Authors' objectives
To assess the effectiveness and safety of nonsurgical repigmentation therapies in localised and generalised vitiligo by means of a meta-analysis.

Searching
MEDLINE and EMBASE were searched from January 1966 to December 1997. The main keywords (including analogs and derivatives) used were: 'vitiligo', 'phototherapy', 'PUVA therapy', 'ultraviolet therapy', 'phenylalanine', 'khellin', 'glucocorticosteroids synthetic' and 'anti-inflammatory agents'. No language restrictions were applied. Other sources searched were abstract books of symposia and congresses, theses, textbooks, monographs, reviews, editorials, letters to the editor, free or rapid communications, and the reference lists from all the articles retrieved. Twenty-one leading authorities in the field of vitiligo and 9 pharmaceutical companies were also contacted for any additional published and unpublished references.

Study selection
Study designs of evaluations included in the review
Randomised and non-randomised controlled trials (RCTs) were included in the review. Non-randomised trials were also analysed as patient series. Since comparative or placebo-controlled trials can contain a description of at least 2 patient series, the total number of patient series exceeded the total number of studies included. Double publications of studies were excluded, as were those that reported on fewer than 5 patients or provided insufficient data on effectiveness.

Specific interventions included in the review
Oral and topical psoralen plus sunlight or artificial UV-A (both sources were termed UV-A), including methoxsalen, trioxsalen, bergapten and unsubstituted psoralen (PS); UV-B broadband and narrowband therapy; phenylalanine plus sunlight or UV-A; oral and topical khellin plus sunlight or UV-A; and corticosteroids (oral, topical, intralesional). Topical corticosteroids were divided into class 3 ('potent corticosteroids'), which included the drugs betamethasone valerate and halometasone, and class 4 (very potent corticosteroids), which included clobetasol propionate. With regard to intralesional administration of corticosteroids, studies using triamcinolone acetonide were included. Excluded were combination therapies and studies that used obsolete drug(s) or dosage schemes.

Participants included in the review
From the description of the included studies given it can be inferred that the participants included were those with localised or generalised vitiligo. Localised vitiligo was defined as vitiligo affecting less than 20% of the total body surface. No other information was available regarding the participants.

Outcomes assessed in the review
The outcome assessed was repigmentation of the affected area and the various side-effects from the interventions. Treatment was regarded as successful when more than 75% repigmentation was achieved.

How were decisions on the relevance of primary studies made?
Two investigators independently assessed the studies for inclusion, and any disagreements were resolved by consultation with a third investigator.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed. They state that the method of randomisation was not reported in any of the included RCTs.
Data extraction
The authors do not state how many of the reviewers performed the data extraction. Data were extracted for the following: number of patients in active and placebo groups, number of responders to the therapy in both the active and the placebo group, treatment duration, number of series reporting side-effects, and number of patients reporting different types of side-effects.

Methods of synthesis
How were the studies combined?
A random-effects model was used to estimate the treatment effect across RCTs. Analysis on patients series was based on sample size weighted averages for each modality, by dividing the total number of patients who achieved more than 75% repigmentation by the total number of patients in the included series.

Treatment specific side-effects were estimated by dividing the number of patients with side-effects by the total number of patients studied in the patient series.

The authors do not provide any assessment of publication bias.

How were differences between studies investigated?
No formal test of heterogeneity was reported, nor an attempt made to evaluate possible causes of heterogeneity that may be present in the combined studies. However, a random-effects model was used to combine RCTs because the study population and treatment outcomes in these trials were expected to be heterogeneous.

Results of the review
For localised vitiligo: 10 RCTs (approximately 381 participants) and 29 patient series (993 participants) were included. For generalised vitiligo: 10 RCTs (approximately 366 participants) and 46 patient series (1,866 participants) were included.

1. Therapies for localised vitiligo.

The mean treatment duration varied from 5 to 8 months.

RCTs: the odds ratio (OR) showed non significant differences between class 4 corticosteroids (OR 1.00, 95% confidence interval, CI: 0.16, 6.21), intralesional corticosteroids (single study OR 1.42, 95% CI: 0.31, 6.47), topical khellin (2 to 3%) plus UV-A (OR 1.18, 95% CI: 0.38, 3.62), or topical khellin (5%) plus UV-A (OR 1.00, 95% CI: 0.39, 2.54) and their respective placebos. Class 3 corticosteroids had a significant OR (14.32, 95% CI: 2.45, 83.72) versus placebo.

Patient series: class 3 corticosteroids had 56% of patients achieving more than 75% repigmentation (95% CI: 50, 62), and class 4 corticosteroids achieved 55% (95% CI: 49, 61).

Side-effects: 97% of the patient series reported side-effects. Of the topical psoralen plus UV-A group, methoxsalen had the highest proportion of patients developing phototoxic reactions (58%, 95% CI: 51, 65), followed by trioxsalen (39%, 95% CI: 23, 56) and PS (25%, 95% CI: 12, 38). Atrophy was the most common side-effect with local corticosteroids occurring mostly in patients receiving intralesional corticosteroids (33%, 95% CI: 22, 43), followed by patients using class 4 corticosteroids (14%, 95% CI: 10, 18) and class 3 corticosteroids (2%, 95% CI: 1, 5). Other less common side-effects were telangiectasia, corticosteroid-induced acne and hypertrichosis. Studies on topical khellin (2, 3 and 5%) plus UV-A did not report any side-effects.

2. Therapies for generalised vitiligo.

The mean treatment duration of photochemotherapies varied between 9 months for phenylalanine plus UV-A and 24 months for oral PS plus UV-A. The treatment with oral minipulse therapy varied between 6 and 24 months.

RCTs: ORs showed significant differences for oral methoxsalen plus sunlight (single study OR 23.37, 95% CI: 1.33,
409.93), oral PS plus sunlight (pooled OR 19.87, 95% CI: 2.37, 166.32), and oral trioxsalen plus sunlight (pooled OR 3.75, 95% CI: 1.24, 11.29) and their respective placebos. Therapies that used phenylalanine plus UV-A (OR 2.24, 95% CI: 0.35, 14.28) or oral khellin plus sunlight (single study OR 13.16, 95% CI: 0.69, 249.48) showed no significant differences between the active drug and placebo.

Patient series: phototherapy with narrowband UV-B had the highest percentage of patients who achieved more than 75% repigmentation (63%, 95% CI: 50, 76), followed by broadband UV-B (57%, 95% CI: 29, 82). Only one study of each was included. Oral methoxsalen plus UV-A and oral bergapten plus UV-A had success rates of 51% (95% CI: 46, 56) and 43% (95% CI: 38, 48), respectively. The differences between the mean success rates of narrowband UV-B, broadband UV-B, and oral methoxsalen plus UV-A were not significant.

Side-effects: 87% of the patient series that were included reported side-effects. Of the oral photochemotherapeutic modalities, methoxsalen had the highest proportion of patients who developed nausea and vomiting (29%, 95% CI: 24, 35), followed by khellin (9%, 95% CI: 2, 16) and PS (8%, 95% CI: 2, 15). Phototoxic reactions were seen mostly in patients taking methoxsalen (25%, 95% CI: 20, 30), followed by bergapten (6%, 95% CI: 4, 8). Abnormal results of liver function tests were observed mostly in patients using khellin (17%, 95% CI: 8, 26). Systemic reactions (headache, dizziness) were reported mostly in patients taking oral PS (24%, 95% CI: 14, 33). Pruritus was most frequently seen with the use of methoxsalen (31%, 95% CI: 26, 37). An increased contrast between normal and depigmented skin was reported mostly with the use of methoxsalen (10%, 95% CI: 6, 13). In comparison with daily intake of corticosteroids, oral minipulse therapy with corticosteroids was associated with a lower mean proportion of patients with systemic and cutaneous side-effects.

Authors' conclusions
The authors state that class 3 corticosteroids and UV-B therapy are the most effective and safest therapies for localised and generalised vitiligo, respectively.

CRD commentary
The review question was stated clearly and the literature research was adequate. The inclusion criteria were defined. No information was provided on how the papers were assessed for validity. Insufficient information was given regarding patient characteristics, e.g. age, sex and race. Heterogeneity was not assessed to ensure that the studies were sufficiently similar for pooling.

The results of the study were adequately presented and the authors' conclusion follows from the results. The results and conclusions should be interpreted cautiously given the above limitations, in particular the uncertainty about the quality of studies included in the review.

Implications of the review for practice and research
Practice: The authors state that 'this review may be used as a basis for the development of evidence-based guidelines for the management of vitiligo'.

They make the following recommendations concerning the choice of the most effective and safest therapy: for patients with localised vitiligo, class 3 corticosteroids are advised as first choice therapy; and when patients exhibit generalised vitiligo, UV-B (narrowband or broadband) therapy or oral methoxsalen plus UV-A is recommended. Despite the absence of side-effects with the use of topical khellin plus UV-A, the authors do not recommended this option because the drug is not shown to be effective in the analysis of RCTs or patient series.

Research: The authors state that 'future clinical trials in vitiligo should evaluate treatment outcome in relation to such variables as localisation and duration of the lesions, skin type, age, quality of life, and compliance of the patients'. In addition, the authors support the performance of follow-up studies on the permanency of therapy-induced repigmentation, in particular for photoradiation.
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