BJD British Journal of Dermatology

Guideline for the diagnosis and management of vitiligo

D.J. Gawkrodger, A.D. Ormerod, L. Shaw, I. Mauri-Sole, M.E. Whitton,*† M.J. Watts, A.V. Anstey, J. Ingham‡ and K. Young‡

British Association of Dermatologists, 4 Fitzroy Square, London W1T 5HQ, U.K.
*Vitiligo Society, 125 Kennington Road, London SE11 6SF, U.K.
†Cochrane Skin Group, Centre of Evidence Based Dermatology, King's Meadow Campus, University of Nottingham NG7 2NR, U.K.
‡Royal College of Physicians, St Andrew's Place, Regent's Park, London NW1 4LE, U.K.

Correspondence
D.J. Gawkrodger, Department of Dermatology, Royal Hallamshire Hospital, Sheffield S10 2JF, U.K.
E-mail: david.gawkrodger@sth.nhs.uk

Accepted for publication
11 August 2008

Key words
diagnosis, guidelines, treatment, vitiligo

Conflicts of interest
No member of the Guideline Development Group has declared any interest in companies whose products are named in the guideline, or has had any sponsorship or consultancy from or with companies whose products are named in the guideline, or has had any editorial fees related to commissioned articles for publications named in the guideline, or has a patent pending or existing related to products named in the guideline. D.J.G. has been chairman of the Vitiligo Society's Medical Advisory Board, and M.E.W. is a patron of the Vitiligo Society.

D.J.G., A.D.O., L.S., I.M.-S., M.E.W., M.J.W. and A.V.A. are members of the Guideline Development Group, and technical support was provided by J.I. and K.Y.

Contents: See Appendix 1

DOI 10.1111/j.1365-2133.2008.08881.x

Summary

This detailed and user-friendly guideline for the diagnosis and management of vitiligo in children and adults aims to give high quality clinical advice, based on the best available evidence and expert consensus, taking into account patient choice and clinical expertise.

The guideline was devised by a structured process and is intended for use by dermatologists and as a resource for interested parties including patients. Recommendations and levels of evidence have been graded according to the method developed by the Scottish Inter-Collegiate Guidelines Network. Where evidence was lacking, research recommendations were made.

The types of vitiligo, process of diagnosis in primary and secondary care, and investigation of vitiligo were assessed. Treatments considered include offering no treatment other than camouflage cosmetics and sunscreens, the use of topical potent or highly potent corticosteroids, of vitamin D analogues, and of topical calcineurin inhibitors, and depigmentation with p-(benzyloxy)phenol. The use of systemic treatment, e.g. corticosteroids, ciclosporin and other immunosuppressive agents was analyzed.

Phototherapy was considered, including narrowband ultraviolet B (UVB), psoralen with ultraviolet A (UVA), and khellin with UVA or UVB, along with combinations of topical preparations and various forms of UV. Surgical treatments that were assessed include full-thickness and split skin grafting, mini (punch) grafts, autologous epidermal cell suspensions, and autologous skin equivalents. The effectiveness of cognitive therapy and psychological treatments was considered.

Therapeutic algorithms using grades of recommendation and levels of evidence have been produced for children and for adults with vitiligo.

Key recommendations

Grades of recommendation/levels of evidence are given (see Tables 1 and 2).

Therapeutic algorithm in children

1. Diagnosis

Where vitiligo is classical, the diagnosis is straightforward and can be made in primary care (D/4) but atypical presentations may require expert assessment by a dermatologist (D/4).

2. No treatment option

In children with skin types I and II, in the consultation it is appropriate to consider, after discussion, whether the initial approach may be to use no active treatment other than use of camouflage cosmetics and sunscreens (D/4).

3. Topical treatment

- Treatment with a potent or very potent topical steroid should be considered for a trial period of no more than 2 months. Skin atrophy has been a common side-effect (B/1+).

Table 1 Levels of evidence (from Scottish Inter-Collegiate Guidelines Network)

	Levels of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Nonanalytical studies, e.g. case reports, case series
4	Expert opinion

RCT, randomized controlled trial.

Table 2 Grades of recommendation (from Scottish Inter-Collegiate Guidelines Network)

	Grades of recommendation
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

RCT, randomized controlled trial.

• Topical pimecrolimus or tacrolimus should be considered as alternatives to the use of a highly potent topical steroid in view of their better short-term safety profile (B/1+).

4. Phototherapy

Narrowband (NB) ultraviolet (UV) B phototherapy should be considered only in children who cannot be adequately managed with more conservative treatments (D/4), who have widespread vitiligo, or have localized vitiligo associated with a significant impact on patient's quality of life (QoL). Ideally, this treatment should be reserved for patients with darker skin types and monitored with serial photographs every 2–3 months (D/3). NB-UVB should be used in preference to PUVA in view of evidence of greater efficacy, safety and lack of clinical trials of PUVA in children (A/1+).

5. Systemic and surgical treatments

The use of oral dexamethasone to arrest progression of vitiligo cannot be recommended due to an unacceptable risk of side-effects (B/2++). There are no studies of surgical treatments in children.

6. Psychological treatments

Clinicians should make an assessment of the psychological and QoL effects of vitiligo on children (C/2++). Psychological interventions should be offered as a way of improving coping mechanisms (D/4). Parents of children with vitiligo should be offered psychological counselling.

Therapeutic algorithm in adults

1. Diagnosis

Where vitiligo is classical, the diagnosis is straightforward and can be made in primary care (D/4) but atypical presentations may require expert assessment by a dermatologist (D/4). A blood test to check thyroid function should be considered in view of the high prevalence of autoimmune thyroid disease in patients with vitiligo (D/3).

2. No treatment option

In adults with skin types I and II, in the consultation it is appropriate to consider, after discussion, whether the initial approach may be to use no active treatment other than use of camouflage cosmetics and sunscreens (D/4).

3. Topical treatment

• In adults with recent onset of vitiligo, treatment with a potent or very potent topical steroid should be considered for a trial period of no more than 2 months. Skin atrophy has been a common side-effect (B/1+).
• Topical pimecrolimus should be considered as an alternative to a topical steroid, based on one study. The side-effect profile of topical pimecrolimus is better than that of a highly potent topical steroid (C/2+).
• Depigmentation with *p*-(benzyloxy)phenol (monobenzyl ether of hydroquinone) should be reserved for adults severely affected by vitiligo (e.g. more than 50% depigmentation or extensive depigmentation on the face or hands) who cannot

or choose not to seek repigmention and who can accept permanently not tanning (D/4).

4. Phototherapy

NB-UVB phototherapy (or PUVA) should be considered for treatment of vitiligo only in adults who cannot be adequately managed with more conservative treatments (D/4), who have widespread vitiligo, or have localized vitiligo with a significant impact on QoL. Ideally, this treatment should be reserved for patients with darker skin types and monitored with serial photographs every 2–3 months (D/3). NB-UVB should be used in preference to oral PUVA in view of evidence of greater efficacy (A/1+).

5. Systemic therapy

The use of oral dexamethasone to arrest progression of vitiligo cannot be recommended due to an unacceptable risk of side-effects (B/2++).

6. Surgical treatments

- Surgical treatments are reserved for cosmetically sensitive sites where there have been no new lesions, no Koebner phenomenon and no extension of the lesion in the previous 12 months (A/1++).
- Split-skin grafting gives better cosmetic and repigmentation results than minigraft procedures and utilizes surgical facilities that are relatively freely available (A/1+). Minigraft is not recommended due to a high incidence of side-effects and poor cosmetic results (A/1+). Other surgical treatments are generally not available.

7. Psychological treatments

Clinicians should make an assessment of the psychological and QoL effects of vitiligo on patients (C/2++). Psychological interventions should be offered as a way of improving coping mechanisms in adults with vitiligo (D/4).

Introduction

Vitiligo is a disease process that results in depigmented areas in the skin. It usually begins after birth and, although it can develop in childhood, the average age at onset is about 20 years.[1] Most commonly, vitiligo produces symmetrical depigmented areas of skin that otherwise appears normal. A less common type is the segmental form in which asymmetrical, one-sided depigmentation develops.

An important aspect of vitiligo is the psychological effect of the disease. Vitiligo is often immediately visible to others and those with the condition may suffer social and emotional consequences including low self-esteem, social anxiety, depression, stigmatization and, in extreme cases, rejection by those around them.[2] In people with a pale white skin colour, vitiligo may cause little concern.

There is increasing evidence to support the view that vitiligo is an autoimmune disease and that it shows a familial trait in about 18% of cases.[3] The diagnosis of vitiligo is in many cases regarded as being straightforward, although this is not always the case. However, the treatment of vitiligo is acknowledged as being difficult. Hence, an evidence-based review of the management of the disease is timely.

Method of guideline development

The development of this guideline was a combined effort involving the Therapy Guidelines and Audit Subcommittee of the British Association of Dermatologists, the Clinical Standards Department of the Royal College of Physicians of London, The Cochrane Skin Group, and the Vitiligo Society. The Guideline Development Group (GDG) included one trainee dermatologist who is also a paediatrician (L.S.), one general practitioner with an interest in dermatology (I.M.-S.), one nurse (M.J.W.), one patient representative of the Vitiligo Society who is also a member of The Cochrane Skin Group (M.E.W.), and three dermatologists (A.V.A., A.D.O. and D.J.G.). Technical and methodological support was provided by the Royal College of Physicians Clinical Standards Department (J.I., K.Y. and Karen Reid), and administrative support by the British Association of Dermatologists. The Cochrane Skin Group has already published a systematic review of interventions for vitiligo.[4]

Aims

The objective of the process was to produce a detailed and user-friendly guideline giving the best available clinical advice for the management of vitiligo, based on the best available evidence and expert consensus, taking into account patient choice and clinical expertise. The guideline is intended for use by dermatologists (with an abbreviated version available for other healthcare professionals) and as a resource for interested parties including patients.

Scope

Diagnosis and management for adults and children with any type of vitiligo were considered. Other depigmenting diseases were considered in the differential diagnosis but their further management was not included.

Audience

The audience for this guideline is healthcare professionals, including doctors, nurses, psychologists, and indeed patients themselves and their carers. Commissioning organizations and health service providers may also find the guideline helpful.

Process

Nine meetings were held over a period of 12 months. A systematic approach was taken to the development of the guideline, using the method developed by the Scottish Inter-Collegiate Guidelines Network (SIGN; http://www.sign.ac.uk/methodology/index.html). In the initial meetings, the questions to be answered were formulated. Subsequently, literature searches were performed to obtain the evidence, which was subsequently appraised. This appraisal was performed in a standardized way according to the method described by SIGN (see Tables 1 and 2).

Tables showing the results were produced and are available on the website (http://www.bad.org.uk). The evidence was discussed at meetings of the group where the level of the evidence and the grade of the recommendations were agreed. Where no evidence was available, consensus statements were drawn up. Lastly, the entire guideline was agreed by the GDG.

Funding, declaration of interests and review

The expenses for the meetings of the GDG were underwritten by the British Association of Dermatologists. The Royal College of Physicians of London bore the costs of the work done by the members from the Clinical Standards Department. The members of the Group were not paid for their work.

The guideline will be reviewed in 5 years time.

What symptoms and signs are suggestive of vitiligo?

Introduction

Vitiligo vulgaris/nonsegmental vitiligo is an acquired chronic depigmentation disorder characterized by white patches. These are often symmetrical and usually increase in size with time. This corresponds with a substantial loss of functioning epidermal and, sometimes, hair follicle melanocytes. Segmental vitiligo is a variant of vitiligo confined to one unilateral segment. One unique segment is involved in most patients but two or more segments on the same or opposite sides may be involved or depigmentation may follow a dermatome distribution or Blaschko's lines. Depigmenting or hypopigmenting skin diseases that are considered in the differential diagnosis of vitiligo are listed in Table 3.

In symmetrical vitiligo, the commonest sites to be affected are the fingers and wrists, the axillae and groins and the body orifices such as the mouth, eyes and genitalia. As the pigment cells are destroyed, sometimes a 'trichrome' appearance of a white centre with an intermediate, pale area around it is found. In vitiligo skin there is no surface change and usually no redness. Very occasionally, inflammation is seen at the advancing edge of a vitiligo macule. Vitiligo can affect melanocytes in the hair roots, resulting in white eyelashes and white hair within the pale skin patches. Depigmentation can affect mucosal areas such as in the mouth. This can be prominent in darkly pigmented people.

Table 3 Differential diagnosis of vitiligo

Halo naevus
Hypopigmented naevus
Idiopathic guttate hypomelanosis
Leprosy
Lichen sclerosus (for genital vitiligo)
Melanoma-associated leucoderma
Melasma
Mycosis fungoides-associated depigmentation
Naevus anaemicus
Naevus of Ito
Piebaldism
Pityriasis alba
Pityriasis versicolor
Postinflammatory depigmentation, e.g. scleroderma, psoriasis, atopic eczema
Post-traumatic depigmentation
Topical or drug-induced depigmentation
Tuberous sclerosis

The three main diseases that can be mistaken for vitiligo are tinea (pityriasis) versicolor, piebaldism and guttate hypomelanosis. Tinea versicolor is a superficial yeast infection that can cause loss of pigment in darker skinned individuals. It presents as pale macules typically on the upper trunk and chest, with a fine dry surface scale. Piebaldism is an autosomal dominant disease in which there is absence of melanocytes from the affected areas of the skin. It usually presents at birth with depigmented areas that are usually near the mid-line on the front, including a forelock of white hair. In idiopathic guttate hypomelanosis, multiple small, white macules are noted, mostly on the trunk or on sun-exposed parts of the limbs. When vitiligo affects only the genital areas, it can be difficult to exclude lichen sclerosus, which sometimes can coexist with vitiligo.

Patients with vitiligo often develop autoimmune thyroid disease or other autoimmune diseases and a history of autoimmune disease in a family member is obtained in 32% of patients.[3] In one series of 41 adults, a history of autoimmune thyroid disease was found in 14 (34%), suggesting that screening for abnormal thyroid function or the presence of autoantibodies to thyroid antigens may be helpful in the management of adults with vitiligo.[3]

As part of the initial assessment, the patient's skin type should be noted. The definitions are shown in Table 4.

Methods

Evidence for this question came from consensus within the GDG.

Evidence statements

General evidence on the diagnosis of vitiligo was considered and a consensus view was made by the group. This specific

Table 4 Skin types (from http://www.dermnetnz.org)

Skin type	Typical features	Tanning ability
I	Pale white skin, blue/hazel eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

question has been addressed recently by Taieb and Picardo,[5] who undertook an assessment and evaluation of vitiligo, including a definition of the disease, in a consensus group (level of evidence 4).

Evidence to recommendations

The group found that, in many cases, the diagnosis of vitiligo is straightforward but some cases present a difficult diagnostic challenge.

Recommendations

1. Where vitiligo is classical, as in the symmetrical types, the diagnosis is straightforward and can be made with confidence in primary care.

Grade of recommendation	D
Level of evidence	4

2. In patients with an atypical presentation, diagnosis is more difficult and referral for expert assessment by a dermatologist is recommended.

Grade of recommendation	D
Level of evidence	4

3. In adults with vitiligo, a blood test to check thyroid function should be considered in view of the high prevalence of autoimmune thyroid disease in patients with vitiligo.

Grade of recommendation	D
Level of evidence	3

What is the accuracy of Wood's light compared with naked eye examination in the diagnosis of vitiligo?

Introduction

Wood's light is a hand-held ultraviolet (UV) irradiation device that emits UVA. It has been used to identify areas of depigmentation that may not be visible to the naked eye, especially in pale skin.

Methods

The GDG considered the limited evidence, consisting of two observational studies, and consensus statements regarding Wood's light.

Evidence statements

Wood's light delineates areas of pigment loss. Actively depigmenting areas may appear larger under UV illumination than with visible light, whereas areas showing repigmentation can appear larger or smaller with UV than with visible light. Thus combined assessment of a selected area in natural and Wood's light is useful.[5] Photography using a UV camera is also reported as useful in documenting pigmentary disorders.[6] Although Wood's light has not been scientifically evaluated, it has potential as a tool for objective assessment of vitiligo in research and clinical trials.

Evidence to recommendations

Wood's light can give the dermatologist additional information about the extent and activity of patches of vitiligo. Experience is needed in the use of the machine and evaluation of the results (level of evidence 4).

Recommendation

1. Wood's light may be of use in the diagnosis of vitiligo and in the demonstration of the extent and activity of the disease in subjects with skin types I and II. Wood's light can be of use in monitoring response to therapy.

Grade of recommendation	D
Level of evidence	4

What is the natural history of vitiligo?

Introduction

Despite being a common condition that may cause severe and long-lasting disability, the epidemiology of vitiligo has not been established with clarity.

Methods

No studies on the natural history of vitiligo were identified by the search of the literature. Evidence and recommendations are based on consensus views.

Evidence statements

The natural history for the condition remains unclear, as no long-term follow-up study has been performed. This is relevant to the large number of therapeutic studies that have been carried out on vitiligo, as few have attempted to assess the longevity of any therapeutic response. There is no convincing evidence to suggest that any treatment has an effect on the natural history of vitiligo.

Textbooks of dermatology usually fail to comment on the natural history of vitiligo. Although some patients have been reported to undergo spontaneous repigmentation, this is probably uncommon. More typically, vitiligo is a chronic persistent disorder that progresses in a step-wise fashion with long periods when the disease is relatively inactive or static interspersed with shorter periods when areas of pigment loss extend. The genetic basis for vitiligo postulates a contribution from multiple recessive alleles at unlinked autosomal loci.[7]

The most detailed attempt at an epidemiological study was performed on the island of Bornholm in 1970–71.[8] This involved a single attempt to establish the prevalence of vitiligo in a population of sufficient size (47 033) to eliminate (or minimize) bias. Age-specific rates were established and showed that vitiligo is rare in the 0–9-year age group, with prevalence rising steadily thereafter to a peak at 60–70 years. Although this does not prove the natural history, it provides indirect evidence consistent with the notion that vitiligo is a life-long condition, with new cases in each age-band joining others who previously developed the condition. This study did not attempt a cross-sectional sample, which might have diagnosed more patients including those who were unaware of the study, or who had mild disease unapparent to them or who chose not to come forward.

A study from South Korea reported progressive disease in > 90% of a series of 318 patients with vitiligo.[9] This was a selected group and the methods used to assess disease progression were crude (patient recall on questionnaire). Nevertheless, it suggested that progression rather than spontaneous resolution is the norm. Finally, an epidemiological study from South America used a case–control design, identifying significant differences in age at presentation between unilateral (younger) and generalized vitiligo,[10] but no differences for rate of disease progression between the two groups (level of evidence 4).

Evidence to recommendations

No study has specifically determined the natural history of vitiligo. Indirect evidence and clinical experience of the GDG suggest that, in most cases, vitiligo is a chronic and persistent disorder characterized by periods of disease activity and often long periods of relative inactivity or stasis. Response to treatment should be considered in the light of this, recognizing that spontaneous repigmentation may occur, albeit uncommonly.

Recommendation

1. The response to treatment of vitiligo should be considered in the context of the natural history, recognizing that spontaneous repigmentation may occur but is uncommon.

Grade of recommendation	D
Level of evidence	4

Research recommendation

1. A longitudinal epidemiological study is needed to define the natural history of vitiligo. This should use photographs combined with computerized image analysis, to quantify how the vitiligo changes with time.

What is the quality of life in patients with vitiligo compared with other skin diseases?

Introduction

Vitiligo can be a psychologically devastating disease which has a significant impact on quality of life (QoL) and self-esteem.[4,11] It may cause social isolation and significant depression,[12,13] create difficulties in sexual relationships, and affect perceived suitability for marriage.[14,15]

Some assessment of the impact of vitiligo on the patient's QoL should be made at the initial consultation, along with an assessment of the disease extent. The assessment of 'quality of life' is likely to be done differently by different clinicians and patients, unless standardized. Vitiligo differs from other diseases as it has no physical symptoms to speak of – its main impact is psychological.

QoL indices are important outcome measures in studies of vitiligo because there may be discrepancy between a researcher's definition of successful outcome and the patient's. For example, a study may show a statistical significance using an outcome measure of > 50% repigmentation when only 10% of patients with vitiligo consider this a successful result.[16] Hence, there is discrepancy between doctor and patient assessment of disease severity which may reflect the fact that psychological factors are important in overall morbidity.[17]

Methods

Several large studies have recorded a dermatology QoL index score (Dermatology Life Quality Index, DLQI) for vitiligo.[2,14,15,18–25] The scores range widely (3·5–15). This

probably reflects the disease severity in the patient group examined, i.e. varying between primary care and tertiary centres. Few studies directly compare QoL scores in vitiligo with other skin diseases. Two studies compared vitiligo and psoriasis using the DLQI.[15,26] Both had patient populations that were not well matched. Two other studies used Skindex and the World Health Organization's GHQ12 scoring system.[27,28]

Evidence statements

One study comparing QoL in vitiligo and psoriasis showed a higher DLQI for psoriasis than vitiligo (mean 6·26 and 4·95, respectively).[26] The scoring pattern was different, with vitiligo scoring lower on the symptoms and treatment subscales and higher on the social, clothing and leisure subscales. This suggests that QoL scales with a weighting on the effect of symptoms and treatment effects underestimate the effect of vitiligo on QoL. DLQI might not be the most appropriate tool for assessing QoL in vitiligo as it may inevitably give a rather low score (level of evidence 2+).

In a study using Skindex and the GHQ12 score vitiligo scored higher than psoriasis on the social functioning subscale and emotions subscale but much lower on the symptoms subscale (level of evidence 2+).[27] The GHQ questionnaire reveals that QoL is more affected by vitiligo than by psoriasis (level of evidence 3).[28]

Race, colour and culture all influence how vitiligo affects QoL. DLQI is higher in studies looking at more racially pigmented groups. Loss of pigmentation may be seen as a threat to racial identity.[29] There may be cultural perceptions that wrongdoing in a previous life causes vitiligo. This stigma may itself affect QoL. There may be lay confusion with leprosy. Vitiligo causes unique psychosocial problems in some parts of the world (level of evidence 3).[30]

Gender also influences the way vitiligo affects QoL. Women are more severely affected, being more likely to be depressed about their appearance and more likely to internalize stigmatization and attribute an internal cause (level of evidence 3).[20] Women with vitiligo scored as highly on the DLQI as did women with psoriasis, whereas men with vitiligo scored significantly lower than men with psoriasis (level of evidence 2+).[26]

Psychological effects are prominent when visible body areas, e.g. the hands and face, are affected (level of evidence 3).[20] Studies of treatments for vitiligo should employ measures of QoL to assess the end result of any treatment, i.e. patient satisfaction with their response to therapy (consensus view of the GDG).

Evidence to recommendations

Vitiligo has an impact on a patient's QoL comparable with that of psoriasis. The DLQI may not be the best tool for measuring QoL in vitiligo, because vitiligo has no physical symptoms and is often not treated. Vitiligo has more impact on QoL in women, in those with racially pigmented skin, and in a cultural setting where there is attribution of blame for disfigurement.

Recommendations

1. Clinicians should make an assessment of the psychological and QoL effects of vitiligo on patients.

Grade of recommendation	C
Level of evidence	2+

2. In therapeutic trials relating to vitiligo, researchers should make the patient's improvement in QoL the most important outcome measure.

Grade of recommendation	D
Level of evidence	4

Research recommendation

1. More research is needed on appropriate QoL assessments for vitiligo and they should always be used as outcome measures.

In all patients with vitiligo, what is the accuracy of a scoring index in showing the outcome of common treatments compared with simple photography?

Introduction

A problem when assessing efficacy of treatment for vitiligo is to quantify the response with an objective, valid and reproducible scoring system. The most important aspect of therapeutic response is how the patient feels about their vitiligo after the treatment (see above). Another, which may well include how a patient feels, is the degree of repigmentation that has occurred. When patients are asked 'what degree of repigmentation do you want?' the answer is 'complete'. However, 100% repigmentation is very rarely achievable and something less has usually to be accepted. Assessment of repigmentation in vitiligo studies usually involves the use of photography or sometimes, the 'rule of nines'. Both methods have serious drawbacks. Inevitably, photography is a two-dimensional medium. The rule of nines is an estimate of surface area. A better method is needed that takes into account more than just the surface area.

Methods

Only three papers were identified, two clinical trials and one observational study.

Evidence statements

The vitiligo area-scoring index (VASI), based on the PASI score for psoriasis,[31] is a quantitative tool that can be used to evaluate the extent of vitiligo based on a composite estimate of the overall area of depigmented patches at baseline and the degree of macular repigmentation within these patches. The VASI correlated well with physician and patient global assessments ($P = 0{\cdot}05$ and $P = 0{\cdot}001$, respectively). A problem with VASI is that it takes into account only the area of vitiligo, and not other factors.

The Vitiligo European Task Force (VETF) assessed vitiligo and treatment outcomes using a system that combines analysis of extent, stage of disease and disease progression.[5] Extent is evaluated by the rule of nines; staging is based on cutaneous and hair pigmentation, and assessment of spreading is based on Wood's light examination. For extent, the investigators' correlations were very close (92% of evaluations were within 1% of the mean value). There were no patients with skin type VI in the study (20% of patients were skin type IV or V, which may not be representative for the U.K.). In addition, the measurements were not always consistent and no κ value was given for interobserver variability for extent of disease.

The use of digitized photographs subjected to morphometric computer analysis to delineate the degree of repigmentation has been described.[32] This method seemed to be workable and compared well with physicians' visual evaluations.

Evidence to recommendations

The response to treatments for vitiligo have typically been analysed using nominal binary scales in which the proportion of treated patients who achieve a specified degree of repigmentation is compared using nonparametric analysis based on physicians' assessment. The VETF tool adds two parameters, namely severity (staging) and progression (spreading). The VETF tool may give a more accurate assessment of vitiligo in research studies and seems to be the current gold standard but is impractical for routine clinic use. Digital photography with morphometric evaluation may be helpful in clinical trials.

Recommendations

1. The VASI and VETF tools offer a more accurate measure of disease extent than simple clinical photography alone (even when combined with computerized morphometry) and should be used in a research setting. Additionally, the VETF assesses severity and spreading.

Grade of recommendation	D
Level of evidence	2+

2. For routine clinical use, serial photographs should be used to monitor response to treatment in vitiligo.

Grade of recommendation	C
Level of evidence	4

Research recommendation

1. Further research is needed to establish a simple, meaningful and reproducible method to monitor treatment response of vitiligo in the clinic and in clinical trials.

In all patients with vitiligo, what is the efficacy of applying betamethasone, clobetasol, fluocinolone, fluticasone or mometasone vs. placebo or other active treatment in terms of condition progression, area reduction and quality of life score?

Introduction

In the management of vitiligo, the physician typically makes an initial assessment of the patient and discusses the disease and treatment options. In many instances, the first-line therapy involves topical medicaments. In most cases, patients are offered advice about use of sunscreens and cosmetic camouflage including fake tanning products. There is evidence from one study that use of cosmetic camouflage can produce an improvement in QoL (DLQI 7·3 to 5·9).[15] With regard to topical therapy that might influence the state of the disease, the use of topical steroids is the usual first-line treatment.

Methods

Seven papers met the criteria for inclusion, underlining the paucity of good quality clinical studies of topical treatments in vitiligo. Only studies in which there were 20 or more evaluations were included. In all trials, only patients with generalized (symmetrical) types of vitiligo were included. In some studies, the researchers had excluded patients with vitiligo on the hands, presumably as they assumed the lesions would not respond to treatment. A left-vs.-right treatment methodology has been used in some studies and this presents potential problems. Studies on children have been separated from those on adults.

Evidence statements

The studies of Clayton[33] and Kandil,[34] although easily criticized, show that the use of a highly potent (clobetasol) or potent (betamethasone) topical steroid can repigment vitiligo but only in a small proportion of cases. Clayton found 15–25% repigmentation in 10 of 23 subjects (ages not stated) and > 75% in two of 23 (the other 11 showed no response), while Kandil found 90–100% repigmentation in six of 23 subjects (ages not given for all but one was aged 12 years)

and 25–90% in three (with six showing 'beginning' repigmentation).[33,34] Clayton found that all steroid users had skin atrophy with clobetasol, a highly potent topical steroid (used for 8 weeks), while Kandil noted hypertrichosis in two subjects and acne in three subjects, related to 4 months use of the potent topical steroid, betamethasone.[33,34]

Westerhof and colleagues,[35] in probably the best controlled study to date of a topical treatment, compared topical fluticasone alone or combined with UVA in 135 adults. They found that the potent topical steroid fluticasone used alone for 9 months induced mean repigmentation of only 9% (compared with UVA alone of 8%) whereas the combination of fluticasone and UVA induced mean repigmentation of 31%: no steroid atrophy was noted in steroid users.

Comparison of a potent or highly potent topical steroid with another topical agent has been made but the studies are not robust. In a left-vs.-right comparison over an 8-week period in 10 adults, topical pimecrolimus was found to give 50–100% repigmentation in eight of 10 patients compared with an equivalent degree of repigmentation in seven of 10 patients treated with clobetasol.[36] A study of topical betamethasone vs. calcipotriol vs. a combination of the two over 5–10 weeks in 15, 16 and 18 adults, respectively, showed > 50% repigmentation in two, one and four, respectively, each out of 15 evaluable cases, with a conclusion that the results favoured the combination of topical betamethasone and calcipotriol.[37]

In children, Khalid *et al.* noted that topical use of the highly potent steroid clobetasol induced better repigmentation than PUVA-sol alone, finding > 50% repigmentation in 15 of 22 (vs. four of 23 for PUVA-sol) following use for 6 months, but six steroid users developed skin atrophy.[38] Another study in 20 children (aged less than 18 years of age) over an 8-week period compared topical clobetasol and tacrolimus and described '41%' repigmentation for clobetasol vs. '49%' repigmentation for tacrolimus.[32]

Evidence to recommendations

There is evidence that very potent or potent topical corticosteroids can repigment vitiligo in adults but the studies that support this statement have often been poorly conducted and side-effects are common if treatment lasts for more than a few weeks. For generalized symmetrical types of vitiligo, topical clobetasol used over 2–6 months repigments vitiligo to some degree. There is weak evidence for clinically meaningful repigmentation with topical betamethasone, used over a period of 4 months, and for topical fluticasone used over 9 months. There are significant potential side-effects, mainly of skin atrophy and hypertrichosis, especially for clobetasol and betamethasone, less so with fluticasone. For generalized symmetrical types of vitiligo, the combination of topical betamethasone with calcipotriol was better than betamethasone alone over a 5–10-week period. The combination of topical fluticasone with UVA used over 9 months was much more effective than fluticasone used alone. In children, topical clobetasol induced repigmentation but skin atrophy was a side-effect.

Recommendations

1. In children, and adults with recent onset of vitiligo, treatment with a potent or very potent topical steroid should be considered for a trial period of no more than 2 months. Although benefits have been observed, skin atrophy has been a common side-effect.

Grade of recommendation	B (by extrapolation)
Level of evidence	1+

2. In patients with skin types I and II, in the consultation it is appropriate to consider, after discussion with the patient, whether the initial approach may be to use no active treatment other than consideration of the use of camouflage cosmetics including fake tanning products and the use of sunscreens.

Grade of recommendation	D
Level of evidence	4

In all patients with vitiligo, what is the efficacy of applying calcipotriol or tacalcitol vs. placebo or an active treatment in terms of condition progression, area reduction and quality of life score?

Introduction

The vitamin D analogues, calcipotriol and tacalcitol, may have a place in the treatment of vitiligo.

Methods

Nine papers met the criteria for inclusion as used for topical corticosteroids. In all trials but one (Chiaverini *et al.*,[39] in which localized forms of vitiligo were included), only patients with generalized (symmetrical) types of vitiligo were studied.

Evidence statements

The best study of calcipotriol is the randomized open left-vs.-right study of Chiaverini *et al.*,[39] in which the effect over a 3–6-month period of the once daily application of calcipotriol is compared in symmetrical target lesions in 24 patients (15 females, nine males; age range 5–59 years) with localized and generalized vitiligo. No repigmentation was noted in 21 of 23 patients after 3–6 months. One patient had 5% repigmentation with calcipotriol; two had repigmentation with and without calcipotriol ($P > 0{\cdot}5$). An unpublished clinical trial of the efficacy of topical calcipotriol vs. vehicle for vitiligo showed no beneficial effect for the calcipotriol over

the vehicle placebo (A. Bibby, LEO Pharma A/S, personal communication, 2008).

A study of topical betamethasone vs. calcipotriol vs. a combination of the two over 5–10 weeks in 15, 16 and 18 adults, respectively, showed > 50% repigmentation in two, one and four each out of 15 evaluable cases.[37] The conclusion was that the results favoured the combination of topical betamethasone and calcipotriol over betamethasone alone. However, the numbers here are too small for a definitive conclusion and there has been no other study of this sort. An open study of twice daily topical calcipotriol (with PUVA in four patients) in 26 patients (16 females, 10 males; age range 5–61 years; 22 Asians) for 3–9 months showed that 17 of 22 receiving monotherapy with calcipotriol had 30–100% repigmentation which was > 50% in 12.[40]

There have been studies of the effect of combining topical calcipotriol with phototherapy (see below).[19,41–44]

Evidence to recommendations

For generalized symmetrical or localized types of vitiligo, topical calcipotriol by itself has no effect in vitiligo and is not recommended. For generalized symmetrical types of vitiligo, the addition of topical calcipotriol to narrowband (NB) UVB does not add any benefit and is not recommended. The use of topical calcipotriol with PUVA may produce earlier repigmentation but it is not clear whether the final degree of repigmentation is enhanced. There is insufficient evidence to make a comment about the use of tacalcitol.

Recommendation

1. The use of topical calcipotriol as a monotherapy is not recommended.

Grade of recommendation	B
Level of evidence	2++

In all patients with vitiligo, what is the efficacy of applying tacrolimus or pimecrolimus vs. placebo or an active treatment in terms of condition progression, area reduction and quality of life score?

Introduction

The calcineurin inhibitors have found use in a variety of inflammatory skin diseases and have been tried in vitiligo.

Methods

Four papers met the criteria for inclusion as used for topical corticosteroids. Studies on children will be considered separately from those on adults.

Evidence statements

Coskun and colleagues,[36] in a left-vs.-right comparison over an 8-week period in 10 adults, compared topical pimecrolimus with topical clobetasol. They found topical pimecrolimus resulted in 50–100% repigmentation in eight of 10 patients, most noticeable for lesions on the trunk or extremities, compared with an equivalent degree of repigmentation in seven of 10 patients treated with clobetasol. No skin atrophy was noted but burning was a side-effect with pimecrolimus. The number of subjects in this study is small, making a reliable conclusion difficult.

In an open proof-of-concept study of 26 children aged over 6 years and adults with generalized symmetrical forms of vitiligo, treated for head and neck lesions with topical 1% pimecrolimus twice daily, total repigmentation of a target lesion was found in 50% of patients after 6 months of therapy.[45]

Twenty children treated over 8 weeks with either topical clobetasol or tacrolimus were shown to have repigmentation that amounted to 41% with clobetasol and 49% with tacrolimus.[32] Lesions on the face and thorax responded better than those on the abdomen or legs: lesions on hands did not respond. Skin atrophy was noted in five of the 20 treated with the steroid, while two of 20 who received tacrolimus noted burning.

Comparisons have been made of topical tacrolimus alone with tacrolimus and Excimer UV radiation. In one study of 14 patients aged over 12 years, 23 vitiligo lesions received a combination of tacrolimus ointment twice daily and Excimer UV twice weekly for 12 weeks and were compared with 20 lesions that received Excimer UV alone for 12 weeks.[46] For the combination of topical tacrolimus and Excimer UV, 16 of 23 had 75% or more repigmentation compared with four of 20 lesions treated using the Excimer alone ($P < 0{\cdot}001$). In UV-exposed areas, i.e. face, neck, trunk or limbs, 75% or more repigmentation was seen in 10 of 13 using the combination treatment compared with none of 13 lesions that received the Excimer alone ($P < 0{\cdot}001$). Side-effects included stinging in the tacrolimus group, moderate erythema at least once in all patients, and bullous lesions in four of 43 lesions. Another study that included only 20 lesions in eight adults, comparing Excimer plus topical tacrolimus vs. Excimer plus placebo, found repigmentation to be more in the tacrolimus/Excimer group.[47]

Further studies on the efficacy of topical calcineurin inhibitors are required. The long-term side-effects of the calcineurin inhibitor drugs are unknown and this should be borne in mind if prolonged treatment (e.g. longer than 12 months) is proposed.

Evidence to recommendations

In adults with generalized symmetrical types of vitiligo, in a small study, topical pimecrolimus for 8 weeks induced 50–100% repigmentation (a similar degree to that seen with topical clobetasol) for lesions on the trunk or extremities. Stinging

was a side-effect. In children with generalized symmetrical vitiligo, topical tacrolimus used over an 8-week period induced nearly 50% repigmentation of vitiligo lesions (a similar degree to that seen with topical clobetasol) for lesions on the face or thorax but not the hands. Stinging was a side-effect. The combination of topical tacrolimus with Excimer UV radiation appeared to enhance the degree of repigmentation over that for Excimer alone, for UV-sensitive sites but not for areas over bony prominences.

Recommendations

1. In adults with symmetrical types of vitiligo, topical pimecrolimus should be considered as an alternative to the use of a topical steroid, based on evidence from one study. The side-effect profile of topical pimecrolimus is better than that of a highly potent topical steroid.

Grade of recommendation	C
Level of evidence	2+

2. In children with vitiligo, topical pimecrolimus or tacrolimus should be considered as alternatives to the use of a highly potent topical steroid in view of their better short-term safety profile.

Grade of recommendation	B
Level of evidence	1+

Research recommendation

1. Further research is needed to clarify the roles of tacrolimus and pimecrolimus in adults and children with vitiligo. A head-to-head study of tacrolimus vs. pimecrolimus is suggested.

In all patients with vitiligo, what is the efficacy of applying *p*-(benzyloxy)phenol (monobenzyl ether of hydroquinone) vs. placebo or an active treatment in terms of reducing areas of pigmentation?

Introduction

The use of medicaments to induce complete depigmentation may be considered in patients with vitiligo under certain situations.

Methods

There were no randomized controlled trials (RCTs). Case studies or consensus reports were considered.

Evidence statements

Several products, some of which are marketed as cosmetics, have been used to reduce pigmentation of the skin. In certain countries such products are legally available over the counter; in others the products are available but not legally. These products may contain mercuric iodide (as in a germicidal soap), antiseptics containing phenolic derivatives and hydroquinone or related chemicals. In vitiligo, depigmentation may be considered as a therapeutic option when the patient has a naturally dark skin and has very obvious vitiligo extensively affecting cosmetically sensitive areas such as the face and backs of the hands. To induce depigmentation, the main method used has been the application of p-(benzyloxy)phenol (monobenzyl ether of hydroquinone, MBEH). There have been concerns about whether p-(benzyloxy)phenol is carcinogenic and it was banned from use in cosmetics in the EU in 2001. More recently, one study has examined the effect of topical 4-methoxyphenol (4MP) as a depigmenting agent.

Only two clinical trials that examine treatments aimed at depigmenting the normally pigmented skin in vitiligo were found. Both met the criteria for inclusion although one had only 13 subjects and the other 18. In both trials, it appears that only patients with generalized (symmetrical) types of vitiligo were included.

In the clinical trial described by Njoo *et al.*,[48] topical 4MP and the Q-switched ruby laser (QSRL) were used as the depigmenting agents. Topical 4MP produced total depigmentation in 11 of 16 subjects (69%; 95% confidence interval, CI 41–90%) with the onset of depigmentation within 4–12 months. Of the 11, four had a recurrence of pigment after 2–36 months. Side-effects of 4MP included mild burning or itching. Four of the five nonresponders to 4MP did depigment when treated using the QSRL. In the group treated using the QSRL, total depigmentation was found in nine of the 13 treated (69%; 95% CI 39–91%) with an onset within 7–14 days. Four had recurrence of pigment after 2–18 months. There were no side-effects in the QSRL group.

In an open study of p-(benzyloxy)phenol (MBEH),[49] 18 patients 'severely' affected by vitiligo (type of vitiligo not stated) were treated with the topical application of 20% MBEH. Eight achieved complete depigmentation after 10 months and three had 'dramatic' depigmentation, but in three there was no effect at all (after 4 months use).

Four papers on the management of vitiligo discuss the consensus view of the place of depigmentation treatment.[50–53] Expert consensus opinion concludes that patients with a dark skin type selected for depigmentation treatments must understand the cultural effects the depigmentation may have. It is usual to consider for depigmentation only subjects in whom the area of skin involved by vitiligo is extensive, usually taken to mean more than 50% of the skin surface area.[54] If there is extensive involvement of the cosmetically sensitive areas of the face and hands, and covering cosmetics are ineffective, depigmentation can be considered although it is usual to treat only the exposed sites.

Hydroquinones and related chemicals may cause side-effects. Irritation and occasionally contact dermatitis are recognized, as is the infrequent occurrence of ochronosis.[55] This had led to the banning of hydroquinones from over-the-counter products in Europe. Of more concern is the possibility of carcinogenesis from hydroquinones.[56] However, this is still a matter for debate.[55]

Evidence to recommendations

In patients with extensive generalized forms of vitiligo, the topical use of MBEH and 4MP or the use of the QSRL are effective in inducing depigmentation. MBEH and 4MP can take a long time to have an effect, with onset of depigmentation often delayed until after 4 months, and may be associated with local irritation and sometimes recurrence of pigmentation. With the QSRL, onset of the effect is much quicker and there are apparently fewer side-effects. This treatment may be preferred. However, there are few papers on this treatment and it is unwise to make a major recommendation based on one report.

Expert consensus recommends that patient selection is important in depigmentation treatment. It is vital that patients with a dark skin type understand the cultural implications. In general, depigmentation is undertaken only when the patient has more than 50% pigment loss in their skin due to vitiligo, or when the depigmentation is extensive in the cosmetically sensitive areas of the hands and face, when depigmentation of the exposed areas can be considered. This treatment is not recommended for children.

Recommendation

1. Depigmentation with *p*-(benzyloxy)phenol (MBEH) or 4MP should be reserved for adults severely affected by vitiligo (e.g. who have more than 50% depigmentation or who have extensive depigmentation on the face or hands) who cannot or choose not to seek repigmentation and who can accept the permanence of never tanning.

Grade of recommendation	D
Level of evidence	4

In all patients with vitiligo, what is the efficacy of a course of narrowband UVB including high-intensity light sources compared with placebo in terms of condition progression, area reduction and quality of life score?

Introduction

Phototherapy with UVB has been used in the treatment of vitiligo for many years. Phototherapy with broadband UVB appeared less effective than PUVA and was less frequently used. In the early 1990s, NB-UVB became widely available in Europe due to its widespread use in psoriasis. NB-UVB appeared to be more effective for treating vitiligo than the broadband UVB that it replaced. It is only recently that the efficacy of NB-UVB in the treatment of vitiligo has been assessed objectively in clinical trials. By convention, NB-UVB is usually given three times each week. An arbitrary limit of 200 NB-UVB treatments for vitiligo has been suggested, although in practice most patients have fewer.[57]

NB-UVB has the advantage for patients of being more acceptable than PUVA because they do not need to take oral medication before exposure to radiation or to wear protective sunglasses. Both PUVA and NB-UVB require a great degree of commitment by the patient. This should be explained at the time of consultation.

Methods

Nine studies identified using a computer-assisted search are included in the evidence table.

Evidence statements

Nine studies were assessed, two of which[31,57] follow the study design of an RCT. The study by Hamzavi and Shapiro[31] is of limited importance due to the small patient numbers, and the fact that most of the patients were white. This study did, however, establish that NB-UVB is an effective treatment for vitiligo compared with no treatment ($P < 0{\cdot}001$). It also highlighted the differential response within patients according to body site.

The most important study, by Yones *et al.*,[57] was the first double-blind, randomized trial of oral PUVA vs. NB-UVB therapy in vitiligo. It demonstrated therapeutic efficacy for both treatment modalities. However, NB-UVB was more effective, easier to administer and produced a better colour match. Vitiligo relapse was reported following both treatments in some patients by 12 months post-therapy.

Three of the remaining seven studies included 50 or more patients, but all three were methodologically weak. The largest, by Menchini *et al.*,[58] was an open study of 734 patients treated with a filtered xenon arc lamp which was claimed to deliver UVB. There were no controls and no attempt to analyse responses statistically. None the less, the authors claimed that this treatment was 'highly effective with no side-effects'. The second largest study, by Westerhof and Nieuweboer-Krobotova,[59] included 175 patients. Response was compared with baseline and no attempt was made to analyse results statistically. The authors concluded that TL-01 phototherapy was as efficient as topical PUVA in inducing repigmentation in vitiligo, but with fewer side-effects. The third largest report, an open study of NB-UVB in the treatment of 51 children with vitiligo, concluded that this was a safe and effective treatment.[22]

The final four reports are small open studies which are not objective or controlled. Three describe responses to the

Excimer laser.[60–62] Each study reports a positive response (i.e. repigmentation) but no data are presented on the amount of repigmentation, or cosmetic acceptability or permanence. A small study that made a good attempt to assess the responses objectively concluded that NB-UVB was effective at treating vitiligo while broadband UVB was not.[19]

Evidence to recommendations

There is good evidence that some patients with vitiligo respond well to phototherapy with NB-UVB. A single randomized double-blind trial comparing oral PUVA with NB-UVB has convincingly demonstrated the superiority of NB-UVB over PUVA. Twelve-month follow-up showed that some patients relapsed and ended up with worse vitiligo than they had before PUVA (28%) or NB-UVB (12%) started. However, maintenance of > 75% repigmentation of surface area was seen in 24% in the PUVA group and 36% in the NB-UVB group.

Recommendations

1. NB-UVB phototherapy should be considered for treatment of vitiligo only in children or adults who cannot be adequately managed with more conservative treatments.

Grade of recommendation	D
Level of evidence	4

2. A trial of NB-UVB therapy should be considered for children or adults with widespread vitiligo, or localized vitiligo associated with a significant impact on patient's QoL. Ideally, this treatment should be reserved for patients with darker skin types.

Grade of recommendation	D
Level of evidence	3

3. Before starting treatment, children, their parents and carers, and adults should be made aware that there is no evidence that NB-UVB phototherapy alters the natural history of vitiligo. They should also be made aware that not all patients respond to this treatment, and that some body sites, such as the hands and feet, respond poorly in all patients. They should also be informed of the limit to the number of treatments due to possible side-effects.

Grade of recommendation	D
Level of evidence	3

4. If phototherapy is to be used for treating nonsegmental vitiligo, NB-UVB should be used in preference to oral PUVA.

Grade of recommendation	A
Level of evidence	1+

5. Evidence is lacking to define an upper limit for the number of treatments with NB-UVB for patients with vitiligo. Taking into account the published data for patients with psoriasis (see below) and in view of the greater susceptibility of vitiliginous skin to sunburn and possible photodamage (due to absence of melanin), it is advised that safety limits for NB-UVB for the treatment of vitiligo are more stringent than those applied to psoriasis, with an arbitrary limit of 200 treatments for skin types I–III. This could be higher for skin types IV–VI at the discretion of the clinician and with the consent of the patient.

Grade of recommendation	D
Level of evidence	3

6. It is recommended that physicians prescribing NB-UVB for vitiligo monitor response closely with the assistance of serial clinical photographs (every 2–3 months), more easily to identify patients who fail to respond adequately or in whom the disease progresses during treatment.

Grade of recommendation	D
Level of evidence	3

In all patients with vitiligo, what is the efficacy of a course of PUVA or PUVA-sol compared with placebo in terms of condition progression, area reduction and quality of life score?

Introduction

Psoralen derived from plants applied to the skin followed by exposure to sunlight has been used as treatment for vitiligo since biblical times. El Mofty in 1948 first published on this treatment in a contemporary journal.[63] Since then, there have been many publications on the efficacy of PUVA in vitiligo.

Methods

Fifteen papers were identified by the computer-assisted search strategy, but only five of these were relevant to the question.

Evidence statements

Two studies used an RCT study design.[57,64] The study by Pathak had a poor assessment method and lacked statistical

analysis but included 366 patients and a placebo group.[64] This study confirmed that PUVA is an effective treatment for vitiligo compared with placebo, yet failed to address the issue of disease progression and impact on QoL. Yones *et al.* compared the efficacy of NB-UVB with oral PUVA in non-segmental vitiligo in a well-conducted study that showed that both treatments were effective.[57] However, PUVA was less effective at inducing repigmentation and the colour match of the repigmented skin was not as good as for NB-UVB. At 12 months follow-up > 25% of PUVA-treated patients had vitiligo that was worse than at baseline. However, a similar proportion of patients had maintained more than 75% improvement in body surface area repigmented at 12 months.

Khalid *et al.* reported on 50 children less than 12 years old with vitiligo, using photographs to compare PUVA-sol with topical clobetasone.[38] They reported a good response to PUVA-sol but used no formal statistical analysis. In a study of 89 patients with vitiligo, Sehgal found three different psoralen products to be efficacious in inducing repigmentation compared with baseline but used no control group and no statistical analysis.[65]

Two studies have compared efficacy of PUVA compared with NB-UVB. Westerhof and Nieuweboer-Krobotova compared PUVA and NB-UVB in 28 patients with vitiligo, reporting 46% repigmentation for the PUVA group.[59] Another (open) study of NB-UVB and PUVA using systemic trimethylpsoralen showed a better response to NB-UVB in 50 subjects.[66]

Evidence to recommendations

Both PUVA and PUVA-sol are efficacious in the treatment of some patients with vitiligo. However, most studies fail adequately to address the degree of this response, its durability or its effect on QoL. PUVA has now been demonstrated to be less effective than NB-UVB in the treatment of vitiligo, and sustained improvement at 12 months following treatment end is seen in < 25% of patients. No study has looked at long-term dangers of PUVA in vitiligo.

Recommendations

1. PUVA therapy should be considered for treatment of vitiligo only in adults who cannot be adequately managed with more conservative treatments. PUVA is not recommended in children.

Grade of recommendation	D
Level of evidence	4

2. If phototherapy is to be used for treating nonsegmental vitiligo, NB-UVB should usually be used in preference to oral PUVA.

Grade of recommendation	A
Level of evidence	1+

3. A trial of PUVA therapy should be considered only for adults with widespread vitiligo, or localized vitiligo associated with a significant impact on patient's QoL. Ideally, this treatment should be reserved for patients with darker skin types.

Grade of recommendation	D
Level of evidence	3

4. Before starting PUVA treatment patients should be made aware that there is no evidence that this treatment alters the natural history of vitiligo. They should also be made aware that not all patients respond, and that some body sites, such as the hands and feet, respond poorly in all patients. They should also be informed of the limit to the number of treatments due to possible side-effects.

Grade of recommendation	D
Level of evidence	3

5. Evidence is lacking to define an upper limit for the number of treatments with PUVA for patients with vitiligo. Taking into account the published data for patients with psoriasis (see below) and in view of the greater susceptibility of vitiligo skin to psoralen-induced burning and possible photodamage (due to absence of melanin), it is advised that safety limits for PUVA in the treatment of vitiligo are more stringent than those for psoriasis, with an arbitrary limit of 150 treatments for patients with skin types I–III. This could be higher for skin types IV–VI at the discretion of the clinician and with the consent of the patient.

Grade of recommendation	D
Level of evidence	3

6. It is recommended that physicians prescribing PUVA for vitiligo monitor response closely using serial clinical photographs (every 2–3 months) to identify patients who fail to respond adequately or in whom the disease progresses during treatment.

Grade of recommendation	D
Level of evidence	3

In all patients with vitiligo, what is the efficacy of a course of khellin with sunlight UVA or UVB compared with PUVA or PUVA-sol in terms of progression, area reduction and quality of life score?

Introduction

Khellin is a naturally occurring furochromone which is a structural isomer of methoxsalen. In combination with UVA or sunlight khellin is reported to induce repigmentation of vitiliginous skin. The exact mechanism of action of khellin plus UVA in vitiligo is unknown.

Methods

Five papers were identified by the computer-assisted search strategy and all five are relevant to the question. However, none of these papers adhered strictly to an RCT design.

Evidence statements

In a study comparing khellin or placebo both with natural sunlight, 12 of 30 in the khellin group showed > 50% repigmentation compared with none in the control group.[67] A left-vs.-right study of 72 patients compared khellin with UVA vs. UVA alone and concluded that repigmentation was due to the UVA, *not* the khellin.[68] A left-vs.-right study compared khellin plus sunlight with vehicle plus sunlight in 41 patients and found no difference between the khellin and placebo groups.[69] However, in a later study the same authors compared a khellin gel and UVA with UVA alone, finding that both groups responded but khellin plus UVA was superior to UVA alone ($P < 0{\cdot}01$).[70] A study with 33 patients compared topical khellin plus UVA with PUVA, concluding that khellin plus UVA may induce repigmentation comparable with that induced by systemic PUVA, but required a longer duration.[71]

Evidence to recommendations

Despite apparent initial promise, research in this area is inconclusive and at times contradictory.

Recommendation

1. There is currently insufficient evidence to recommend khellin with UV in the treatment of vitiligo.

Grade of recommendation	D
Level of evidence	3

Late complications of PUVA or narrowband UVB therapy in patients with vitiligo: are patients who have received large doses of PUVA (more than 150 treatment sessions) or narrowband UVB (more than 150 treatment sessions) at increased risk of developing premalignant or malignant skin changes?

Introduction

It is not uncommon for patients with vitiligo to be given large numbers of PUVA or UVB treatments, occasionally over a relatively short period. As the areas of vitiligo have no melanin they are particularly susceptible to the damaging effects of UVB (or PUVA) and may therefore be more susceptible to developing premalignant or malignant changes.

Methods

There is only one study on vitiligo in which the issue of chronic cutaneous damage with long-term PUVA is specifically assessed.[72]

Evidence statements

Harrist *et al.* followed up annually with a skin examination 596 patients with vitiligo treated with PUVA (230 for up to 55 months) but did not include a control group.[72] No skin cancers were observed, but vitiligo and perilesional skin showed dermal changes of chronic photodamage.

There is a paucity of studies of skin cancer in vitiligo, but there are retrospective reports from centres that have treated patients with vitiligo with phototherapies over long periods of time. Wildfang *et al.* reported no actinic keratoses, lentigines or skin cancer in a retrospective study on 59 patients with vitiligo treated with PUVA.[73] Chuan *et al.* reported no actinic keratoses or skin cancer in 21 patients with vitiligo treated with PUVA followed for up to 7 years.[74] Westerhof and Schallreuter reported no skin cancer in > 2500 patients (but not in a study).[75] Halder *et al.* in a study of 326 patients with vitiligo treated with PUVA with 4 years of follow up reported no actinic keratoses, cutaneous carcinomas or lentigines, but acknowledged that the follow-up period was almost certainly too short to detect an increase in skin cancer.[76]

Reports of skin cancer in patients with vitiligo treated with PUVA are limited. Buckley and Rogers describe a patient who developed multiple invasive squamous cell carcinomas in areas of vitiligo which had failed to repigment despite a prolonged continuous course of PUVA.[77] A similar patient had multiple squamous cell carcinomas *in situ* in vitiligo areas following PUVA therapy over a 9-year period.[78] Multiple bizarre-looking lentigines were reported in a patient with vitiligo following years of topical and systemic PUVA, but with no malignancy and benign histology.[79] Park *et al.* reported a patient with vitiligo who developed a squamous cell carcinoma in an area of vitiligo following long-term PUVA.[80]

Evidence to recommendations

The risk of skin cancer in patients with vitiligo treated with PUVA is currently unclear. There is no long-term follow-up study of the type carried out by Stern and Lange which established the clear cancer risk for PUVA in patients with psoriasis.[81] Despite some authors' claims that high doses of PUVA in vitiligo are safe, it is counterintuitive to believe that patients with vitiligo are at a lower risk of skin cancer with PUVA than patients who have psoriasis. Indeed, the absence of functional melanocytes could put patients with vitiligo at a greater risk. In the absence of persuasive evidence to the contrary, it is logical to recommend more stringent limits on PUVA for vitiligo than apply for psoriasis.

Recommendations

1. In view of uncertainty regarding the cancer risk, clinicians prescribing NB-UVB or PUVA should be cautious in prescribing these treatments in vitiligo. A clear explanation of the risks and benefits of treatment must be given *before* treatment, with a Patient Information Leaflet written in lay terms.

Grade of recommendation	D
Level of evidence	3

2. Patients treated with PUVA or UVB should have their treatment closely supervised by a consultant dermatologist and the treatment regimen for patients with skin types I–III should not exceed 200 treatments for NB-UVB and 150 treatments for PUVA. This recommendation is based on published evidence for patients with psoriasis. Evidence is lacking to define an upper limit for patients with skin types IV–VI for NB-UVB or PUVA.

Grade of recommendation	D
Level of evidence	4

3. In most patients, NB-UVB should be used in preference to PUVA.

Grade of recommendation	A
Level of evidence	1+

Research recommendation

1. In view of the possible long-term risk of skin cancer with extended courses of NB-UVB or PUVA in patients with vitiligo, further research to define this potential risk is recommended.

In all patients with vitiligo, what is the efficacy of a course of narrowband UVB with a vitamin D analogue compared with narrowband UVB with placebo in terms of condition progression, area reduction and quality of life score?

Introduction

The use of combination treatments has been commonplace in the treatment of vitiligo.

Methods

Authors have attempted to assess whether the combination of a topical vitamin D analogue with NB-UVB is more effective than NB-UVB alone.

Evidence statements

For calcipotriol, there are two studies with directly contradictory results. In a small single-blinded RCT with 20 patients, there was no additional benefit from adding calcipotriol to NB-UVB when compared with UVB alone.[82] In contrast, a slightly larger open study with 24 patients showed that the combination of calcipotriol with NB-UVB was more effective than UVB alone.[83] In a similar randomized but open-label study with 32 patients, the combination of tacalcitol with NB-UVB was more effective at inducing repigmentation in vitiligo than UVB alone.[84] Another open, bilateral comparison study with 20 subjects compared NB-UVB with NB-UVB and calcipotriene; results suggested a better response to the combination but the results were inconclusive.[85]

Two studies attempted to assess the response of vitiligo to the Excimer laser with and without topical tacrolimus. A double-blind study in eight patients whose vitiligo was treated with the Excimer laser with tacrolimus ointment 0·1% or placebo showed better results for the tacrolimus-treated group.[47] This study failed to include a tacrolimus-only limb or a Excimer laser-only limb so the results are hard to interpret. A second study compared Excimer monotherapy with Excimer and tacrolimus ointment and reported a superior response to the combination but also failed to include a tacrolimus-only limb or an ointment placebo with the Excimer.[46]

A combination study of 27 patients found no benefit of combining NB-UVB with vitamin B_{12} and folate vs. NB-UVB as monotherapy.[86] In addition, mention is made of the treatment of vitiligo using topical application of pseudocatalase and calcium in combination with UVB therapy or Dead Sea climatotherapy reported by Schallreuter *et al.*[87,88] In an open study of 33 patients, complete repigmentation on the face and hands was reported in 90% of the group starting within 2–4 months.[87] This treatment cannot be considered further as it was not a controlled study and the work has not been reproduced.

Evidence to recommendations

There is no convincing evidence to suggest that topical vitamin D analogues in combination with NB-UVB phototherapy are superior to NB-UVB alone.

Recommendation

1. Topical vitamin D analogues in combination with NB-UVB therapy should not be used in the treatment of vitiligo.

Grade of recommendation	C
Level of evidence	3

In all patients with vitiligo, what is the efficacy of a course of PUVA with a vitamin D analogue compared with PUVA with placebo in terms of condition progression, area reduction and quality of life score?

Introduction

The use of combination therapies has been common in the treatment of vitiligo.

Methods

Studies were identified which have attempted to assess whether PUVA or PUVA-sol in combination with a vitamin D analogue was more effective than PUVA or PUVA-sol alone.

Evidence statements

Five studies were identified – two used an RCT design. A study of 27 patients treated with PUVA monotherapy or PUVA with calcipotriol showed an earlier and better overall response for the combination than for PUVA monotherapy.[41] These findings were similar to the second RCT of 19 patients in which the combination of PUVA with calcipotriol was more effective and faster than PUVA alone.[43] In contrast, another study showed no improvement for the combination of PUVA with calcipotriol compared with PUVA alone.[42] Other open studies report the combination of calcipotriol with PUVA to be more effective than PUVA alone, especially at initiating repigmentation.[40,44]

Evidence to recommendations

Five small studies fail to provide convincing evidence for an additional therapeutic effect for PUVA combined with a vitamin D analogue compared with PUVA monotherapy.

Recommendation

1. Topical vitamin D analogues in combination with PUVA therapy should not be used in the treatment of vitiligo.

Grade of recommendation	C
Level of evidence	3

In all patients with vitiligo, what is the efficacy of systemic (i.e. orally and parenterally administered) treatments, including corticosteroids, ciclosporin and other immunosuppressive agents, in terms of condition progression, area reduction and quality of life score?

Introduction

There is evidence that in many cases autoimmune mechanisms are involved in causing vitiligo. It is not surprising that systemic immunosuppressive treatments have been used in patients with vitiligo.

Methods

There is only one satisfactory RCT of any systemic treatment for vitiligo, a double-blind placebo-controlled trial of *Gingko biloba* extract. This product is said to have antioxidant and immunomodulatory properties. The study looked at cessation of progression in spreading generalized and focal types of vitiligo and at repigmentation.[89]

Evidence statements

Numerous open studies lacking any comparator arm have suggested a beneficial effect for systemic treatments, often of oral corticosteroids, on patients (often with Asian skin types) with usually generalized (symmetrical) forms of vitiligo.[90–96] These have been excluded from consideration here. The paper of Pasricha and Khera has been excluded as the effects of treatment are unclear – the trial design is suboptimal.[97] The study of Orecchia *et al.* regarding the use of phenylalanine was excluded as it had fewer than 20 subjects in comparator groups.[98]

Some other studies, usually also lacking a comparator, were of mixed treatment modalities, e.g. including some sort of phototherapy, and are excluded from consideration here although they may be considered elsewhere.[99–107]

A double-blind placebo-controlled trial looked at the effect of *G. biloba* extract for 6 months, in adults with spreading generalized and focal types of vitiligo, and also on repigmentation, in 47 subjects divided into two groups.[89] The authors showed that the *G. biloba* extract induced cessation of activity of the vitiligo in all subjects with acrofacial type (placebo

induced cessation in one of six), in a third of those with symmetrical type called here 'vulgaris' (placebo one of six) and in a quarter with focal type (placebo seven of 10).[89] The *G. biloba* extract was associated with some degree of repigmentation in four of nine with focal, two of nine with vulgaris and four of seven with acrofacial type, whereas only two subjects with focal type who had placebo experienced any repigmentation. The conclusion seems to be that *G. biloba* extract can arrest active vitiligo of the acrofacial type. This is the only study on *G. biloba* extract, and it is therefore unwise to place too much reliance on this result without confirmation of a beneficial effect.

Azathioprine has not been tried as a monotherapy in vitiligo but, at a dose of 0·75 mg kg^{-1} daily, has been combined with PUVA in adults with symmetrical types of vitiligo.[101] Earlier (after five treatments compared with six) and a greater degree of repigmentation (58% compared with 25%) was noted in the group that received azathioprine and PUVA (compared with PUVA alone), without any serious side-effects. No recommendation can be made based on this single study.

A well-conducted but open study of 25 European adults with active generalized types of vitiligo (and four with stable disease) examined the effect of oral dexamethasone 10 mg twice a week for 24 weeks, evaluating pigment change using photographs.[108] The authors showed that disease progression was arrested in 22 of the 25 subjects with active vitiligo, after a mean treatment of 18 ± 5 weeks. 'Marked' repigmentation (51–75%) occurred in two subjects (7%) and 'moderate' or 'slight' repigmentation (26–50%; < 25%) was noted in three (10%), with no response being found in 21 (72%). Side-effects were common, being seen in 20 of 29 subjects, and included weight gain, acne, menstrual irregularity and hypertrichosis.

One study of intralesional triamcinolone in 35 patients with one (12 subjects) or more (23 subjects) areas of vitiligo is worthy of mention.[109] The 25 patients were randomly allocated to receive weekly injections of triamcinolone (0·1 mL of 10 mg mL^{-1} strength) for 8 weeks, vs. 10 who received distilled water. Seventeen of the treatment group (69%) vs. six in the control group (60%) had a 'fair-to-excellent' response, indicating that the intralesional triamcinolone was no better than placebo.

Evidence to recommendations

In adult patients with active generalized (symmetrical) types of vitiligo, oral dexamethasone 10 mg twice weekly can arrest the progression of the disease after a mean of 18 weeks, but there is poor objective evidence for repigmentation and side-effects are common. The use of oral *G. biloba* extract in active generalized vitiligo cannot be recommended unless further studies confirm the effect of the one reported study.

There is no convincing evidence at present that any systemic treatment (apart from PUVA) has a role in the treatment of vitiligo.

Recommendation

1. The use of oral dexamethasone to arrest progression of vitiligo cannot be recommended due to an unacceptable risk of side-effects.

Grade of recommendation	B
Level of evidence	2++

In patients with vitiligo what is the efficacy of a skin graft and of various forms of placebo in terms of condition progression, area reduction and quality of life score? This may include punch grafts, full-thickness skin graft, split-thickness skin graft, autologous epidermal cell suspension, and autologous skin equivalent (commercial skin equivalent)

Introduction

Surgical interventions are based on the idea of transplanting functional melanocytes to the depigmented area. To be successful this requires preparation of the affected area with debridement, laser peeling of the skin, suction blisters or removal of punch biopsies. There are several methods of varied sophistication for harvesting melanocytes, the simplest being by punch biopsy. These techniques require a donor site, which may be scarred and in which vitiligo may be induced by the Koebner phenomenon.

Methods

It is difficult to design RCTs for treatments that use skin grafts. Many papers refer to methodology or small patient series. Case series, cohorts or randomized clinical trials of 20 or more patients were included. A systematic review has looked at a set of 39 nonrandomized studies carried out prior to 1998, so only papers that followed were selected. Eleven papers were identified, of which five were RCTs, five case series and one a systematic review.

Evidence statements

Njoo *et al.* performed a systematic review that evaluated 39 studies assessing split-thickness graft, minigraft using punch biopsies, epidermal suction blisters as preparation and donor and transplantation of noncultured cell suspension or cultured melanocytes.[110] The highest mean success rates (87%) were achieved with split-skin grafting (95% CI 82–91%) and epidermal blister grafting (87%; 95% CI 83–90%). The mean success rate of five culturing techniques varied from 13% to 53%. However, in four of the five culturing methods, fewer than 20 patients were studied and there was insufficient evidence. Minigrafting had the highest rates of adverse effects,

with poor colour match in < 10%, cobblestone appearance in 27%, milia in 13%, partial take in 11% and thick margins in 5%. Split-skin grafting and epidermal blister grafting were recommended as the most effective and safest techniques. Barman *et al.* studied 50 patients in an RCT comparing punch graft followed by PUVA with punch graft followed by topical fluocinolone acetonide and found spread of pigment similar in each group, both of which had significant side-effects as above.[111] Khandpur *et al.*, in an RCT of 64 patients, compared minipunch grafting with split-skin grafting: 15 of 34 (44%) punch grafts had excellent (> 75%) repigmentation, compared with 25 of 30 (83%) of the split-skin grafts.[112] Cosmetic results were better with split-skin grafts.

Ozdemir and colleagues, in an unblended RCT, studied 20 patients comparing, within patients, suction blister alone with suction blister grafting, suction and a split-skin graft or area of thin split-skin graft.[113] Using suction blisters, repigmentation was 25–65% as compared with 90% with split-skin graft.[114] Gupta and Kumar, in a retrospective series of 143 patients, evaluated suction blister transfer supplemented by PUVA.[114] The success rate was 50% and was higher in segmental or focal disease and in patients under 20 years. The results were not affected by site. Kim and Kang reported a case series of 40 patients using suction blister transfer who were followed up for 3 months–2·5 years.[115] Of these, 71–73% had complete repigmentation but relapse was more common in patients with progressive disease (40%) than in those with stable vitiligo (10%).

Van Geel and colleagues, in a high-quality RCT that included 28 patients, looked at autologous cell suspension applied to laser-debrided skin followed by NB-UVB or PUVA, compared with a placebo application to another area, and analysed images of the outcome.[116] Pigmentation was seen only in sites receiving cell suspension and progressed from 55% to 77%, showing > 70% repigmentation between 3 and 12 months. Pianigiani *et al.* reported a case series of 93 patients treated with laser abrasion and grafting of cultured epidermal cells and NB-UVB and followed for 18 months.[117] Complete repigmentation was seen in 60% and partial (> 50%) in 30%. Relapses were not seen at 18 months. Pandya and colleagues studied 27 patients in a case series allocated to dermabrasion and application of cultured melanocytes or dermabrasion with application of autologous disaggregated epidermal cell suspension.[118] Excellent responses of > 90% repigmentation were seen in 50% and 52%, respectively, with no scarring. There were more good responses in the noncultured group.

Chen *et al.*, in a case series of 120 patients treated with laser abrasion followed by application of cultured epidermal cells, observed > 90% repigmentation in 84%, 90–100% coverage in localized disease, 54% in stable generalized vitiligo, and only 14% in active generalized vitiligo.[119] Guerra *et al.* reported 32 patients treated with programmed diathermy (TIMED surgery) to prepared sites followed by the application of autologous cultured epidermal cells, and found 88–96% repigmentation, with less successful repigmentation on the extremities (8%) and in a periorificial distribution (35%).[120] Guerra *et al.* also evaluated the use of skin preparation using erbium-YAG laser followed by application of cultured epidermal cells in 21 patients with vitiligo.[121] Repigmentation was noted in 76%. The same authors treated six patients with piebaldism using this technique, with good results.[122]

Evidence to recommendations

Surgical techniques were among the most effective interventions in the systematic review and have been assessed in RCTs. They are limited by their invasive nature and often studies applied only to a target area which may not equate to any perceived benefit for the patient, unless the area is particularly disfiguring, e.g. lips or eyelids. There was some evidence for successful treatment of such difficult sites, but results are less good in the extremities and around orifices. The least scarring is seen with the method using laser-abraded skin preparation and application of cell suspensions. This requires special facilities. A 'lab in a box' kit for producing cell suspensions has been produced recently (Recell®; Clinical Cell Culture Europe Ltd, Cambridge, U.K.) but has not been evaluated in any meaningful studies. Surgical treatment gives a high rate of successful repigmentation that appears to be durable in patients with stable inactive vitiligo. Patient selection is important.

Recommendations

1. Surgical treatments in vitiligo should be used only for cosmetically sensitive sites where there have been no new lesions, no Koebner phenomenon and no extension of the lesion in the previous 12 months.

Grade of recommendation	A
Level of evidence	1++

2. Split-skin grafting is the best option when a surgical treatment is required.

Grade of recommendation	A
Level of evidence	1+

3. Minigraft is not recommended due to a high incidence of side-effects and poor cosmetic results including cobblestone appearance and polka dot appearance.

Grade of recommendation	A
Level of evidence	1+

4. Autologous epidermal suspension applied to laser-abraded lesions followed by NB-UVB or PUVA therapy is the optimal

surgical transplantation procedure but does require special facilities.

Grade of recommendation	A
Level of evidence	1+

5. Expanding the autologous cells in tissue culture prior to grafting is feasible and treats larger areas successfully, without the need for additional phototherapy. However, the culturing introduces growth factors leading to uncertain risks and cultures can fail, reducing the value of the procedure.

Grade of recommendation	D
Level of evidence	3

6. Transfer of suction blisters is an alternative transplantation method, which shows evidence of benefit over placebo but gives less good coverage than split-skin grafting or laser and cell suspension.

Grade of recommendation	B
Level of evidence	1+

In all patients with vitiligo, what is the efficacy of cognitive therapy vs. psychological support or no treatment in terms of condition progression, area reduction and quality of life score?

Introduction

Cognitive behavioural techniques (CBT) may help patients to cope with skin diseases. There is some suggestion that QoL and coping mechanisms improve over time in vitiligo.[123] Cognitive strategies rather than avoidance or concealment may be associated with better coping.[124] This suggests that cognitive behavioural strategies are potentially helpful (level of evidence 3).

Methods

Two papers were identified which addressed the question.[2,125] The first study was small, with only seven patients in each treatment arm.[2] The intervention was not purely CBT but involved training in practical coping strategies with general psychological support. This intervention cannot be blinded and this introduces potential bias. The second study was an RCT of 45 patients randomized into three arms: one received group CBT, one group received person-centred therapy and the other group were controls.[125] Whereas the first study used individual therapy the second one used group therapy which did not allow for the individual assessment of participants. This study did not show that group CBT was effective in improving the condition or improving QoL score.

Evidence statements

The first study compared before, after, and a nontreatment arm.[2] The CBT intervention arm showed a sustained improvement in QoL, self-esteem and body image. The effects reported were statistically and clinically significant with patients 'coming into the normal range'. Given the methodological limitations it did not offer sound evidence of the benefit of CBT but it did offer some support for the intervention used. Patients' own cognitive strategies may help coping over time. CBT may offer benefit to patients with vitiligo. Only one study has looked at this directly and it was small in size.[2] Parents of children affected by vitiligo are often very concerned.

Evidence to recommendations

Despite the small evidence base on CBT the GDG feels that psychological support and strategies to cope with the psychological effects of disfigurement are an important part of the treatment of vitiligo. This is reflected in the views expressed by the members of the Vitiligo Society. The value of the support given by patient organizations should not be underestimated. Patients should be given information about the Vitiligo Society as part of the management of the disorder. Parents of children with vitiligo may require psychological counselling.

Recommendation

1. Psychological interventions should be offered as a way of improving coping mechanisms in patients with vitiligo. Parents of affected children should be offered psychological counselling.

Grade of recommendation	D
Level of evidence	4

Footnote: The organization 'Changing Faces' (The Squire Centre, 33–37 University Street, London WC1E 6JN, U.K.: http://www.changingfaces.org.uk) can give practical help and support to patients and their families. They advise that adjustment is not related to extent of disfigurement but is helped by quality social support, realistic information about treatment options and effective coping strategies, especially on how to manage social anxiety.

Research recommendations

During the development of this guideline it was apparent that more research effort needs to be put into the scientific

investigation of the causes of vitiligo. Anyone reading the guideline will be struck by the paucity of effective treatments available and the lack of treatments specifically introduced for vitiligo itself. Almost all treatments have been borrowed from therapies whose prime target is another disease. Not even the greater understanding of the science underlying vitiligo, e.g. evidence of autoimmune disease or of oxidative stress in melanocytes, has resulted yet in a treatment specifically tailored towards vitiligo. The interrogation of the available studies and clinical trials did throw up some questions pertinent to the currently available treatments and research recommendations based on these are detailed below.

1. A longitudinal epidemiological study is needed to define the natural history of vitiligo. This should use photographs combined with computerized image analysis, to quantify how the vitiligo changes with time.

2. More research is needed on more appropriate QoL tools in vitiligo and they should always be used as outcome measures on studies in vitiligo.

3. Further research is needed to establish simple, meaningful and reproducible methods of monitoring accurately the response of vitiligo to treatment both in the clinic and in clinical trials.

4. Further research is needed to clarify the roles of tacrolimus and pimecrolimus in adults and children with vitiligo. A head-to-head study of tacrolimus vs. pimecrolimus is suggested.

5. In view of the possible long-term risk of skin cancer with extended courses of NB-UVB or PUVA in patients with vitiligo, further research to define this potential risk is recommended.

Final recommendations

The recommendations have been distilled and set into the form of algorithms for use by dermatologists and other physicians for the treatment of children and adults with vitiligo. The level of the recommendation and the level of the evidence are shown in parentheses. It is anticipated that phototherapy and surgical treatments will be available only to dermatologists (and their associates) but other approaches, e.g. topical treatments [with the exception of the use of p-(benzyloxy)phenol] and psychological support, may be widely available.

Assessment, prognosis and social impact in children and adults

1. Diagnosis of vitiligo

Where vitiligo is classical, as in the symmetrical types, the diagnosis is straightforward and can be made with confidence in primary care (D/4). In patients with an atypical presentation, diagnosis is more difficult and referral for expert assessment by a dermatologist is recommended (D/4). Assessment of skin type is useful in the initial examination, together with photographs to record the extent of the disease. Wood's light may be of benefit in the diagnosis of vitiligo and in the demonstration of the extent and activity of the disease in subjects with skin types I and II. Wood's light can be of use in monitoring response to therapy (D/4). A blood test to check thyroid function should be considered in view of the high prevalence of autoimmune thyroid disease in adults with vitiligo (D/3).

2. Natural history

A longitudinal epidemiological study is needed to define the natural history of vitiligo with time. This should use photographs combined with computerized image analysis, to quantify how the vitiligo changes with time (D/4). The response of vitiligo to treatment should be considered in the context of the natural history, recognizing that spontaneous repigmentation may occur but is uncommon (D/4).

3. Psychological impact

Clinicians should make an assessment of the psychological and QoL effects of vitiligo on patients (C/2++). In therapeutic trials relating to vitiligo, researchers should make the patient's improvement in QoL the most important outcome measure (D/4).

4. Assessment tools

In a research setting, the VASI and VETF assessment tools offer a more accurate measurement of disease extent than simple clinical photography alone (even when combined with computerized morphometry). The VETF gives further assessment of severity and spreading (D/2+). In clinical practice, serial photographs should be used to record progress (C/4).

Therapeutic algorithm in children

1. No treatment option

In children with skin types I and II, in the consultation it is appropriate to consider, after discussion with the patient, whether the initial approach may be to use no active treatment other than consideration of the use of camouflage cosmetics and sunscreens (D/4).

2. Topical treatment

- In all children with vitiligo who are under 18 years, treatment with a potent or very potent topical steroid should be considered for a trial period of no more than 2 months. Although benefits have been observed, skin atrophy has been a common side-effect (B/1+).
- In children with vitiligo, topical pimecrolimus or tacrolimus should be considered as alternatives to the use of a highly potent topical steroid in view of their better short-term safety profile (B/1+).

3. Phototherapy

• NB-UVB phototherapy should be considered for treatment of vitiligo only in children who cannot be adequately managed with more conservative treatments (D/4), who have widespread vitiligo, or have localized vitiligo associated with a significant impact on patient's QoL. Ideally, this treatment should be reserved for patients with darker skin types and monitored with serial photographs every 2–3 months (D/3).
• If phototherapy is to be used for treating nonsegmental vitiligo, NB-UVB should be used in preference to PUVA in view of evidence of greater efficacy, safety and lack of clinical trials of PUVA in children (A/1+).
• Taking into account the published data for patients with psoriasis and in view of the greater susceptibility of vitiligo skin to sunburn and photodamage due to absence of melanin, it is advised that safety limits for the treatment of vitiligo are more stringent than those applied to psoriasis, with an arbitrary limit for NB-UVB of 200 treatments for skin types I–III. Evidence is lacking to define an upper limit for skin types IV–VI (D/3).

4. Systemic therapy

The use of oral dexamethasone to arrest progression of vitiligo cannot be recommended due to an unacceptable risk of side-effects (B/2++).

5. Surgical treatment

There are no studies of surgical treatment in children and it is not recommended.

6. Psychological treatments

Psychological interventions should be offered as a way of improving coping mechanisms in children with vitiligo (D/4). Parents of children with vitiligo should be offered psychological counselling.

Therapeutic algorithm in adults

1. No treatment option

In adults with skin types I and II, in the consultation it is appropriate to consider, after discussion with the patient, whether the initial approach may be to use no active treatment other than consideration of the use of camouflage cosmetics and sunscreens (D/4).

2. Topical treatment

• In adults with recent onset of vitiligo, treatment with a potent or very potent topical steroid should be considered for a trial period of no more than 2 months. Although benefits have been observed, skin atrophy has been a common side-effect (B/1+).
• In adults with symmetrical types of vitiligo, topical pimecrolimus should be considered as an alternative to the use of a topical steroid, based on one study. The side-effect profile of topical pimecrolimus is better than that of a highly potent topical steroid (C/2+).
• Depigmentation with p-(benzyloxy)phenol (MBEH) should be reserved for patients severely affected by vitiligo (e.g. who have more than 50% depigmentation or who have extensive depigmentation on the face or hands) who cannot or choose not to seek repigmention and who can accept the permanence of never tanning (D/4).

3. Phototherapy

• NB-UVB phototherapy (or PUVA) should be considered for treatment of vitiligo only in patients who cannot be adequately managed with more conservative treatments (D/4), who have widespread vitiligo, or have localized vitiligo associated with a significant impact on patient's QoL. Ideally, this treatment should be reserved for patients with darker skin types and monitored with serial photographs every 2–3 months (D/3).
• If phototherapy is to be used for treating nonsegmental vitiligo, NB-UVB should be used in preference to oral PUVA in view of evidence of greater efficacy (A/1+).
• Taking into account the data published for patients with psoriasis and in view of the greater susceptibility of vitiliginous skin to sunburn and photodamage due to absence of melanin, it is advised that safety limits for the treatment of vitiligo are more stringent than those applied to psoriasis, with an arbitrary limit of 200 treatments with NB-UVB for patients with skin types I–III, and 150 treatments with PUVA for patients with skin types I–III. Evidence is lacking to define an upper limit for the number of treatments with NB-UVB or PUVA for patients with skin types IV–VI (D/3).

4. Systemic therapy

The use of oral dexamethasone to arrest progression of vitiligo cannot be recommended due to an unacceptable risk of side-effects (B/2++).

5. Surgical treatments

• Surgical treatments are best reserved for cosmetically sensitive sites in patients in whom there have been no new lesions, no Koebner phenomenon and no extension of the lesion in the previous 12 months (A/1++).
• Split-skin grafting gives better cosmetic and repigmentation results than minigraft procedures and utilizes surgical facilities that are relatively freely available (A/1+). Minigraft is not recommended due to a high incidence of side-effects and poor cosmetic results (A/1+).
• Autologous epidermal suspension applied to laser-abraded lesions followed by NB-UVB or PUVA therapy is the optimal

surgical transplantation procedure but requires special facilities (A/1+). Expanding the autologous cells in tissue culture prior to grafting is feasible and can treat larger areas successfully, without the need for additional phototherapy (D/3).

• Transfer of suction blisters is an alternative transplantation method, which shows evidence of benefit over placebo but gives less good coverage than split-skin grafting or laser and cell suspension (B/1+).

6. Psychological treatments

Psychological interventions should be offered as a way of improving coping mechanisms in patients with vitiligo (D/4).

References

1 Nordlund JJ, Majumder PP. Recent investigations on vitiligo vulgaris. *Dermatol Clin* 1997; **15**:69–78.

2 Papadopoulos L, Bor R, Legg C. Coping with the disfiguring effects of vitiligo: a preliminary investigation into the effects of cognitive-behavioural therapy. *Br J Med Psychol* 1999; **72**:385–96.

3 Mason CP, Gawkrodger DJ. Vitiligo presentation in adults. *Clin Exp Dermatol* 2005; **30**:344–5.

4 Whitton ME, Ashcroft DM, Barrett CW, Gonzalez U. Interventions for vitiligo. *Cochrane Database Syst Rev* 2006; **1**:CD003263.

5 Taieb A, Picardo M. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. *Pigment Cell Res* 2007; **20**:27–35.

6 Fulton JE Jr. Utilizing the ultraviolet (UV detect) camera to enhance the appearance of photodamage and other skin conditions. *Dermatol Surg* 1997; **23**:163–9.

7 Nath SK, Majumder PP, Nordlund JJ. Genetic epidemiology of vitiligo: multilocus recessivity cross-validated. *Am J Hum Genet* 1994; **55**:981–90.

8 Howitz J, Schwartz M, Thomsen K. Prevalence of vitiligo. *Arch Dermatol* 1977; **113**:47–52.

9 Chun WH, Hann S-H. The progression of nonsegmental vitiligo: clinical analysis of 318 patients. *Int J Dermatol* 1997; **36**:908–10.

10 Barona MI, Arrunategui A, Falabella R, Alzatwe A. An epidemiologic case–control study in a population with vitiligo. *J Am Acad Dermatol* 1995; **33**:621–5.

11 Firooz A, Bouzari N, Fallah N *et al.* What patients with vitiligo believe about their condition. *Int J Dermatol* 2004; **43**:811–14.

12 McMichael AJ, Shaw K, Cayce K *et al.* Facial blemishes and QoL. *J Cosmet Dermatol* 2004; **17**:107–13.

13 Mattoo SK, Handa S, Kaur L *et al.* Psychiatric morbidity in vitiligo: prevalence and correlates in India. *J Eur Acad Dermatol Venereol* 2002; **16**:573–8.

14 Parsad D, Pandhi R, Dogra S *et al.* DLQI score in vitiligo and its impact on treatment outcome. *Br J Dermatol* 2003; **148**:373–4.

15 Ongenae K, Dierckxsens L, Brochez L *et al.* Quality of life and stigmatization profile in a cohort of vitiligo patients and effect of the use of camouflage. *Dermatology* 2005; **210**:279–85.

16 van Geel NAC, Ongenae K, Vander Haeghen YMSJ, Naeyaert JM. Autologous transplantation techniques for vitiligo: how to evaluate treatment outcome. *Eur J Dermatol* 2004; **14**:46–51.

17 Porter JP, Beuf AH, Nordlund JJ, Lerner AB. Personal responses of patients to vitiligo: the importance of the patient–physician interaction. *Arch Dermatol* 1978; **114**:1384–5.

18 Agarwal S, Ramam M, Sharma VK *et al.* A randomized placebo-controlled double-blind study of levamisole in the treatment of limited and slowly spreading vitiligo. *Br J Dermatol* 2005; **153**:163–6.

19 Hartmann A, Lurz C, Hamm H *et al.* Narrow-band UVB 311 nm vs. broad-band UVB therapy in combination with topical calcipotriol vs. placebo in vitiligo. *Int J Dermatol* 2005; **44**:736–42.

20 Ongenae K, van Geel N, De Schepper S, Naeyaert JM. Effect of vitiligo on self-reported health-related quality of life. *Br J Dermatol* 2005; **152**:1165–72.

21 Aghaei S, Sodaifi M, Jafari P *et al.* DLQI scores in vitiligo: reliability and validity of the Persian version. *BMC Dermatol* 2004; **4**:8.

22 Njoo MD, Boss JD, Westerhof W. Treatment of generalised vitiligo in children with narrow-band (TL-01) UVB radiation therapy. *J Am Acad Dermatol* 2000; **42**:245–53.

23 Kent GG, Al'Abadie MSK. Psychologic effects of vitiligo: a critical incident analysis. *J Am Acad Dermatol* 1996; **35**:895–8.

24 Kent GG, Al'Abadie MSK. Factors affecting responses on DLQI items amongst vitiligo sufferers. *Clin Exp Dermatol* 1996; **21**:330–3.

25 Kent GG. Correlates of perceived stigma in vitiligo. *Psychol Health* 1999; **14**:241–51.

26 Stangier U, Gieler U, Ehlers A. Measuring adjustment to chronic skin disorders: validation of a self-report measure. *Psychol Assess* 2003; **15**:532–49.

27 Sampogna F, Picardi A, Chren M-M *et al.* Association between poorer QoL and psychiatric morbidity in patients with different dermatological conditions. *Psychosom Med* 2004; **66**:620–4.

28 Sharma N, Koranne RV, Singh RK. Psychiatric morbidity in psoriasis and vitiligo: a comparative study. *J Dermatol* 2001; **28**:419–23.

29 Porter JR, Beuf AH. Racial variation in reaction to physical stigma: a study of degree of disturbance by vitiligo among black and white patients. *J Health Soc Behav* 1991; **32**:192–204.

30 Papadopoulos L, Bor R, Walker C *et al.* Different shades of meaning: illness beliefs among vitiligo sufferers. *Psychology* 2002; **7**:425–33.

31 Hamzavi I, Shapiro J. Parametric modelling of narrow band UV-B phototherapy for vitiligo using a novel quantitative tool. *Arch Dermatol* 2004; **140**:677–83.

32 Lepe V, Moncada B, Castanedo-Cazares JP *et al.* A double-blind randomized trial of 0·1% tacrolimus vs. 0·05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003; **139**:581–5.

33 Clayton R. A double-blind trial of 0·05% clobetasol propionate in the treatment of vitiligo. *Br J Dermatol* 1977; **96**:71–3.

34 Kandil E. Treatment of vitiligo with 0·1 per cent betamethasone 17-valerate in isopropyl alcohol – a double-blind trial. *Br J Dermatol* 1974; **91**:457–60.

35 Westerhof W, Nieuweboer-Krobotova L, Mulder PGH, Glazenburg EJ. Left–right comparison study of the combination of fluticasone propionate and UV-A vs. either fluticasone propionate or UV-A alone for the long-term treatment of vitiligo. *Arch Dermatol* 1999; **135**:1061–6.

36 Coskun B, Saral Y, Turgut D. Topical 0·05% clobetasol propionate versus 1% pimecrolimus ointment in vitiligo. *Eur J Dermatol* 2005; **15**:88–91.

37 Kumaran MS, Kaur I, Kumar B. Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *J Eur Acad Dermatol Venereol* 2006; **20**:269–73.

38 Khalid M, Mujtaba G, Haroon TS. Comparison of 0·05% clobetasol propionate cream and topical Puvasol in childhood vitiligo. *Int J Dermatol* 1995; **34**:203–5.

39 Chiaverini C, Passeron T, Ortonne JP. Treatment of vitiligo by topical calcipotriol. *J Eur Acad Dermatol Venereol* 2002; **16**:137–8.

40 Ameen M, Exarchou V, Chu AC. Topical calcipotriol as monotherapy and in combination with psoralen plus ultraviolet A in the treatment of vitiligo. *Br J Dermatol* 2001; **145**:476–9.
41 Ermis O, Alpsoy E, Cetin L, Yilmaz E. Is the efficacy of psoralen plus ultraviolet-A therapy for vitiligo enhanced by concurrent topical calcipotriol? A placebo-controlled double-blind study. *Br J Dermatol* 2001; **145**:472–5.
42 Baysal V, Yildirim M, Erel A, Kesici D. Is the combination of calcipotriol and PUVA effective in vitiligo? *J Eur Acad Dermatol Venereol* 2003; **17**:299–302.
43 Parsad D, Saini R, Verma N. Combination of PUVAsol and topical calcipotriol in vitiligo. *Dermatology* 1998; **197**:167–70.
44 Cherif F, Azaiz MI, Ben Hamida A *et al.* Calcipotriol and PUVA as treatment for vitiligo. *Dermatol Online J* 2003; **9**:4.
45 Boone B, Ongenae K, van Geel N *et al.* Topical pimecrolimus in the treatment of vitiligo. *Eur J Dermatol* 2007; **17**:55–61.
46 Passeron T, Ostovari N, Zakaria W *et al.* Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. *Arch Dermatol* 2004; **140**:1065–9.
47 Kawalek AZ, Spencer JM, Phelps RG. Combined excimer laser and topical tacrolimus for the treatment of vitiligo: a pilot study. *Dermatol Surg* 2004; **30**:130–5.
48 Njoo MD, Vodegel RM, Westerhof W. Depigmentation therapy in vitiligo universalis with topical 4-methoxyphenol and the Q-switched ruby laser. *J Am Acad Dermatol* 2000; **42**:760–9.
49 Mosher DB, Parrish JA, Fitzpatrick TB. Monobenzylether of hydroquinone. A retrospective study of treatment of 18 vitiligo patients and a review of the literature. *Br J Dermatol* 1977; **97**:669–79.
50 Shaffrali F, Gawkrodger D. Management of vitiligo. *Clin Exp Dermatol* 2000; **25**:575–9.
51 Bolognia JL, Lapia K, Somma S. Depigmentation therapy. *Dermatol Ther* 2001; **14**:29–34.
52 Le Poole C, Boissy RE. Vitiligo. *Semin Cutan Med Surg* 1997; **16**:3–14.
53 Kenney JA Jr, Grimes PE. How we treat vitiligo. *Cutis* 1983; **32**:347–8.
54 Antoniou C, Katsambas A. Guidelines for the treatment of vitiligo. *Drugs* 1992; **43**:490–8.
55 Nordlund JJ, Grimes PE, Ortonne JP. The safety of hydroquinone. *J Eur Acad Dermatol Venereol* 2006; **20**:781–7.
56 Kooyers TJ, Westerhof W. Toxicology and health risks of hydroquinone in skin lightening formulations. *J Eur Acad Dermatol Venereol* 2006; **20**:777–80.
57 Yones SS, Palmer RA, Garibaldinos TM, Hawk JLM. Randomised double-blind trial of treatment of vitiligo. Efficacy of psoralen-UVA vs. narrowband-UVB therapy. *Arch Dermatol* 2007; **143**:578–84.
58 Menchini G, Tsoureli-Nikita E, Hercogova J. Narrow-band UV-B micro-phototherapy: a new treatment for vitiligo. *J Eur Acad Dermatol Venereol* 2003; **17**:171–7.
59 Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs. topical psoralen plus UVA. *Arch Dermatol* 1997; **133**:1525–8.
60 Spencer JM, Nossa R, Ajmeri J. Treatment of vitiligo with the 308-nm excimer laser: a pilot study. *J Am Acad Dermatol* 2002; **46**:727–31.
61 Hofer A, Hassan AS, Legat FJ *et al.* The efficacy of excimer laser (308 nm) for vitiligo at different body sites. *J Eur Acad Dermatol Venereol* 2006; **20**:558–64.
62 Hong SB, Park HH, Lee MH. Short-term effects of 308-nm xenon-chloride excimer laser and narrow-band ultraviolet B in the treatment of vitiligo: a comparative study. *J Korean Med Sci* 2005; **20**:273–8.
63 El Mofty AM. A preliminary clinical report on the treatment of leucoderma with *Ammi majus* Linn. *J Egypt Med Assoc* 1948; **31**:651–65.
64 Pathak MA. Mechanisms of psoralen photosensitization reactions. *Natl Cancer Inst Monogr* 1984; **66**:41–6.
65 Sehgal VN. A comparative clinical evaluation of trimethylpsoralen, psoralen and 8-methoxypsoralen in treating vitiligo. *Int J Dermatol* 1975; **14**:205–8.
66 Bhatnagar A, Kanwar AJ, Parsad D. Comparison of systemic PUVA and NB-UVB in the treatment of vitiligo: an open prospective study. *J Eur Acad Dermatol Venereol* 2007; **21**:638–42.
67 Abdel-Fattah A, Aboul-Enein MN, Wassel GM, El-Menshawi BS. An approach to treatment of vitiligo by khellin. *Dermatologica* 1982; **165**:136–40.
68 Procaccini EM, Riccio G, Montfrecola G. Ineffectiveness of topical khellin in photochemotherapy of vitiligo. *J Dermatolog Treat* 1995; **6**:117–20.
69 Orecchia G, Perfetti L. Photochemotherapy with topical khellin and sunlight in vitiligo. *Dermatology* 1992; **184**:120–3.
70 Orecchia G, Sangalli ME, Gazzaniga A, Giordano F. Topical photochemotherapy of vitiligo with new khellin formulation: preliminary clinical results. *J Dermatolog Treat* 1998; **9**:65–9.
71 Valkova S, Trashlieva M, Christova P. Treatment of vitiligo with local khellin and UVA: comparison with systemic PUVA. *Clin Exp Dermatol* 2004; **29**:180–4.
72 Harrist TJ, Pathak MA, Mosher DB, Fitzpatrick TB. Chronic cutaneous effects of long-term psoralen and ultraviolet radiation therapy in patients with vitiligo. *Natl Cancer Inst Monogr* 1984; **66**:191–6.
73 Wildfang IL, Jacobsen FK, Thestrup-Pedersen K. PUVA treatment of vitiligo. A retrospective study of 59 patients. *Acta Derm Venereol (Stockh)* 1992; **72**:305–6.
74 Chuan MT, Tsai YJ, Wu MC. Effectiveness of psoralen photochemotherapy for vitiligo. *J Formos Med Assoc* 1999; **98**:335–40.
75 Westerhof W, Schallreuter KU. PUVA for vitiligo and skin cancer. *Clin Exp Dermatol* 1996; **22**:54.
76 Halder RM, Battle EF, Smith EM. Cutaneous malignancies in patients treated with psoralen photochemotherapy (PUVA) for vitiligo. *Arch Dermatol* 1995; **131**:734–5.
77 Buckley DA, Rogers S. Multiple keratoses and squamous carcinoma after PUVA treatment of vitiligo. *Clin Exp Dermatol* 1996; **21**:43–5.
78 Takeda H, Mitsuhashi Y, Kondo S. Multiple squamous cell carcinomas *in situ* in vitiligo lesions after long-term PUVA therapy. *J Am Acad Dermatol* 1998; **38**:268–70.
79 Abdel Naser MB, Wollina U, El Okby M, El Shiemy S. Psoralen plus ultraviolet-A irradiation-induced lentigines arising in vitiligo: involvement of vitiliginous and normal appearing skin. *Clin Exp Dermatol* 2004; **29**:380–2.
80 Park HS, Lee YS, Chun DK. Squamous cell carcinoma in vitiligo lesion after long-term PUVA therapy. *J Eur Acad Dermatol Venereol* 2003; **17**:578–80.
81 Stern RS, Lange R. Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment. *J Invest Dermatol* 1988; **91**:120–4.
82 Ada S, Sahin S, Boztepe G *et al.* No additional effect of topical calcipotriol on narrow-band UVB phototherapy in patients with generalised vitiligo. *Photodermatol Photoimmunol Photomed* 2005; **21**:79–83.
83 Goktas EO, Aydin F, Senturk N *et al.* Combination of narrow-band UVB and topical calcipotriol for the treatment of vitiligo. *J Eur Acad Dermatol Venereol* 2006; **20**:553–7.

84 Leone G, Pacifico P, Lacovelli P *et al.* Tacalcitol and narrow-band phototherapy in patients with vitiligo. *Clin Exp Dermatol* 2006; **31**:200–5.
85 Kullavanijaya P, Lim HW. Topical calcipotriene and narrowband ultraviolet B in the treatment of vitiligo. *Photodermatol Photoimmunol Photomed* 2004; **20**:248–51.
86 Tjioe M, Gerritsen MJ, Juhlin L, van de Kerkhof PC Treatment of vitiligo vulgaris with narrow band UVB (311 nm) for one year and the effect of addition of folic acid and vitamin B12. *Acta Derm Venereol (Stockh)* 2002; **82**: 369–72. Erratum in: *Acta Derm Venereol (Stockh)* 2002; **82**: 485.
87 Schallreuter KU, Wood JM, Lemke KR, Levenig C. Treatment of vitiligo with a topical application of pseudocatalase and calcium in combination with short-term UVB exposure: a case study on 33 patients. *Dermatology* 1995; **190**:223–9.
88 Schallreuter KU, Moore J, Behrens-Williams S *et al.* Rapid initiation of repigmentation in vitiligo with Dead Sea climatotherapy in combination with pseudocatalase (PC-KUS). *Int J Dermatol* 2002; **41**:482–7.
89 Parsad D, Pandhi R, Juneja A. Effectiveness of oral *Ginkgo biloba* in treating limited, slowly spreading vitiligo. *Clin Exp Dermatol* 2003; **28**:285–7.
90 Banerjee K, Barbhuiya J, Ghosh A *et al.* The efficacy of low-dose oral corticosteroids in the treatment of vitiligo patient. *Indian J Dermatol Venereol Leprol* 2003; **69**:135–7.
91 Seiter S, Ugurel S, Tilgen W, Reinhold U. Use of high-dose methylprednisolone pulse therapy in patients with progressive and stable vitiligo. *Int J Dermatol* 2000; **39**:624–7.
92 Kim SM, Lee HS, Hann SK. The efficacy of low-dose oral corticosteroids in the treatment of vitiligo patients. *Int J Dermatol* 1999; **38**:546–50.
93 Pasricha JS, Khaitan BK. Oral mini-pulse therapy with betamethasone in vitiligo patients having extensive or fast-spreading disease. *Int J Dermatol* 1993; **32**:753–7.
94 Schulpis CH, Antoniou C, Michas T, Strarigos J. Phenylalanine plus ultraviolet light: preliminary report of a promising treatment for childhood vitiligo. *Pediatr Dermatol* 1989; **6**:332–5.
95 Hernandez Perez E. Vitiligo treated with ACTH. *Int J Dermatol* 1979; **18**:578–9.
96 Imamura S, Tagami H. Treatment of vitiligo with oral corticosteroids. *Dermatologica* 1976; **153**:179–85.
97 Pasricha JS, Khera V. Effect of prolonged treatment with levamisole on vitiligo with limited and slow-spreading disease. *Int J Dermatol* 1994; **33**:584–7.
98 Orecchia G, Perfetti L, Borghini F, Malagoli P. Phenylalanine in the treatment of vitiligo. *Ann Ital Dermatol Clin Sper* 1992; **46**:143–6.
99 Don P, Iuga A, Dacko A, Hardick K. Treatment of vitiligo with broadband ultraviolet B and vitamins. *Int J Dermatol* 2006; **45**:63–5.
100 Mulekar SV. Stable vitiligo treated by a combination of low-dose oral pulse betamethasone and autologous, noncultured melanocyte-keratinocyte cell transplantation. *Dermatol Surg* 2006; **32**:536–41.
101 Radmanesh M, Saedi K. The efficacy of combined PUVA and low-dose azathioprine for early and enhanced repigmentation in vitiligo patients. *J Dermatolog Treat* 2006; **17**:151–3.
102 Handa S, Pandhi R, Kaur I. Vitiligo: a retrospective comparative analysis of treatment modalities in 500 patients. *J Dermatol* 2001; **28**:461–6.
103 Juhlin L, Olsson MJ. Improvement of vitiligo after oral treatment with vitamin B12 and folic acid and the importance of sun exposure. *Acta Derm Venereol (Stockh)* 1997; **77**:460–2.
104 Al Khawajah MM. The failure of L-phenylalanine and UVA in the treatment of vitiligo. *J Dermatolog Treat* 1996; **7**:181–2.
105 Salafia A. Vitiligo. Successful treatment with dapsone. *Chron Dermatol* 1995; **5**:171–88.
106 Patel IK, Vora NS, Dave JN *et al.* Comparative study of various drug regimens in vitiligo. *Indian J Dermatol Venereol Leprol* 1993; **59**:247–50.
107 Farah FS, Kurban AK, Charglassian HT. The treatment of vitiligo with psoralens and triamcinolone by mouth. *Br J Dermatol* 1967; **79**:89–91.
108 Radakovic-Fijan S, Fürnsinn-Friedl AM, Hönigsmann H, Tanew A. Oral dexamethasone pulse treatment for vitiligo. *J Am Acad Dermatol* 2001; **44**:814–17.
109 Vasistha LK, Singh G. Vitiligo and intralesional steroids. *Indian J Med Res* 1979; **69**:308–11.
110 Njoo MD, Westerhoff W, Bos JD, Bossuyt PM. A systematic review of autologous transplantation methods in vitiligo. *Arch Dermatol* 1998; **134**:1543–9.
111 Barman KD, Khaitan BK, Verma K. A comparative study of punch grafting followed by topical corticosteroid versus punch grafting followed by PUVA therapy in stable vitiligo. *Dermatol Surg* 2004; **30**:49–53.
112 Khandpur S, Sharma VK, Manchandra Y. Comparison of minipunch grafting versus split skin grafting in chronic stable vitiligo. *Dermatol Surg* 2005; **31**:436–41.
113 Ozdemir M, Cetinkale O, Wolf R *et al.* Comparison of two surgical approaches for treating vitiligo – a preliminary study. *Int J Dermatol* 2002; **41**:135–8.
114 Gupta S, Kumar B. Epidermal grafting in vitiligo: influence of age, site of lesion and type of disease on outcome. *J Am Acad Dermatol* 2003; **49**:99–104.
115 Kim HY, Kang KY. Epidermal grafts for the treatment of stable and progressive vitiligo. *J Am Acad Dermatol* 1999; **40**:412–17.
116 van Geel NA, Ongenae K, De Mil M *et al.* Double-blind placebo-controlled study of autologous transplanted epidermal cell suspensions for repigmenting vitiligo. *Arch Dermatol* 2004; **140**:1203–8.
117 Pianigiani E, Risulo M, Andreassi A *et al.* Autologous epidermal cultures and narrow-band ultraviolet B in the treatment of vitiligo. *Dermatol Surg* 2005; **31**:155–9.
118 Pandya V, Parma KS, Shah BJ, Bilimoria FE. A study of autologous melanocyte transfer in treatment of chronic stable vitiligo. *Indian J Dermatol Venereol Leprol* 2005; **71**:393–7.
119 Chen YF, Yang PY, Hu DN *et al.* Treatment of vitiligo by transplantation of cultured pure melanocyte suspension – analysis of 120 cases. *J Am Acad Dermatol* 2004; **51**:68–74.
120 Guerra L, Cappirro S, Melchi F *et al.* Treatment of stable vitiligo by TimedSurgery and transplantation of cultured epidermal grafts. *Arch Dermatol* 2000; **136**:1380–9.
121 Guerra L, Primavera G, Raskovic D *et al.* Erbium YAG laser and cultured epidermis in the surgical therapy of stable vitiligo. *Arch Dermatol* 2003; **139**:1303–10.
122 Guerra L, Primavera G, Raskovic D *et al.* Permanent repigmentation of piebaldism by erbium YAG laser and autologous cultured epidermis. *Br J Dermatol* 2004; **150**:715–21.
123 Papadopoulos L, Bor R, Legg C. Psychological factors in cutaneous disease; an overview of research. *Psychol Health Med* 1999; **4**:107–26.
124 Thomson AR, Kent G, Smith JA. Living with vitiligo: dealing with difference. *Br J Health Psychol* 2002; **7**:213–25.
125 Papadopoulos L, Walker C, Anrhis L. Living with vitiligo: a controlled investigation into the effects of group cognitive-behavioural and person-centred therapies. *Dermatol Psychosom* 2004; **5**:172–7.

Appendix 1. Contents

Key recommendations:
The main points of note.

Introduction: D.J. Gawkrodger
Includes method of guideline development, aims, scope, audience, process, funding, declaration of interests and review.

Symptoms and signs: A.D. Ormerod
What symptoms and signs are suggestive of vitiligo?

Wood's light: A.D. Ormerod
What is the accuracy of Wood's light compared with naked eye examination in the diagnosis of vitiligo?

Natural history: A.V. Anstey
What is the natural history of vitiligo?

Quality of life: L. Shaw, I. Mauri-Sole
What is the quality of life in patients with vitiligo compared with other skin diseases?

Scoring indices: M.J. Watts, M.E. Whitton
In all patients with vitiligo, what is the accuracy of a scoring index in showing the outcome of common treatments compared with simple photography?

Topical treatments: D.J. Gawkrodger
Includes: In all patients with vitiligo, what is the efficacy of applying betamethasone, clobetasol, fluocinolone, fluticasone or mometasone vs. placebo or other active treatment in terms of condition progression, area reduction and quality of life score?
In all patients with vitiligo, what is the efficacy of applying calcipotriol or tacalcitol vs. placebo or an active treatment in terms of condition progression, area reduction and quality of life score?
In all patients with vitiligo, what is the efficacy of applying tacrolimus or pimecrolimus vs. placebo or an active treatment in terms of condition progression, area reduction and quality of life score?
In all patients with vitiligo, what is the efficacy of applying p-(benzyloxy)phenol (monobenzyl ether of hydroquinone) vs. placebo or an active treatment in terms of reducing areas of pigmentation?

Phototherapy: A.V. Anstey
Includes: In all patients with vitiligo, what is the efficacy of a course of narrowband UVB including high-intensity light sources compared with placebo in terms of condition progression, area reduction and quality of life score?
In all patients with vitiligo, what is the efficacy of a course of PUVA or PUVA-sol compared with placebo in terms of condition progression, area reduction and quality of life score?
In all patients with vitiligo, what is the efficacy of a course of khellin with sunlight UVA or UVB compared with PUVA or PUVA-sol in terms of progression, area reduction and quality of life score?
Late complications of PUVA or narrowband UVB therapy in patients with vitiligo: are patients who have received large doses of PUVA (more than 150 treatment sessions) or narrowband UVB (more than 150 treatment sessions) at increased risk of developing premalignant or malignant skin changes?

Combination phototherapy: A.V. Anstey
Includes: In all patients with vitiligo, what is the efficacy of a course of narrowband UVB with a vitamin D analogue compared with narrowband UVB with placebo in terms of condition progression, area reduction and quality of life score?
In all patients with vitiligo, what is the efficacy of a course of PUVA with a vitamin D analogue compared with PUVA with placebo in terms of condition progression, area reduction and quality of life score?

Systemic therapies: D.J. Gawkrodger
In all patients with vitiligo, what is the efficacy of systemic (i.e. orally and parenterally administered) treatments, including corticosteroids, ciclosporin and other immunosuppressive agents, in terms of condition progression, area reduction and quality of life score?

Surgical treatments: A.D. Ormerod
In patients with vitiligo what is the efficacy of a skin graft and of various forms of placebo in terms of condition progression, area reduction and quality of life score? This may include punch grafts, full-thickness skin graft, split-thickness skin graft, autologous epidermal cell suspension, and autologous skin equivalent (commercial skin equivalent).

Psychological treatments: L. Shaw, I. Mauri-Sole
In all patients with vitiligo, what is the efficacy of cognitive therapy vs. psychological support or no treatment in terms of condition progression, area reduction and quality of life score?

Research recommendations:
Areas for future research to improve treatment of vitiligo are suggested.

Final recommendations:
An approach to the overall management of vitiligo is outlined based on the evidence evaluated in this guideline.

