to 53.3%. The absolute response rate for the two-compound gel using the Total Sign Score was estimated at 39.9% (95% CI 37.7 to 42.4), while rates for comparators ranged from 5.1% to 33.6%. The two-compound gel ranked first for every safety outcome apart from ‘all adverse events’, where it ranked third.

Full effect estimates and 95% confidence intervals were reported for all outcomes.

**Authors’ conclusions**
Two-compound formulation calcipotriol and betamethasone dipropionate gel may be safer and more effective than other topical therapies used for treating moderately severe psoriasis of the scalp.

**CRD commentary**
The objectives and inclusion criteria of the review were clear in most respects but were not fully adhered to, as one of the included studies did not meet inclusion criteria for sample size nor for comparators. The authors’ choice of instruments to measure efficacy was well justified (by reference to guidelines) but the rationale for extracting efficacy data at four weeks and safety data at eight weeks was not entirely clear. Although multiple relevant sources were searched, it was possible that some studies were missed as the search was limited to studies in English and no specific attempts were made to retrieve unpublished studies except from a single pharmaceutical company. Search terms were not reported.

Quality appeared to be high for most included trials. The pooling of direct and indirect evidence was questionable, as
there was high heterogeneity for some of the direct comparisons ($I^2=72\% \text{ to } 87\%$) and even higher heterogeneity for
several of the indirect estimates ($I^2=0\% \text{ to } 97\%$). For efficacy outcomes, this appeared to contravene the requirement
that the relative efficacy of the intervention was consistent in different trials, and suggested that even the direct
comparisons may not have been suitable for pooling. As the authors noted, there were clinical and methodological
differences between the trials. There were few trials and about half the comparisons involved indirect estimates. As the
authors made clear, the trial was funded by the manufacturers of the two-compound gel; one of the authors was
employed by this company at the time of writing; this may represent a conflict of interest. It was unclear whether the
review findings applied to mild psoriasis, as the text was inconsistent.

In view of limitations of the review, especially differences between the trials and use of indirect comparisons, the
reliability of the authors' conclusions is unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that two-compound formulation calcipotriol and betamethasone dipropionate gel may be
the best treatment for moderately severe psoriasis of the scalp.

**Research:** The authors did not state any implications for further research.

**Funding**

LEO Pharma A/S (manufacturers of the two-compound gel evaluated in the review).

**Bibliographic details**

Bottomley JM, Taylor RS, Ryttov J. The effectiveness of two-compound formulation calcipotriol and betamethasone
dipropionate gel in the treatment of moderately severe scalp psoriasis: a systematic review of direct and indirect
evidence. Current Medical Research and Opinion 2011; 27(1): 251-268

**PubMedID**

21142838

**DOI**

10.1185/03007995.2010.541022

**Original Paper URL**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Administration, Topical; Algorithms; Anti-Inflammatory Agents /administration & dosage /adverse effects /economics;
Betamethasone /administration & dosage /adverse effects /analog & derivatives; Calcitriol /administration & dosage
/adverse effects /analog & derivatives; Chemistry, Pharmaceutical; Drug Combinations; Evidence-Based Practice;
Gels; Humans; Psoriasis /complications /drug therapy /pathology; Scalp Dermatoses /complications /drug therapy
/pathology; Severity of Illness Index; Treatment Outcome

**AccessionNumber**

12011000639

**Date bibliographic record published**

28/07/2012

**Date abstract record published**

10/12/2012

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.