Interventions for melasma (Review)

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[Intervention Review]

Interventions for melasma

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ABSTRACT

Background

Melasma is an acquired symmetrical pigmentary disorder where confluent grey-brown patches typically appear on the face. Available treatments for melasma are unsatisfactory.

Objectives

To assess interventions used in the management of all types of melasma: epidermal, dermal, and mixed.

Search strategy

In May 2010 we searched the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (Clinical Trials) in *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, and LILACS. Reference lists of articles and ongoing trials registries were also searched.

Selection criteria

Randomised controlled trials that evaluated topical and systemic interventions for melasma.

Data collection and analysis

Study selection, assessment of methodological quality, data extraction, and analysis was carried out by two authors independently.

Main results

We included 20 studies with a total of 2125 participants covering 23 different treatments. Statistical pooling of the data was not possible due to the heterogeneity of treatments.

Each study involved a different set of interventions. They can be grouped into those including a bleaching agent such as hydroquinone, triple-combination creams (hydroquinone, tretinoin, and fluocinolone acetonide), and combination therapies (hydroquinone cream and glycolic acid peels), as well as less conventional therapies including rucinol, vitamin C iontophoresis, and skin-lightening complexes like Thiospot and Gigawhite.

Triple-combination cream was significantly more effective at lightening melasma than hydroquinone alone (RR 1.58, 95% CI 1.26 to 1.97) or when compared to the dual combinations of tretinoin and hydroquinone (RR 2.75, 95% CI 1.59 to 4.74), tretinoin and

fluocinolone acetonide (RR 14.00, 95% CI 4.43 to 44.25), or hydroquinone and fluocinolone acetonide (RR 10.50, 95% CI 3.85 to 28.60).

Azelaic acid (20%) was significantly more effective than 2% hydroquinone (RR 1.25, 95% CI 1.06 to 1.48) at lightening melasma but not when compared to 4% hydroquinone (RR 1.11, 95% CI 0.94 to 1.32).

In two studies where tretinoin was compared to placebo, participants rated their melasma as significantly improved in one (RR 13, 95% CI 1.88 to 89.74) but not the other. In both studies by other objective measures tretinoin treatment significantly reduced the severity of melasma.

Thiospot was more effective than placebo (SMD -2.61, 95% CI -3.76 to -1.47).

The adverse events most commonly reported were mild and transient such as skin irritation, itching, burning, and stinging.

Authors' conclusions

The quality of studies evaluating melasma treatments was generally poor and available treatments inadequate. High-quality randomised controlled trials on well-defined participants with long-term outcomes to determine the duration of response are needed.

PLAIN LANGUAGE SUMMARY

Treatments for melasma (darker than normal skin occurring in patches)

Melasma is a psychologically distressing skin disorder also known as 'chloasma' or 'mask of pregnancy'. Darker patches of skin gradually develop on the cheeks, forehead, nose, and upper lip. It is more common in women and is associated with pregnancy and medication containing hormones. Melasma is divided into three types: epidermal, dermal, and mixed melasma. Epidermal melasma is the most superficial with an increase in the skin pigment (melanin) in the top layer of skin (epidermis). In dermal melasma, there is increased skin pigment in the second deeper layer of the skin (the dermis). Mixed melasma is a combination of epidermal and dermal melasma.

Conventional treatments for melasma include sunscreens, bleaching creams (e.g. hydroquinone), acne creams (e.g. azelaic acid), topical retinoids (e.g. tretinoin), and facial peels where an acid solution is used to remove outer layers of the skin (e.g. glycolic acid peels). Some treatments incorporate a combination approach such as triple-combination cream (hydroquinone, tretinoin, and steroid). There is inadequate information available at present to determine the best treatment for melasma.

We included 20 studies with a total of 2125 participants covering 23 different treatments. Triple-combination cream was significantly more effective at lightening melasma when compared to hydroquinone alone or to dual combinations such as tretinoin and hydroquinone, tretinoin and fluocinolone acetonide, or hydroquinone and fluocinolone acetonide. Tretinoin was more effective at lightening melasma compared to placebo, as was the skin-whitening complex Thiospot. However, many studies were of a poor quality with a only small number of participants.

The side-effects reported most frequently by both participants and clinicians were dry, red, and sore skin. No serious side-effects were seen.

More evidence is needed on other treatments which are widely used, including the role of sunscreens which were recommended in almost all studies. There is a need for high-quality studies comparing the treatments for this difficult to manage condition. For example, studies should have a minimum follow-up period of 6 months and should clearly categorise participant groups such as age, type of melasma, and duration of the condition at the start of the trial so that these differences can be considered when assessing results. Addtionally, study outcomes should include participants' views in a standardised manner because they may perceive the degree of skin lightening differently to the trial investigators.

BACKGROUND

Description of the condition

Definition and epidemiology

Melasma is an acquired increased pigmentation of the skin characterised by symmetrical and confluent grey-brown patches mostly on the areas of the face exposed to the sun, such as the cheek bones, forehead, and chin. It may occasionally affect other areas such as the neck and forearms (Newcomer 1961). Its clinical and histological presentation does not differ between men and women, apart from being more common in women. There are few studies showing how many people are affected. A study done in Mexico (Estrada-Castanon 1992) and a study done in Peru (Failmezger 1992) found melasma to be present in 4% to 10% of new dermatology hospital referrals. A survey of 2000 black participants at a private clinic in Washington found melasma to be the third most common pigmentary disorder of the skin (Halder 1983). Melasma is thought to be more common in people of Hispanic and Asian origin (Newcomer 1961).

Causes

Melasma occurs most commonly in women of childbearing age (Pandya 2007). The majority of cases seem to be related to pregnancy, use of oral contraceptives and some other drugs, such as antiepileptics (Sanchez 1981). Exposure to the sun appears to be important for the development of melasma (Sanchez 1981). The condition may also occur in men (Vázquez 1988). There seems to be a familial predisposition for the development of melasma but the exact risk is unknown.

Melasma may be caused by a hormonal mechanism but this has not been proven (Pérez 1983). A case control study of 108 non-pregnant women with melasma found a significant association with increased thyroid antibodies in the blood (Lawrence 1997).

Clinical features and symptoms

Melasma is usually a clinical diagnosis. Microscopic skin studies suggest that there may be two differentiated types of melasma and a third mixed type:

1. Epidermal-type melasma, characterised by increased melanin (skin pigment) in the epidermis (the outer layer of the skin).
2. Dermal-type melasma, characterised by increased melanin in the dermis (the deeper layer of the skin).
3. Mixed-type melasma, a combination of epidermal and dermal melasma in the same person.

It may be important to distinguish between different categories of melasma as it has been suggested that dermal-type melasma may be less responsive to conventional therapy (Pathak 1986). This distinction can be made in clinical practice by using a Wood's lamp.

A Wood's lamp examination is a test which uses ultraviolet light to look closely at the skin. The level of melanin deposition can be differentiated using Wood's lamp. In people with light-coloured skin (e.g. Fitzpatrick skin types I to IV), epidermal melasma becomes more pronounced (Gupta 2006). The dark colour due to pigment in the outer epidermal layer of the skin is accentuated while in dermal melasma the colour of the deeper dermal pigments is decreased during Wood's lamp examination. This contrast is less marked in darker skin types. Fitzpatrick devised a description of skin types known as the Fitzpatrick skin type classification. This classification denotes six different skin types based on constitutional colour and result of exposure to ultraviolet radiation (tanning). In general; skin type I and II is white skin, with type I always burning and type II sometimes burning, skin type III is olive skin which sometimes burns, type IV is brown skin which rarely burns, and type V and VI are respectively dark brown skin which rarely burns and black skin which never burns.

Melasma usually lasts for several years. It may present as odd streaking on the face causing significant cosmetic disfigurement. Pregnancy-related melasma may persist for several months after delivery and melasma related to hormonal treatments may persist long after stopping oral contraceptive hormones. Melasma is a chronic disease and recurrences are common especially after re-exposure to the sun (Sanchez 1981).

Description of the intervention

Treatment is often unsatisfactory and has been associated with side-effects such as local irritation, scarring, and residual patches of lighter colour on the skin.

Available therapies consist of preparations applied to the skin and recently laser therapy. These are listed below.

1. Sunscreens that block ultraviolet light
2. Topical steroids
3. Topical retinoids
4. Azelaic acid & kojic acid
5. Bleaching agents such as hydroquinone
6. Peeling agents such as glycolic acid
7. Laser therapy
8. Combined therapies
9. Other therapies

Why it is important to do this review

The currently available treatments for melasma are unsatisfactory. There are a wide range of treatments available, response to which is variable. Some treatments may have significant side-effects. The other problem is the chronic and relapsing nature of melasma, such that any response achieved will need to be maintained. We undertook this Cochrane systematic review of treatments for melasma

because it is a common and distressing condition and we wished to assess the effectiveness of the variety of treatments that are used.

OBJECTIVES

Main objective

To assess the effects of treatment to limit or reduce melasma and prevent recurrence.

Secondary objectives

- To clarify as far as possible, the optimal regimen for preventing and treating melasma.
- To see whether factors such as race, sex, geography, seasonal variation, and skin colour affect treatment response.
- To determine the incidence of adverse reactions and side-effects with different therapies.
- To identify the need for further studies.

METHODS

Criteria for considering studies for this review

Types of studies

We considered published or unpublished randomised controlled trials (RCTs) related to the treatment of melasma. We considered open label trials where placebo use was possible if the assessment of outcomes was done blindly. Where placebo use was not possible (e.g. laser therapy), we considered trials either if the assessment was done blindly or with objective-validated scales. This is a deviation from the original protocol, our initial criteria to exclude all open label trials where placebo use was possible was too stringent.

We initially excluded open label trials where placebo use was possible as knowledge of the assigned intervention may impact on outcomes. If however, the outcome assessors were not aware of the assigned intervention, the assessment may be less biased. This was the reason we deviated from our initial protocol which was possibly too exclusive.

We did not consider quasi-randomised trials and information from trials in which the unit of randomisation was different to the unit of analysis when addressing the effects of treatment (e.g. randomised people analysed by individual lesions).

Types of participants

People of all age groups and ethnic backgrounds who had a clinical diagnosis of melasma made by a physician.

Types of interventions

We considered all types of interventions, this included studies that compared at least one active treatment with a control which may be a placebo or an alternative intervention.

Types of outcome measures

Primary outcomes

Participant-assessed response including:
a) Impact on quality of life.
b) Participant-assessed changes in melasma severity.

Secondary outcomes

a) Physician assessed changes in melasma severity including:
1. Improvement assessed by subjective evaluation technique (e.g. physicians global assessment or Melasma Area and Severity Index).
2. Improvement assessed by objective evaluation techniques (e.g. using a reflectance spectrophotometer or histology).
3. Time needed for improvement of melasma.

b) Adverse events, either those sufficiently serious enough to stop the intervention or minor adverse events not requiring withdrawal.
c) Long-term remission rate (greater than 12 months).

Search methods for identification of studies

Electronic searches

On 25th May 2010 we searched the following databases:

- We searched the Cochrane Skin Group Specialised Register using the terms: “melasma or chloasma or (mask and pregnancy)”;
- We searched the Cochrane Central Register of Controlled Trials (Clinical Trials) in *The Cochrane Library* using the search strategy in Appendix 1;
- We searched MEDLINE (from 2004 to present) using the search strategy in Appendix 2;
- We searched EMBASE (from 2006 to present) using the search strategy in Appendix 3;
- We searched LILACS (Latin American and Caribbean Health Science Information database) (from inception to present) using the search strategy in Appendix 4; and
- We searched PsycINFO (from inception to present) using the MEDLINE search strategy.

The UK Cochrane Centre (UKCC) has an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2003 and in EMBASE to 2005. Further searching has been undertaken for this review by the Cochrane Skin Group to cover the years that have not been searched by the UKCC.

Ongoing Trials

We searched the following ongoing trials registers on 1st June 2009 using the terms 'Melasma' and 'Chloasma':

- The metaRegister of controlled trials (www.controlled-trials.com).
- The U.S. National Institute of Health ongoing trials register (www.clinicaltrials.gov).
- The Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The Ongoing Skin Trials register (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

Reference lists

We checked the references from included and excluded studies for possible references to further RCTs.

Language

We imposed no language restrictions when searching for publications and sought translations where necessary. Three studies were translated from Chinese with the help of Dr Chiu and two studies from Spanish with the help of Dr Christina Macano.

Data collection and analysis

Selection of studies

Two of us (RR, JH) identified and checked titles and abstracts from the searches. If the study did not refer to a randomised controlled trial on melasma it was excluded. We (RR, JH) independently assessed each study to determine whether it met the predefined selection criteria. We included open label trials even when placebo use was possible as long as they were randomised and the outcome assessor-blinded. If placebo use was not possible, we included trials if the assessment was done blindly or with objective validated scales. Any differences in opinion were resolved through discussion. If this was not possible, we planned to discuss the paper with a third author (AS), however this was not necessary as there was little disagreement over which papers to include.

Data extraction and management

Two of us (RR, JH) developed and piloted a data extraction form in order to summarise the trials. We (RR, JH) extracted data independently and subsequently checked for discrepancies. Differences were resolved by discussion. Data was checked and entered by one of us (RR).

Assessment of risk of bias in included studies

Two of us (RR, JH) performed the quality assessment and independently judged the components on the quality assessment form. We assessed the risk of bias and the methodological quality of included studies using the following components of internal and external validity for each included study, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). The main criteria we considered were:
a) the method of generation of the randomisation sequence;
b) the method of allocation concealment - it was considered 'adequate' if the assignment could not be foreseen. Trials without evidence of adequate allocation concealment were included initially and we planned to do a sensitivity analysis to investigate whether reported allocation concealment was associated with modifications in the effect magnitude or direction;
c) who was blinded and not blinded;
d) loss to follow up: trials where losses to follow up were greater than 20% or those with highly differential withdrawal rate between groups (> 15% difference between groups) would be initially included, and a sensitivity analysis carried out to address their impact on the conclusions and results of the meta-analysis;
e) intention-to-treat analysis: the review focused on intention-to-treat analysis of data as far as possible and highlighted the clinical outcomes. An intention-to-treat (ITT) analysis includes all participants randomised into the trial irrespective of what happened subsequently. Data from participants who did not complete the trial will be considered for the time they remained in the study;
f) comparability of the two treatment groups in each arm.
This data recorded in the 'Risk of bias' table for each included study can be found in the 'Characteristics of included studies' table.

Measures of treatment effect

Two of us (RR, JH) analysed the data with input from a statistician. We calculated mean differences for continuous outcomes (with 95% confidence interval). We expressed the results as risk ratio (RR) and 95% confidence intervals (CI) for dichotomous outcomes. This analysis differed slightly from the plan in our protocol which was to express results for dichotomous outcomes as

odds ratios. We did not pool data as the interventions and outcomes measured were not appreciably similar. The data has been summarised for each trial as a narrative.

Unit of analysis issues

Some of the studies in this review used a 'within patient' design, where two interventions were allocated randomly to the left and right side of the face. These studies potentially give more accurate estimates of treatment effect since the comparison is made within the same participant rather than between two different groups of participants. A paired data analysis should therefore be applied to data from within participant studies which is not possible within the Review Manager software. As interventions used in the trials were all different, there was no usable data to combine with parallel group studies. There were no cross-over trials. For studies which had more than two intervention groups, pair-wise comparisons were made between intervention groups, which if investigated alone would meet the criteria for inclusion to the review.

Dealing with missing data

Where there was uncertainty or missing data we contacted the trial authors for clarification.

Assessment of heterogeneity

We had planned to investigate possible reasons for heterogeneity such as severity of melasma, race, sex etc. The studies were clinically heterogenous for variables such as race and type and duration of melasma.

Data synthesis

We have presented the results from the individual trials. Quantitative pooling of data was not possible because of the diversity of therapies evaluated and the heterogeneity of the studies. A detailed description of individual studies is presented in the 'Characteristics of included studies' table. Our primary outcome measure was improvement in quality of life measures or participant-rated improvement in melasma. However, as none of the included trials used quality of life measures and only a few had participant-reported outcomes, we invariably had to use the clinician rating.

Subgroup analysis and investigation of heterogeneity

We did no subgroup analysis due to the wide variety of interventions and small sample sizes. As no trials were combined, it was irrelevant to investigate for heterogeneity. In future updates of this review we will look for sources of heterogeneity (e.g. Fitzpatrick skin type, epidermal, or dermal melasma) if appropriate.

Sensitivity analysis

We did no sensitivity analysis as we did not pool any trials. We had intended to carry out sensitivity analyses to address the impact on studies that had a greater than 20% dropout or those with a differential withdrawal rate between the groups (> 15% difference between groups). We had also planned to do a sensitivity analysis if there was clear evidence that the study groups were unbalanced to suggest confounding. No studies fell into this category. This will be done in updates of the review if relevant.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

In total we identified 257 citations from electronic searches. We obtained full text copies of papers for 56 papers from which we have included 20 trials. We identified eleven studies online from ongoing trial registers.

Included studies

We included 20 randomised controlled trials (RCTs) with a total of 2125 participants which met our inclusion criteria (Baliña 1991b; Chan 2008; Ejaz 2008; Ennes 2000; Espinal-Perez 2004; Francisco-Diaz 2004; Griffiths 1993; Guevara 2003; Huh 2003; Hurley 2002; Khemis 2007; Kimbrough-Green 1994; Leenutaphong 1999; Lim 1997; Lim 1999; Sivayathorn 1995; Taylor 2003; Thirion 2006; Vázquez 1983; Wang 2004).
Full details are described in the 'Characteristics of included studies' table.

Design

All included studies were randomised controlled trials. Of the 20 included RCTs, 7 were right/left comparison studies (Espinal-Perez 2004; Francisco-Diaz 2004; Huh 2003; Hurley 2002; Khemis 2007; Lim 1997; Lim 1999). Thirteen studies compared 1 or more active interventions. Placebo-controlled studies were undertaken by Francisco-Diaz 2004, Griffiths 1993, Huh 2003, Khemis 2007, Kimbrough-Green 1994, Leenutaphong 1999, and Thirion 2006. Ennes 2000 was described as a placebo-controlled trial but the 'placebo arm' received a cream containing two sunscreens.
Duration of follow up varied between 8 weeks to 10 months.

Setting

The 20 included trials were conducted in different parts of the world. Sixteen were single-institution studies. The studies by Lim 1997 and Lim 1999 were conducted in Singapore, Ejaz 2008 in Pakistan, Ennes 2000 in Brazil, Espinal-Perez 2004 in Mexico, Francisco-Diaz 2004 in the Philippines, Griffiths 1993, Guevara 2003, Hurley 2002, and Kimbrough-Green 1994 in USA, Huh 2003 in Korea, Khemis 2007 in France, Leenutaphong 1999 in Thailand, Thirion 2006 in Belgium, Vázquez 1983 in Puerto-Rico, and Wang 2004 in Taiwan.

Four studies were multicentre studies (Baliña 1991b in Brazil, Peru, Uruguay, Venezuela, and Argentina; Chan 2008 in Korea, the Philippines, Singapore, and Hong Kong; Sivayathorn 1995 in Thailand and the Philippines; and Taylor 2003 in 13 dermatology departments in the USA).

Participants

All studies included adult participants. The studies by Baliña 1991b, Espinal-Perez 2004, Griffiths 1993, Guevara 2003, Huh 2003, Hurley 2002, Khemis 2007, Lim 1997, Lim 1999, Thirion 2006, Vázquez 1983, and Wang 2004 only included female participants. In the rest (8 studies) participants of both sexes were included though there was a marked predominance of female participants reflecting the nature of the condition which affects mostly women.

Four studies included only epidermal melasma and excluded dermal or mixed melasma (Ejaz 2008; Guevara 2003; Lim 1997; Lim 1999). The studies by Baliña 1991b, Espinal-Perez 2004, Francisco-Diaz 2004, Hurley 2002, Khemis 2007, Sivayathorn 1995, and Wang 2004 excluded participants with dermal melasma. In 5 studies the type of melasma was not specified (Ennes 2000; Huh 2003; Taylor 2003; Thirion 2006; Vázquez 1983). The rest of the studies included a mix of epidermal, dermal, and mixed melasma.

The studies by Chan 2008, Guevara 2003, Hurley 2002, Khemis 2007, Kimbrough-Green 1994, Leenutaphong 1999, and Lim 1997 were confined to participants with moderate to severe melasma. The inclusion criteria in the Taylor 2003 trial was a melasma severity score of > 2 which translates to moderate to severe melasma, while the Huh 2003 study required a luminance (L) value difference of greater than 2.0 between lesional and normal skin. The L, a, b system recommended by the Commision Internationale de l'Eclairage was used to measure luminance (Westerhof 1995). The L value expresses the relative brightness of colour ranging from black (L = 0) to white (L = 100). In the rest of the studies the severity of melasma at baseline was not described.

Two other studies with unique inclusion criteria were Wang 2004 where criteria for inclusion was unresponsiveness to hydroquinone for at least 3 months, and Thirion 2006 which included participants with forehead melasma.

The number of participants evaluated in the studies varied from 10 to 641.

Interventions

Each study was concerned with a unique set of interventions. They can be grouped into:

- those including a bleaching agent such as hydroquinone (Baliña 1991b; Chan 2008; Espinal-Perez 2004; Hurley 2002; Sivayathorn 1995; Vázquez 1983; Wang 2004);
- those including azelaic acid (Baliña 1991b; Sivayathorn 1995);
- those including a topical retinoid; tretinoin (Griffiths 1993; Kimbrough-Green 1994) and isotretinoin (Leenutaphong 1999);
- those including topical antioxidant ascorbic acid (Espinal-Perez 2004);
- combination creams such as hydroquinone and sunscreen (Ennes 2000); hydroquinone, tretinoin and fluocinolone acetonide (Chan 2008 and Taylor 2003); hydroquinone and tretinoin (Taylor 2003); fluocinolone and tretinoin (Taylor 2003); hydroquinone and fluocinolone (Taylor 2003); hydroquinone, glycolic acid, vitamins C and E and sunscreen (Guevara 2003); hydroquinone and glycolic acid (Lim 1997; Lim 1999); hydroquinone, glycolic acid and kojic acid (Lim 1999);
- combination therapies such as hydroquinone cream and glycolic acid peels (Hurley 2002); hydroquinone and glycolic acid cream and glycolic acid peels (Lim 1997); hydroquinone cream and intense pulsed light (Wang 2004); tretinoin cream and Jessner's solution peel (Ejaz 2008); tretinoin cream and salicylic acid peel (Ejaz 2008);
- less conventional therapies. Khemis 2007 investigated the efficacy of rucinol serum, a substance able to inhibit tyrosinase and other enzymes involved in melanogenesis, while Huh 2003 compared Vitamin C iontophoresis to distilled water iontophoresis. Thirion 2006 tested a composite whitening formulation, Thiospot, available over the counter, and Francisco-Diaz 2004 investigated the efficacy of a botanical extract, Gigawhite;
- studies where a cream containing sunscreens was compared to another agent (Ennes 2000; Guevara 2003); while Vázquez 1983 investigated the additional benefit of a sunscreen by comparing hydroquinone in one arm and hydroquinone and sunscreen in another. In many other studies the use of a sunscreen was recommended or provided in addition to study creams.

Outcomes

A large variety of outcomes were reported in the included studies. All studies assessed outcomes as lightening of melasma. There was however considerable variation as to how this was reported. In most studies improvement was assessed subjectively by a clinician. A variety of scoring systems for the subjective evaluation of pigmentation were used. The most common was the melasma

area and severity index (MASI) score which attempts to quantify pigmentation area, darkness, and homogeneity (Chan 2008; Ejaz 2008; Francisco-Diaz 2004; Guevara 2003; Hurley 2002; Kimbrough-Green 1994; Leenutaphong 1999). Griffiths 1993 assessed improvement on a scale of much worse (-2) to much improved (+2), while Taylor 2003 used the melasma severity rating scale. Four studies scored the percentage of improvement (Francisco-Diaz 2004; Lim 1997; Lim 1999; Sivayathorn 1995). However, the descriptions relating to the response varied; for example Sivayathorn 1995 described lightening of pigmentation by 50% to 75% as good, > 75% as an excellent response, and described improvement of more than 50% as treatment success and less than 50% as no response. Lim 1997, however, described improvement in colour of melasma according to the categories no change, 0% to 33% lighter as slight improvement, and 34% to 66% as moderate improvement.

Baliña 1991b, Ennes 2000, Khemis 2007, Sivayathorn 1995, Thirion 2006, and Vázquez 1983 devised their own scale for physicians to score improvement in pigmentation. This differed for each study. For example, Baliña 1991b used excellent, good, fair, and poor responses, while Thirion 2006 graded improvement on a scale of 0 (absent) to 3 (intense) pigmentation.

Thirteen studies included an objective evaluation of melasma. Reflectance spectroscopy using a mexameter or colorimeter were the most common methods of objective assessment (Espinal-Perez 2004; Francisco-Diaz 2004; Griffiths 1993; Guevara 2003; Huh 2003; Hurley 2002; Khemis 2007; Kimbrough-Green 1994; Leenutaphong 1999; Thirion 2006; Wang 2004). In the Baliña 1991b and Sivayathorn 1995 studies, the objective assessment was measurement of the decrease in size of the melasma lesions while Francisco-Diaz 2004 measured the area of melasma. Additional forms of objective evaluation of melasma were used in Griffiths 1993 and Kimbrough-Green 1994 (evaluation of epidermal pigment on histology) while Thirion 2006 used corneomelametry to quantify melanin in the stratum corneum. Seven studies did not include any form of objective outcome measure.

Only one study assessed the effect of treatment on participants' quality of life (Khemis 2007). However, this was only reported for the second phase of the study, the open label extension, results of which have been excluded from this review. Two studies reported on participant satisfaction (Chan 2008 and Wang 2004). Nine of the 20 studies had no participant self-assessment of improvement (Baliña 1991b; Ejaz 2008; Ennes 2000; Griffiths 1993; Kimbrough-Green 1994; Leenutaphong 1999; Sivayathorn 1995; Taylor 2003; Thirion 2006).

The duration of the studies varied widely (8 weeks to 10 months) and this was mostly related to the variety of outcomes observed, for example, initiation of lightening of melasma or maintenance of lightening effect. The studies of longest duration were by Griffiths 1993, Kimbrough-Green 1994, and Leenutaphong 1999 in which study creams were applied for 40 weeks. The studies by Ejaz 2008 and Wang 2004 had a maintenance phase where treatment was mostly discontinued and maintenance of lightening was investigated, though in Wang 2004 these results were excluded from this review as they were not measured in the control group.

Adverse events were not reported at all in one study (Thirion 2006), while in the study by Hurley 2002 side-effects in the control group were not reported.

Excluded studies

We excluded 30 studies, mostly because they were not randomised or they failed to meet our inclusion criteria. The table 'Characteristics of excluded studies' lists the studies that were excluded.

Ongoing studies

We identified 11 ongoing studies from searching the ongoing trial registers. Details about them are in the 'Characteristics of ongoing studies' table. We hope to assess these in a future update of this review when they have been completed.

Studies awaiting classification

There are 11 studies which are awaiting assessment and are listed in the 'Characteristics of studies awaiting classification'. Among them:

The study by Haddad 2003 is an RCT comparing 4% hydroquinone to a skin-whitening complex. The number of participants in each group is inconsistent between the table and the text, so we have written to the trial authors for clarification about the number of participants who achieved a response.

Poli 1997 published a trial comparing a combination cream, Trio-D, versus vehicle on women with melasma. The response rates in the treatment and placebo arm quoted in the text did not correspond to the raw data provided in the tables. We await replies to our request for clarification in these two studies.

When we wrote to authors of Verallo-Rowell 2002 to ask for clarification about the conclusion of the study that Melfade was significantly more effective than hydroquinone as the colorimetric readings for the two sides did not appear very different, the authors replied that they would look into it. We are awaiting the return of the data extraction form.

Table 1 lists all the authors we contacted for further information.

Table 1. Authors we tried to contact for clarification

Name/Date of Paper	Date written	Request	Answer	Result
Baliña 1991a	10/05/09	If all participants were included in multicentre trial Baliña 1991b?	Yes	All participants were included in the multicentre trial, this paper was excluded
Francisco-Diaz 2004	10/05/09	In the participant self-assessment in the text it was stated '2 participants did not improve and 1 worsened' but the results section states that all participants improved between 25% to 90%	No	Results from the participant self-assessment were excluded
Garg 2008	10/05/09	If data presented was mean +/- SD or mean +/- SE and how participants were allocated to groups?	Yes	Participants were randomised according to application sequence (quasi-randomisation) and paper excluded
Haddad 2003	10/05/09	To comment on the discrepancy in the number of participants in the groups between the table and text, Which was correct?	No	No progress
Piquero Martin 1988	10/05/09	If all participants were also included in multicentre trial Baliña 1991b?	No	Paper excluded as the aims, interventions, outcomes, and participants were identical to Baliña 1991b and likely to have been included
Poli 1997	10/05/09	The raw values presented and results calculated were different, was there an error in the analysis?	No	No progress
Verallo-Rowell 1989	10/05/09	If all participants were also included in multicentre trial Sivayathorn 1995?	Yes	All participants were included in the multicentre trial, this paper was excluded
Verallo-Rowell 2002	10/05/09	The primary outcome of melanin difference was stated as significantly different though numbers appeared similar, authors asked for P value. Also discrepancy in the number of outcomes between table and text?	Yes	There are unresolved inconsistencies between the published and author derived data. We are awaiting return of the data extraction form

Table 1. Authors we tried to contact for clarification (*Continued*)

Ongoing trial- ISRCTN84133969 Wolkerstorfer	01/06/09	Publication requested	Yes	No progress
Ongoing trial- NCT00467233 Alam	01/06/09	Publication requested	Yes	Study still recruiting, no progress
Ongoing trial- NCT00500162 Hassun	01/06/09	Publication requested	No	No progress
Ongoing trial- NCT00509977 Alam	01/06/09	Publication requested	Yes	Study still recruiting, no progress
Ongoing trial- NCT00616239 Pandya	01/06/09	Publication requested	No	No progress
Ongoing trial- NCT00717652 Alexandre	01/06/09	Publication requested	Yes	Study still recruiting, no progress
Ongoing trial- NCT00848458 Schmidt	01/06/09	Publication requested	No	No progress
Ongoing trial- NCT00863278 Passeron	01/06/09	Publication requested	Yes	Study still recruiting, no progress

SD = standard deviation
SE = standard error
BD = twice-daily

Risk of bias in included studies

Many of the elements assessed in the risk of bias for each of the included studies (see 'Characteristics of included studies') were lacking in most of the studies. Our judgements about each methodological quality item for each included study have been summarised in Figure 1 and our judgements about each methodological quality item presented as percentages across all the included studies have been summarised in Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

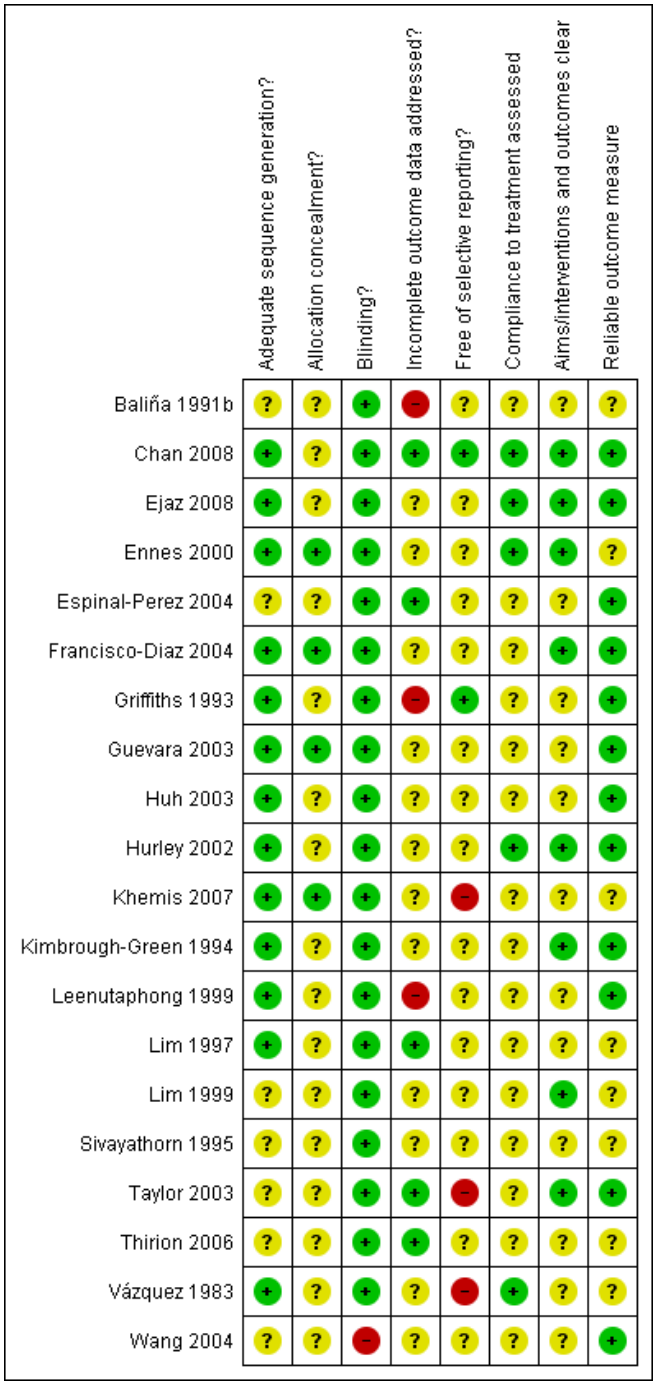
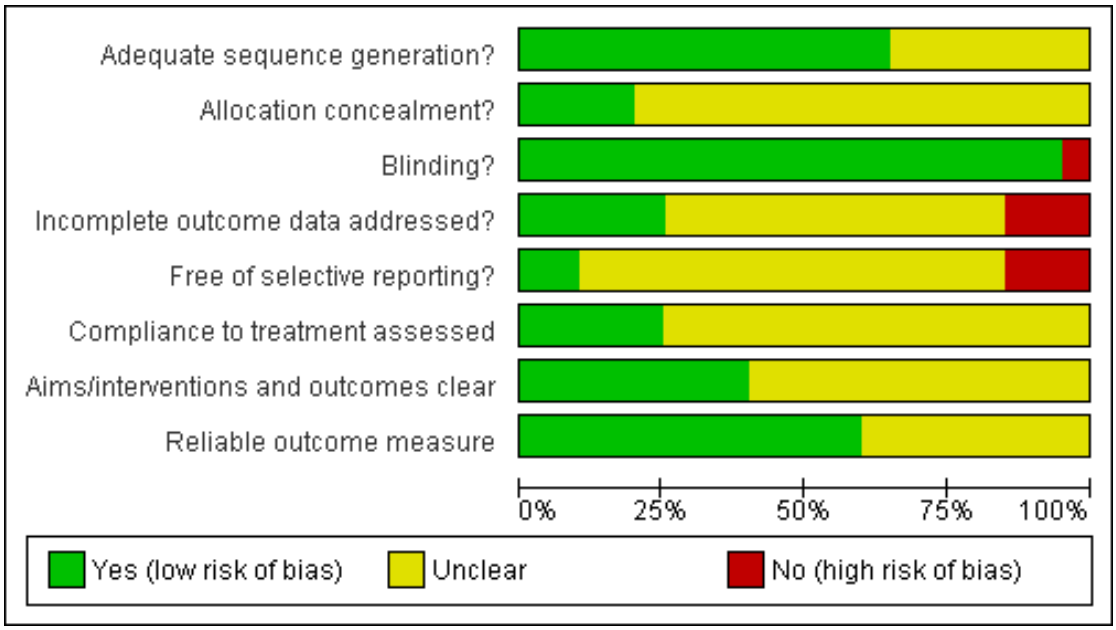


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

All the included studies were stated to be randomised. However, the method of randomisation was only described in 13 studies. Allocation concealment was adequate in 4/20 studies and unclear in 16/20 studies.

Blinding

Ten studies were stated to be double-blind with no further detail of who was blinded (Baliña 1991b; Ennes 2000; Espinal-Perez 2004; Francisco-Diaz 2004; Guevara 2003; Huh 2003; Lim 1999; Sivayathorn 1995; Thirion 2006; Vázquez 1983). In five other studies also described as double-blind, it was stated that the participant and investigator were blinded (Ejaz 2008; Griffiths 1993; Khemis 2007; Kimbrough-Green 1994; Leenutaphong 1999). In Ejaz 2008 it was also specified that the investigator assessing outcome was blinded. Four studies were single-blind and in all four the outcome assessor was stated to be blinded (Chan 2008; Hurley 2002; Lim 1997; Taylor 2003).

Incomplete outcome data

Participant losses ranged from 0% to 26%. It was unclear how many participants were lost to follow up in Huh 2003. No reference was made to withdrawals but results were only available for 26 of the 29 participants. Reasons for participant loss were described in all studies except for Guevara 2003 and Khemis 2007. Incomplete outcome data was only adequately addressed in 5 studies (Chan 2008; Espinal-Perez 2004; Lim 1997; Taylor 2003; Thirion 2006). Although an intention-to-treat analysis was stated to be done in Sivayathorn 1995, the analysis did not include all the participants who were randomised.

Other potential sources of bias

Baseline characteristics

Baseline participant characteristics were not specified for each group in 6 studies (Ennes 2000; Griffiths 1993; Guevara 2003; Taylor 2003; Thirion 2006; Vázquez 1983). However, in the studies by Ennes 2000 and Taylor 2003 it was stated that there was

no significant differences in the demographic parameters between the groups. In other studies baseline characteristics appeared to be similar for each group.

Aims

The aims of the studies were generally well-defined.

Interventions

While the dose and duration of the intervention was often described, in most studies there was concomitant use of a sunscreen. Details of the sunscreen co-intervention, either the SPF (Sun Protection Factor) or frequency of application, were scarce. The studies by Ejaz 2008, Espinal-Perez 2004, and Leenutaphong 1999 were the only studies which stated that there was regular use of a sunscreen accounting for the short duration of action of most sunscreens. However, the study by Espinal-Perez 2004 failed to provide details on the SPF of the sunscreen. It was also unclear in many studies whether the sunscreen was provided along with study agents or if participants had to purchase them separately.

Statistics

Statistical analysis was generally adequate although in the Taylor 2003 study a pooled analysis was performed and the results of two trials were combined and presented together with no mention of investigation or correction of heterogeneity.

Effects of interventions

In this section we have presented the results for the effects of interventions only for studies that examined the primary and secondary outcomes of interest in this review. Of the 20 trials included, only 2 had similar interventions (Griffiths 1993; Kimbrough-Green 1994). The results of these 2 trials were not pooled as there was clinical heterogeneity. The study by Griffiths 1993 was on participants with white skin and had a higher proportion of epidermal melasma, whereas the participants in the study by Kimbrough-Green 1994 had black skin and had more dermal melasma.

We did not perform any calculations on number needed to treat. Most of the trials had scale-based outcomes, the baseline characteristics, time frame, and outcomes measured were not homogeneous and comparison between values would be misleading.

We did not find the outcome measures we had expected when we wrote the protocol. None of the studies addressed the primary outcome of effect of treatment on quality of life and only 11 of the 20 studies included participant-assessed changes in melasma severity. In the Khemis 2007 study, one of the intended outcomes was effects of rucinol treatment on quality of life. However, these results from a questionnaire to participants at 12 weeks were not presented. In the Chan 2008 and Wang 2004 studies quality of life was not specifically addressed but participants were asked to rate satisfaction with treatment.

The secondary outcome measures of physician-assessed changes in melasma severity and adverse events are reported below. None of the studies were longer than 12 months and consequently we have not been able to evaluate the long-term remission rate set out in the protocol. Melasma is a chronic relapsing disorder and the long-term maintenance of unpigmented skin is the most clinically relevant. Additionally none of the studies set out to evaluate the time-to-improvement of melasma, a factor which may affect compliance to treatment. In two studies (Chan 2008; Ennes 2000) an earlier onset of action of the study product was noted, though this was not one of the pre-defined outcome measures.

The included studies have been addressed below in the order in which they were grouped together in the section 'Included studies' > 'Interventions'.

Primary outcomes

Participant-related clinical response relating to:

a) Impact on quality of life.

b) Participant-assessed changes in melasma severity.

As discussed above under 'Included studies > 'Outcomes', our Primary outcome a) (the impact on quality of life) was not addressed by the included studies. Our Primary outcome b) (participant-assessed changes in melasma severity) was reported in a variety of ways which we have taken below to assess this outcome.

Those including a bleaching agent such as hydroquinone

(Chan 2008; Espinal-Perez 2004; Hurley 2002; Vázquez 1983; Wang 2004)

Chan 2008 conducted a multicentre trial in 9 centres (Korea, the Philippines, Singapore, and Hong Kong) on 260 South East Asian participants who were randomised to triple-combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) cream or 4% hydroquinone cream for 8 weeks.

Participants assessed self-improvement using a static global assessment score. A score of 0 related to clear and 1 related to minor hyperpigmentation. Significantly more participants in the triple-combination group (87/125) compared to the 4% hydroquinone group (57/129) achieved a score of 0 or 1 (RR 1.58, 95% CI 1.26 to 1.97; Analysis 1.1). In this trial the participants overall satisfaction with treatment was assessed by means of a questionnaire. Significantly more participants (71%) in the triple-combination group versus 50% in the hydroquinone group were satisfied or very satisfied (trial authors report P = 0.005).

Espinal-Perez 2004 conducted a split face trial on 16 participants in Mexico. Sixteen female participants were randomised to 5% L-ascorbic acid or 4% hydroquinone to the right or left side of the face for 16 weeks. Participants assessed their own improvement according to categories mild (less than 25%), moderate (25% to

49%), good (50% to 74%), and excellent (> 75%). Taking good or excellent response as indicating treatment success, the hydroquinone-treated side was significantly better with 15/16 having a good or excellent response compared to 10/16 on the L-ascorbic acid side (the trial authors stated P = 0.001).

Hurley 2002 conducted a split face trial on 21 participants with moderate to severe melasma in Texas, USA. Participants were Hispanic women with epidermal or mixed melasma and were randomised to receive either 4% hydroquinone cream or 4% hydroquinone cream and 20% to 30% glycolic acid peels every 2 weeks applied either to the right or left side of the face for 8 weeks. Eleven of 18 participants felt there was more improvement on the peeled side versus 4/18 on the non-peeled side. One of the 18 felt there was no difference between the 2 sides. However, this data is incomplete as two participants did not complete the global evaluation.

Vázquez 1983 compared 3% hydroquinone and a broad spectrum sunscreen to 3% hydroquinone and placebo cream in 59 participants in Puerto Rico. This study aimed to establish the effect of the addition of a sunscreen. A broad spectrum sunscreen was applied once a day in the morning. However, no details of the sunscreen SPF were provided or if participants could reapply during the day. In the participant-assessed self-improvement the differences between the groups were unclear. In the sunscreen and hydroquinone group 8 reported marked improvement, 14 moderate improvement, and 5 slight improvement. In the hydroquinone and placebo group 7 reported marked improvement, 14 moderate improvement, and 4 slight improvement. One woman felt her condition worsened. Overall 100% of the participants reported improvement from baseline in the hydroquinone and sunscreen group, versus 96.2% in the hydroquinone and placebo group.

In Taiwan Wang 2004 randomised 33 participants with mixed-type melasma previously unresponsive to hydroquinone to receive either 4% hydroquinone cream or 4 sessions of intense pulsed light and 4% hydroquinone cream over 16 weeks. Intense pulsed light is a broad spectrum light with wavelengths ranging from 400 nm to 1200 nm which penetrate the skin's surface and targets specific elements in the skin such as melanin. The frequency of hydroquinone application in either group is unclear. The rationale for hydroquinone in the control arm where participants had been shown to be unresponsive is also unclear. Some participants had also used tretinoin, azelaic acid, and L-ascorbic acid. There was a co-intervention of a broad spectrum sunscreen. In the hydroquinone-only group, 64% of the participants were slightly satisfied and 36% were unsatisfied. In the pulsed light group and hydroquinone group, a higher proportion of participants were satisfied (76.5% of participants slightly satisfied or satisfied, and 23.5% were unsatisfied).

Those including combination creams

(Guevara 2003; Lim 1997; Lim 1999)

In Texas, USA, Guevara 2003 conducted a trial on 39 Hispanic women comparing a combination cream containing 4% hydroquinone, 10% buffered glycolic acid, vitamins C and E, and sunscreen, to sunscreen alone for epidermal melasma only. Participants applied either the combination cream or sunscreen twice daily to the full face for 12 weeks. Four people were lost to follow up and it is unclear which group this was from. No reasons for the loss to follow up were provided.

In the combination cream group 19/20 participants noted a moderate, obvious, or very marked improvement and 1/20 a slight improvement. In the placebo group 13/15 participants noted a moderate or obvious improvement, and 2/15 did not notice a difference.

In a small split face study of 10 participants in Singapore with moderate to severe epidermal melasma, Lim 1997 compared glycolic acid peels applied every 3 weeks in addition to glycolic acid and hydroquinone cream applied twice daily for 24 weeks, to glycolic and hydroquinone cream only twice daily for 24 weeks. The glycolic acid peels were started at 20% for 5 minutes and the concentration increased to 70% as tolerated. All participants also had a pre-treatment period of 2 weeks of 8% AHA (alpha hydroxy acid) skin-smoothing cream twice daily to both sides of the face. The participants self-evaluation showed that a higher proportion of people noticed an improvement on the side that was peeled. Five out of 10 had 34% to 66% improvement and 5/10 had a 0% to 33% improvement. In the non-peeled group, 2/10 had a 34% to 66% improvement, 7/10 had a 0% to 33% improvement, and 1 had no improvement.

In another study in Singapore Lim 1999 compared a cream containing 2% hydroquinone, 10% glycolic acid, and 2% kojic acid, to a cream containing 2% hydroquinone and 10% glycolic acid both applied twice daily for 12 weeks in a split face trial. Forty-five per cent of participants felt there was greater improvement on the kojic acid side while 7.5% of participants noticed greater improvement on the hydroquinone and glycolic acid only side, 47.5% felt there was no difference between the sides.

All three trials above were conducted on participants with epidermal melasma only (Guevara 2003; Lim 1997; Lim 1999).

Those including less conventional therapies

(Huh 2003; Francisco-Diaz 2004)

In the Philippines Francisco-Diaz 2004 conducted a split face trial on 28 women with mixed melasma. Participants applied Gigawhite solution or placebo to either the right or left side of the face twice daily for 12 weeks. Gigawhite is a complex of botanical origin containing mallow, peppermint leaf, *Primula veris*, *Alchemilia vulgaris*, *Mellissa officinales* leaf extract, and *Achillea millefolium* extract. There was also a co-intervention of SPF-60 sunscreen. Two participants were lost to follow up. The participants' self-assessment was poorly reported. Three participants had a greater than 90% improvement, 15 had a greater than 50% improvement, and

7 participants a greater than 25% improvement. It is unclear if this was compared to baseline or if compared to the placebo side. It is also stated that two participants had no improvement and one had worsening of melasma; these three appear to have been unaccounted in the self-assessment above.

In Korea Huh 2003 conducted a split face trial on 29 women with melasma. The requirement for entry to the trial was a difference in the luminance value measured with a colorimeter of greater than 2 between the normal and melasma areas. It is unclear how many participants were lost to follow up. Outcomes were measured in 26 participants and it is assumed 3 were lost to follow up. Participants were randomised to receive either Vitamin C iontophoresis in a magnesium-L-ascorbyl-2-phosphate (MAP) solution or distilled water iontophoresis to the right or left side of the face for 8 minutes twice a week for 12 weeks. Vitamin C is known to inhibit melanin formation. However, Vitamin C is quickly oxidised and decomposes easily. MAP, a stable water based solution, was used to resolve this problem. The authors proposed that iontophoresis enhances Vitamin C penetration through the skin.

Participants assessed their own improvement according to the categories; greater than 75% improvement, 50% to 75% improvement, 25% to 50%, less than 25% or worse. The same number in the vitamin C group (16/29) as well as the distilled water group (16/29) rated their improvement as greater than 50%.

Secondary outcomes

a) Physician-assessed changes in melasma severity including:

1. Improvement assessed by subjective evaluation technique (e.g. physicians global assessment or Melasma Area and Severity Index (MASI)).
2. Improvement assessed by objective evaluation techniques (e.g. using a reflectance spectrophotometer or histology).
3. Time needed for improvement of melasma.

b) Adverse events, either those sufficiently serious enough to stop the intervention or minor adverse events not requiring withdrawal.

c) Long-term remission rate (greater than 12 months).

As discussed above, our Secondary outcome a) (Physician-assessed changes in melasma severity) was assessed using a variety of subjective and objective evaluation methods. Our Secondary outcome b) (Adverse events) was also addressed but not our third outcome of long-term remission rate.

Those including a bleaching agent such as hydroquinone

(Baliña 1991b; Chan 2008; Espinal-Perez 2004; Hurley 2002; Sivayathorn 1995; Vázquez 1983; Wang 2004)

Two trials of azelaic acid compared to hydroquinone were included (Baliña 1991b; Sivayathorn 1995). Baliña 1991b compared 20% azelaic acid to 4% hydroquinone, while Sivayathorn 1995 compared 20% azelaic acid to 2% hydroquinone. Most studies of hydroquinone have used the 4% strength. Sivayathorn et al chose the 2% hydroquinone strength as there were ethical obstacles to using placebo for 6 months. This trial aimed to demonstrate the superior efficacy of azelaic acid. The two studies reached different conclusions and this is likely to be due to the different concentrations of the hydroquinone comparator.

The trial conducted by Baliña 1991b was a multicentre South American trial on 329 women with epidermal or mixed melasma. There was a large loss to follow up (86 participants) though the differential loss to follow up between the groups was not significant. Assessments were performed on 122 participants in the azelaic acid group and 121 participants in the hydroquinone group. There was no significant difference in the two groups with regard to overall response or reduction in pigmentary intensity. Both subjective and objective assessments were made. Using the participants who had a good to excellent response as 'treatment success', 71.9% of those in the hydroquinone group had success versus 64.8% in the azelaic acid group (RR 1.11, 95% CI 0.94 to 1.32; Analysis 2.1). The authors also included an objective measure of reduction in lesion size in the two groups, of which no significant difference was demonstrated. There was limited data and no mean or standard deviations (SDs) for lesion size was provided.

Most of the side-effects were mild and transient occurring more frequently in the azelaic acid group (18/122) versus the hydroquinone group (1/121) (RR 17.85, CI 2.42 to 131.64; Analysis 2.2).

The trial conducted by Sivayathorn 1995 was also a multicentre trial. Participants (340) with epidermal or mixed melasma from 5 dermatology units in Thailand and the Philippines were randomised to 20% azelaic acid cream or 2% hydroquinone cream. Forty participants were lost to follow up, 20 from each group. Although an intention-to-treat analysis was stated to be done, the percentages of participants in each category did not correlate with the numbers randomised to each group. We have therefore presented the data in this review as the per protocol analysis, those who completed the 24 weeks. Physicians rated response according to the categories excellent, good, moderate, or poor. Good or excellent response was taken as treatment success. Significantly more participants in the azelaic acid group (75.5%) achieved a good or excellent response compared to the 2% hydroquinone group (47.1%). The percentage improvement was also scored according to categories less than 25%, 25% to 50%, 50% to 75%, and greater than 75%. Taking an improvement of greater than 50% as treatment success, significantly more participants in the azelaic acid group improved by more than 50% (RR 1.25, 95% CI 1.06 to 1.48; Analysis 3.1). However, no statistically significant difference between the groups was found on the objective measures of reduction in lesion size (mean and SDs not provided).

Mild adverse events including, itching, burning, and erythema were reported in 61/147 in the azelaic acid group and 22/153 in the hydroquinone group. Marked local irritation was reported in 15 participants in the azelaic acid group and 2 participants in the

hydroquinone group. Overall more participants in the azelaic acid group had adverse events compared to the hydroquinone group (RR 3.30, 95% CI 2.21 to 4.91; Analysis 3.2).

In the multicentre trial by Chan 2008 comparing triple-combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) cream to 4% hydroquinone cream, the melasma severity scale was used by physicians to assess response. A score of 0 relates to the presence of no melasma and 1 relates to the presence of mild melasma. Significantly more participants in the triple-combination group achieved a score of 0 or 1 (the trial authors stated P < 0.001, RR 1.63, 95% CI 1.25 to 2.13; Analysis 1.2). Triple-combination cream also had an earlier onset of action with significant differences in the score evident at week four.

Treatment-related adverse effects however were also significantly more frequent in the triple-combination group compared to hydroquinone (RR 3.55, 95% CI 2.23 to 5.65; Analysis 1.3). The most commonly reported side-effects were erythema, irritation, and discomfort of the skin though this was stated to be mostly mild in intensity. In this trial participants were also asked how much the side-effects bothered them. Significantly more (77%) of those in the hydroquinone group were not bothered at all by side-effects compared to 43% in the triple-combination cream group.

In the Espinal-Perez 2004 split face trial, only an objective assessment of improvement was made. Colorimetric assessment was performed by obtaining the melanin index difference between the lesional and perilesional areas. This was performed at the beginning and the end of the study. The mean colorimetric improvement was not significantly different for the hydroquinone (4.1) versus the ascorbic acid (2.8) side. There was, however, more irritation from hydroquinone (11/16) compared to L-ascorbic acid (1/16). The trial authors concluded that, although hydroquinone showed a better response in the subjective assessment, there was no difference objectively. Additionally, ascorbic acid had fewer side-effects.

In the Hurley 2002 trial the physicians assessed improvement with subjective and objective measures. While there was a significant improvement from baseline in both groups there was no significant difference between the sides in terms of mexameter readings. There was also no significant difference in improvement in MASI scores between the two groups (mean and SD for the groups were not provided). The trial authors concluded that the use of 4% hydroquinone is effective in the treatment of melasma but the addition of 4 glycolic acid peels did not enhance the effect of hydroquinone. Four participants developed significant erythema though no peeling or erosions occurred secondary to the peels. There was no comment on adverse events from hydroquinone.

The Vázquez 1983 trial only included a subjective assessment of improvement. The physicians rated a higher proportion of participants in the hydroquinone and sunscreen group (96.3%) as improved compared to the hydroquinone-only group (80.8%). In the sunscreen group, 4 had marked improvement, 13 moderate, 9 slight, and 1 no improvement. In the placebo group, 5 had marked improvement, 6 moderate, 10 slight, and 5 no improvement. Although no statistical analysis was conducted, the trial authors concluded that hydroquinone is the main stay of therapy and addition of a sunscreen has a positive effect.

Nine participants developed irritation, stinging, and burning which was reported to be minor and transient, resolving with continued use and this was attributed to hydroquinone. It is unclear which arm this was in as both groups received hydroquinone.

The physicians in the Wang 2004 study assessed improvement objectively using a mexameter. There was a statistically significant difference (authors report P < 0.05) between the groups with a greater reduction in the melanin index score in the hydroquinone and pulsed light group. Participants in the intense pulsed light group achieved an average of 39.8% improvement compared to a mean improvement of 11.6% in the hydroquinone-only group. The number of adverse events was reported to be low and no more detailed data was presented. In this study a further mexameter measurement was made at 36 weeks in the pulsed light group only and not in the hydroquinone group and is therefore not included in this review.

Those including azelaic acid

These studies (Baliña 1991b; Sivayathorn 1995) were discussed above.

Those including a topical retinoid

Tretinoin (Griffiths 1993; Kimbrough-Green 1994)

Isotretinoin (Leenutaphong 1999)

The three studies investigating the benefit of a topical retinoid were of the longest duration.

Two American studies with a total of 80 participants reported the effect of 0.01% tretinoin cream versus placebo on melasma (Griffiths 1993; Kimbrough-Green 1994). The two trials were not pooled due to clinical heterogeneity. The study by Griffiths et al was on 50 Caucasian women with 94% epidermal, 4% dermal, and 2% mixed melasma. The study by Kimbrough-Green et al was on 30 black people with moderate to severe melasma only. The type of melasma was also different with a lower proportion of epidermal melasma (43%) and a higher proportion of dermal melasma (37%) which is more resistant to treatment; 20% had mixed melasma.

In Griffiths 1993 12 participants were lost to follow up and 38 people included in the analysis; 19 in the tretinoin and 19 in the placebo group. Assessment of improvement was made with both subjective and objective measures. At 40 weeks there was a significant difference and 13/19 in the tretinoin group were improved or much improved compared to 1/19 in the placebo group (the trial authors stated P = 0.0006, RR 13, 95% CI 1.88 to 89.74; Analysis 4.1). The overall severity of melasma was also evaluated using a Wood's lamp on a 0 to 9 scale; 0 is no melasma

and 9 severe melasma. Tretinoin treatment significantly reduced the severity of melasma compared to placebo (SMD -0.85, 95% CI -1.51 to -0.18; Analysis 4.2).

The significant improvement seen was also confirmed on colorimetry. In the tretinoin group there was an increase in luminance (L value) from baseline 58.5 (SD 3.9) to 59.4 (SD 3.1) versus a decrease in the placebo group from 60.0 (SD 2.6) to 59.7 (SD 2.6) at 40 weeks. The onset of improvement is slow and the first significant improvement occurred at 24 weeks of tretinoin treatment.

Although adverse reactions were noted, the numbers recorded were confusing. Moderate skin reactions defined as moderate redness and peeling on at least 2 visits was noted in 22/25 tretinoin participants and 7/24 placeb participants. In a further five tretinoin participants the reaction was severe. This would imply that 27 participants in tretinoin group had a moderate or severe adverse event, when only 26 participants received tretinoin.

In the Kimbrough-Green 1994 study 2 participants were lost to follow up in the placebo group and 28 participants included in the analysis; 15 in the tretinoin group and 13 in the placebo group. At 40 weeks 11/15 in the tretinoin group were improved or much improved compared to 6/13 in the placebo group. There was no significant difference between the groups (the trial authors stated P = 0.07, RR 1.59, 95% CI 0.82 to 3.08; Analysis 4.1). Although no difference was found between the groups on the scale of much worse to much improved, when the MASI score was used a significant difference was detected at 40 weeks. In the tretinoin group there was a mean reduction in MASI score by 32% compared to a mean reduction in the placebo group by 10% (P = 0.03). The significant improvement noted on the subjective MASI evaluation was also confirmed on colorimetry (the trial authors stated P = 0.02, SMD 0.83, 95% CI 0.05 to 1.61; Analysis 4.3).

There were more adverse events in the tretinoin group with mild erythema and/or peeling in 10/15 participants versus 1/15 in the placebo group (RR 10.0, 95% CI 1.46 to 68.69; Analysis 4.4). Reduction of side-effects did not require use of any other medication and was achieved with more application of emollient. None of the participants experienced hyperpigmentation or gross depigmentation.

In Thailand Leenutaphong 1999 compared 0.05% isotretinoin gel to placebo. Thirty Thai participants with moderate to severe melasma were randomised to receive either isotretinoin gel or colour-matched vehicle twice daily for 40 weeks. Seven were lost to follow up. Participants were also supplied with a broad spectrum sunscreen SPF-28 applied daily and before sun exposure. At 40 weeks there was a reduction in the MASI (melasma area and severity index) score in both the isotretinoin group as well as the placebo group. There was however no significant difference in the reduction of MASI between the groups (the trial authors stated P = 0.4337, SMD 0.07, 95% CI -0.75 to 0.89; Analysis 5.1). Using the colorimeter, a melanin area and melanin index score was calculated for each participant. In the isotretinoin group there was a reduction in the MASI score by 47% versus 34% reduction in the placebo group. The trial authors stated that the difference in reduction between the groups was not significant.

Four out of 15 in the isotretinoin group had mild erythema or peeling versus 0/15 in the placebo group. This was transient and resolved after 4 weeks with continued use. The authors concluded that isotretinoin did not have any significant lightening effect on melasma in these Thai participants. The lightening effect seen in both groups was ascribed to the broad spectrum sunscreen.

Those including combination creams

(Espinal-Perez 2004 discussed above; Ennes 2000; Chan 2008 as above; Taylor 2003; Guevara 2003; Lim 1997; Lim 1999)

In Brazil Ennes 2000 compared a cream containing 4% hydroquinone and 2 sunscreens with a SPF-15 to a cream containing 2 sunscreens with a SPF-15 both applied for 12 weeks. In addition, participants applied a SPF-30 sunscreen every morning. No explanation was given for the need of three different sunscreens in each arm.

Forty-eight participants were randomised and 3 were lost to follow up (all from the hydroquinone group). Improvement was assessed according to one of three categories: total improvement, partial improvement, or failure. Eight participants in the hydroquinone group showed total improvement and 12 had partial improvement. In the sunscreen-only group, 2 had total improvement, 14 had partial improvement, and there were 4 failures. Outcomes were not reported in five participants. The difference between the treatments was stated to be statistically significant though it is unclear which category of improvement was analysed (trial authors report P = 0.0082). This significant difference between the groups was evident from week three. The trial authors also assessed tolerability of the study products. There was no difference in the tolerability between the groups. Adverse events, mostly erythema, were reported in 6/21 of those in the hydroquinone and sunscreen group, versus 5/24 in the sunscreen-only group (RR 1.37, 95% CI 0.49 to 3.85; Analysis 6.1). Serious adverse events did not occur.

In the USA Taylor 2003 conducted two trials to compare triple-combination cream with three dual-combination agents. The two trials were stated to be similar in protocol, participants, and study agents, and reported together. The participants (641) were randomly assigned to 1 of 4 groups: triple-combination cream (4% hydroquinone, tretinoin 0.05%, and fluocinolone acetonide 0.01%) n = 161, dual-combination agent (tretinoin 0.05% and 4% hydroquinone) n = 158, dual-combination agent (tretinoin 0.05% and fluocinolone acetonide 0.01%) n = 161, or dual-combination agent (4% hydroquinone and fluocinolone acetonide 0.01%) n = 161, daily at night for 8 weeks.

The trial authors stated their assessment was objective. However, none of the conventional objective assessments, e.g. reflectance spectroscopy, were used and outcome measures presented were the authors own 8-point scale of global improvement.

Of those receiving the triple-combination cream, 26.1% had complete clearing of melasma compared to 9.5%, 1.9%, and 2.5% respectively in each of the dual-combination creams. Triple-combination cream was significantly more effective than tretinoin and hydroquinone (RR 2.75, 95% CI 1.59 to 4.74; Analysis 7.1), or tretinoin and fluocinolone acetonide (RR 14.00, 95% CI 4.43 to 44.25; Analysis 8.1), or hydroquinone and fluocinolone acetonide (RR 10.50, 95%CI 3.85 to 28.60; Analysis 9.1) in treating melasma. The trial authors report P < 0.001 for improvement from triple-combination cream versus each of the dual-combination creams. Side-effects were erythema, desquamation (loss of the outer layer of skin by peeling or shedding), burning, dryness, and pruritus. Side-effects were seen most commonly in the dual-combination group, tretinoin and hydroquinone (80%), followed by the tretinoin and fluocinolone acetonide (65%) group, and the triple-combination cream (63%). The hydroquinone and fluocinolone acetonide group was the most tolerated with 34% having side-effects. However, the only participant in the study to develop skin atrophy was in this group.

In the Guevara 2003 study improvement in pigmentation was assessed objectively using the mexameter and subjectively with MASI assessments. There was a significant decrease in mexameter readings using the combination cream compared to sunscreen alone (the trial authors reported that the mean difference between the group scores was 19.8 (SD 6.24) P < 0.0001). There was also a statistically significant difference between the groups in terms of reduction in MASI score (trial authors stated P = 0.01). The mean and SDs for each group were lacking in this trial.

The side-effects reported by participants were all either mild or moderate, and included burning, itching, dryness, redness, and peeling. No serious side-effects were seen. Mild dryness and erythema was noted in 12/20 and 11/20 respectively, and mild burning in 7/20 of those treated with the combination cream versus 0/15 who had dryness, 1/15 redness, and 3/15 mild burning in the sunscreen group (RR 19.05, 95% CI 1.22 to 298.21; Analysis 10.1), (RR 8.25, 95% CI 1.19 to 57.10 Analysis 10.2), (RR 1.75, 95% CI 0.54 to 5.67; Analysis 10.3). The most common moderate reaction was peeling in 6/20 in the combination cream group versus 0/15 in the sunscreen group (RR 9.90, 95% CI 0.60 to 163.20; Analysis 10.4).

In the Lim 1997 study only subjective assessment of improvement was made. Improvement in melasma was graded on a scale of -1 (worse compared to baseline), 0 (no change), 1 (0% to 33% lighter), 2 (34% to 66% lighter), and 3 (> 66% lighter). At the end of 26 weeks there was no significant difference between the groups. The mean score in the peeled side was 1.4 versus 1 in the non-peeled side (no SDs provided). Adverse events were stinging and redness post-peel which was transient. One participant had a burn after the 20% glycolic acid peel resulting in hyperpigmentation which cleared in 2 months. No side-effects in the non-peeled group were mentioned in the text.

In the Lim 1999 study the physician-subjective assessment found that on the side of face treated with kojic acid, a higher proportion of participants (24/40) had greater than 50% improvement compared to the hydroquinone and glycolic acid side (19/40). The side treated with kojic acid also showed a faster response rate. When the physicians were asked to compare the side treated with kojic acid to the other side, 42.5% thought there was greater improvement on the kojic acid-treated side and 12.5% on the hydroquinone and glycolic acid only side; 45% could not tell the difference. The improvement in the kojic acid group was not statistically significant (trial authors report P = 0.9).

All participants were reported to have redness, stinging, and mild exfoliation and this was seen on both sides of the face. These adverse events settled by the third week of the study. No further details were provided.

Those including combination therapies

(Hurley 2002 as above; Lim 1997 as above; Wang 2004 as above; Ejaz 2008)

In Pakistan Ejaz 2008 conducted a trial to compare Jessner's (14% salicylic acid, 14% lactic acid, 14% resorcinol in alcohol) peel to 30% salicylic acid peel after 2 weeks of priming with 0.05% tretinoin cream nightly. Sixty participants with epidermal melasma were randomised to receive either Jessner's peel or salicylic acid peel for 5 minutes every 2 weeks for 12 weeks. Participants then entered a 12-week follow-up period. There were 3 withdrawals at the end of 12 weeks and 14 withdrawals at 24 weeks.

The authors found no statistically significant difference between the groups in terms of reduction in MASI at 12 weeks (SMD 0.08, 95% CI -0.44 to 0.61; Analysis 11.1) or 24 weeks (SMD -0.09, 95% CI-0.71 to 0.52; Analysis 11.2). Eight out of 34 participants in the Jessner's group had adverse events (all excessive crusting) versus 10/26 in the salicylic acid group (4 crusting, 2 sunburn, 2 pigmentation, and 2 acneiform eruption) (RR 1.63, 95% CI 0.75 to 3.55; Analysis 11.3). It is stated that none of the side-effects were severe enough to stop treatment.

Those including less conventional therapies

(Khemis 2007; Huh 2003; Thirion 2006; Francisco-Diaz 2004)

In France Khemis 2007 conducted a split face trial on 32 women with moderate to severe melasma. Participants were randomised to rucinol serum or placebo to the right or left side of the face, they were also provided with a broad spectrum sunscreen SPF-60. There were 4 withdrawals, and 28 participants completed the 12-week study. There was also an open label extension of the study for 3 months during which time participants received rucinol on both sides of the face, the results of which are not reported in this review. A clinical pigmentation score from 0 (no pigmentation) to 10 (brown pigmentation of high intensity) was allocated for different regions of the face (forehead, malar (cheek) region, and chin) and a mean taken. A significantly lower pigmentation score

was achieved on the side treated with rucinol (P = 0.027 reported). The mean clinical pigmentation score at baseline in the rucinol group was 7.5 (SD 1.9) and at 12 weeks it was 6.2 (SD 2.3). In the placebo group the score at baseline was 7.5 (SD 1.9) and at 12 weeks was 6.7 (SD 2.1). The small reduction in score seen in the placebo group was attributed to sunscreen use. Although a reduction in the clinical pigmentation score was also seen at the earlier assessment of 8 weeks, the score was not significantly different from baseline and rucinol may have a slower onset of action. Colorimetric assessments using the chromameter confirmed that the rucinol-treated side was significantly lighter and less yellow at 12 weeks. The L, a, b system was used. The L value expresses the relative brightness of colour (the higher value the better), the 'a' value records erythema and the 'b' value skin tanning. The mean and SDs were not provided at baseline (trial authors stated P = 0.013 for the 'L' value and P = 0.008 for the 'b' value). There was also a tendency to less erythema (P = 0.051 for 'a').

There were 12 adverse events reported, the majority of which were mild. The authors felt only one was related to the study product, a small depigmented spot due to placebo. It is unclear if the numbers of adverse events include the extended phase of the study.

In the Huh 2003 study although the participants' self-assessment detected no difference between the treatments, objective evaluation using a colorimeter found a significant difference with more improvement on vitamin-C-treated side (the trial authors stated P = 0.03). At baseline the mean difference in the L value between the melasma and normal area on the vitamin C side was 4.6. At 12 weeks, the mean difference in the L value was 2.78. On the distilled water side the mean difference in the L value at baseline was 4.45 and at 12 weeks, 3.87. In participants treated with vitamin C iontophoresis, there was mild sensation of electric shock in 6/29 participants, itching, and erythema in 2 participants each as well as a burning sensation in 1 participant and dryness in another. No side-effects of the distilled water iontophoresis were mentioned.

Thirion et al conducted a trial in Belgium on 27 women with melasma affecting the forehead for at least 6 months (Thirion 2006). It is unclear if participants were excluded if they had melasma elsewhere (e.g. cheeks or chin). No explanation is given as to why the authors limited inclusion to forehead melasma. Participants were randomised to Thiospot intensive, a cosmetic-whitening formulation containing ethyl linoleate, thioctic acid, octadecanedioic acid, lactic acid, and ethylhexylmethoxycinnamate, or Eucerin non-whitening skin care both applied twice daily for 3 months. Thiospot is purported to inhibit the enzyme tyrosinase involved in melanin synthesis. There was a significant difference between the groups. At three months the group receiving Thiospot had lighter skin with a lower melanin index measured using a mexameter (the trial authors stated P < 0.01, SMD -2.61, 95% CI -3.76 to -1.47; Analysis 12.1). The significant improvement in melasma in the Thiospot group was also confirmed on the other objective measurements of video-recorded ultraviolet light reflection, corneomelametry, as well as the physician's subjective assessment.

Adverse events were not mentioned in the text.

In the Francisco-Diaz 2004 study after 12 weeks, the decrease in the MASI was not significantly different for the 2 sides, although there was greater decrease on the Gigawhite-treated side. There was a decrease in MASI by 18.5% (mean) on the Gigawhite side compared to 13.5% (mean) on the placebo side. Although no significant differences were noted on subjective measures, the colorimeter analysis found a significant difference with improvement of 6.9% (mean) in luminance on the Gigawhite side compared to 1.03% (mean) on the placebo side at 12 weeks (the trial authors stated P = 0.013). There were no adverse effects due to Gigawhite or placebo.

DISCUSSION

Summary of main results

The large number of different treatments (23) evaluated supports the view that there is no standard therapy for melasma. Most of the studies were unable to provide robust evidence about the many choices of treatment options. We found weak evidence of the effects of some of the interventions used in the management of melasma including some less conventional therapies. Results have been presented for individual studies as data pooling was not possible. Most of the included trials compared two or more active treatments and consequently the RR reported may be lower than if placebo-controlled trials were conducted. Additionally some studies may fail to reach statistical significance due to this same reason and care has to be exercised in not concluding that none of the treatments work.

The most common intervention among the included trials was topical hydroquinone (seven RCTs). The formulation of hydroquinone used was mostly as 4% hydroquinone cream. All the trials using hydroquinone compared two active interventions and there were no placebo-controlled trials. Hydroquinone (4%) was compared to 20% azelaic acid and to 5% ascorbic acid in separate trials. No significant difference in skin lightening was found by the physicians, although in the trial involving ascorbic acid a significant difference in favour of hydroquinone was noted by those participants who self-assessed. When hydroquinone cream was compared to combination therapy of hydroquinone cream and glycolic acid peels, no significant difference was found. In both arms there was a significant improvement from baseline. Hydroquinone (4%) was not as effective as triple-combination cream (hydroquinone, tretinoin, and steroid) or as effective as when combined with intense pulsed light treatment. Lower strengths of hydroquinone were used in the study by Sivayathorn 1995 (2% hydroquinone) and Vázquez 1983 (3% hydroquinone). Hydroquinone (2%) was not as effective as 20% azelaic acid in treating melasma according

to the physicians in the Sivayathorn 1995 study though no difference was noted on objective measures. More benefit in terms of depigmentation was noted when 3% hydroquinone was combined with a daily sunscreen in the Vázquez 1983 study.

Topical retinoids were used in three RCTs. Tretinoin was significantly more effective than placebo in lightening melasma by objective measures in those with white and black skin, though in the latter trial, no difference was found for one of the subjective outcome measures. When topical isotretinoin, a chemically-related structure to tretinoin was used, no difference was found to placebo.

A variety of combination creams were used. The combination of hydroquinone and sunscreen was significantly more effective than sunscreen alone as was the combination of hydroquinone, glycolic acid, vitamins, and sunscreen compared to sunscreen alone. In the largest study in the review the triple-combination cream (hydroquinone, tretinoin, and steroid) was more effective than any of the agents in a dual-combination cream. In two other studies using combination creams there was no difference between hydroquinone, glycolic acid, and kojic acid cream versus hydroquinone and glycolic acid cream, or between hydroquinone and glycolic acid cream versus combination therapy of hydroquinone and glycolic acid cream and glycolic acid peels.

No significant difference was found between Jessner's peels and salicylic acid peels both with tretinoin priming.

Four RCTs of unconventional therapies were found all of which suggested some efficacy. Rucinol serum was more effective at lightening melasma compared to placebo as was the skin-whitening complex Thiospot, containing ethyl linoleate, thioctic acid, octadecanedioic acid, lactic acid, and ethylhexylmethoxycinnamate. Vitamin C iontophoresis which is used to increase penetration of vitamin C in the skin was compared to distilled water iontophoresis and was significantly more effective on objective measures though the participants in the study could not tell the difference. Similarly in the trial of a botanical extract, Gigawhite 5%, no significant differences to placebo were noted on subjective measures by the physicians though colorimeter analysis showed that the side treated with Gigawhite was significantly lighter.

Adverse events reported in the studies were mostly mild and transient such as skin irritation, pruritus, burning, and stinging.

Overall completeness and applicability of evidence

We found 20 studies altogether of 23 different interventions. The lack of replication of the studies in itself limits the overall applicability of results. The studies we identified were not sufficient to address all the objectives of the review. It is disappointing that no studies provided quality of life data and none examined the long-term effects of the interventions. Additionally a significant number of studies did not include participant assessment which in our view is an important measure of successful treatment.

All the RCTs assessed therapies aimed at depigmenting melasma rather than other approaches such as cosmetic camouflage, laser therapy, or even preventative measures such as the use of a sunscreen. The only study which investigated the benefit of a sunscreen used it in addition to hydroquinone and the results were poorly reported. We did not find any trials of sunscreen versus placebo although it is worth pointing out that in most trials the use of a sunscreen was recommended. It is also worth noting that just over the half (11) of the included studies were industry-sponsored, e.g. by the manufacturing company, whereby only positive studies are likely to be reported.

Quality of the evidence

We included 20 randomised controlled trials involving 2125 participants. In general, there was low methodological quality and a lack of reliable outcome assessments. There was considerable variation in the methods used for scoring improvement in pigmentation and it is difficult to assess the validity of the results. There was also a striking scarcity of placebo-controlled trials. Only seven placebo-controlled trials were conducted. The lightening of the skin noted in the groups receiving placebo varied, but in some were considerable (2% to 60%). In six of the seven trials, there was a co-intervention of a sunscreen and the improvement seen in the placebo group was attributed to this. Most studies poorly documented the details of the sunscreen co-intervention or if it was similar across the groups in each trial. There is a case series of 200 participants that concluded that sunscreen improves melasma (Lakhdar 2007). It is possible that in some studies the benefit seen could have been due to different patterns of use of sunscreen between the groups studied.

Potential biases in the review process

It is possible that all relevant studies have not been included in this review and that some unpublished trials were not found. Every effort has been made to locate such studies though in many studies authors failed to respond to additional requests for information. Considering the wide number of different countries in which the trials were conducted, some may be less well represented in the databases searched and may have escaped our searches.

Some studies containing potentially useful data had to be excluded as those with melasma were lumped together with people with a range of other hyperpigmentary skin conditions. Our pre-specified criteria of excluding studies which were open label where placebo use was possible and if not outcome assessor-blinded also meant that further studies were excluded.

Finally, the variety of scoring systems, descriptions relating to improvement, as well as the inadequate reporting of many of the trials may have led to misunderstanding during our evaluation of effect in the individual studies.

Agreements and disagreements with other studies or reviews

The results of our review are in general agreement with the comments of Rendon 2006 in a review by the Pigmentary Disorders Academy aimed at estimating the clinical efficacy of the different treatments available for melasma. The group consensus was that first-line therapy should consist of effective topical therapies mainly the triple-combination cream or if unavailable, dual combinations (hydroquinone and glycolic acid), or single agents of hydroquinone, tretinoin, or azelaic acid. Second-line therapy recommended was peels alone or in combination with topical therapy. We found evidence of effect of all the above treatments but were unable to conclude which was the best. Rendon 2006 also noted that given the variations of assessing treatments it was difficult to make effective comparisons.

A systematic review by Gupta and colleagues concluded that combining topical agents such as hydroquinone, tretinoin, and a corticosteroid, in addition to regular sunscreen use, is the mainstay of treatment (Gupta 2006). Other lightening agents mentioned include monotherapy of tretinoin, azelaic acid or hydroquinone, chemical peels, laser treatments, and intense pulsed light therapy. Kojic acid, isopropylcatechol, N-acetyl-4-cysteaminylphenol, flavonoid extracts, and oral pycnogenol were also reviewed but the Gupta and colleagues felt more investigation was needed before they could be recommended. We found no RCTs assessing the latter four compounds which fulfilled our inclusion criteria.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from this review is insufficient to provide clear guidelines for practice. We found low-quality RCT evidence for a number of different interventions producing varying degrees of skin lightening. All comparisons were evaluated in only one study each apart from the comparison of tretinoin versus placebo (two studies). Tretinoin was beneficial in both white and dark skin participants with a higher proportion of dermal melasma, though in the latter group, the effect was less marked. Triple-combination cream may be more effective than hydroquinone alone or when compared to any of the individual constituents as a dual combination.

Our review also found limited evidence for other combination creams. Hydroquinone combined with a sunscreen, or hydroquinone combined with glycolic acid, vitamins, and sunscreen are more effective than a sunscreen alone. There is also limited evidence for the combination therapy of hydroquinone cream combined with intense pulsed light being more effective than hydroquinone cream alone.

Rucinol serum and a skin-whitening complex, Thiospot, may also be useful. In four trials comparing vitamin C iontophoresis to distilled water iontophoresis, Gigawhite botanical extract to placebo, 4% hydroquinone to 5% ascorbic acid, and 20% azelaic acid to 2% hydroquinone, evidence of significant differences between the interventions was less clear. This was because by some of the outcome measures no differences were found whereas with other outcome measures significant differences were noted. In the study by Huh 2003 comparing vitamin C iontophoresis to distilled water iontophoresis, statistically significant results were found on the colorimeter analysis, but the participants in the study could not tell the difference between the sides treated. Similarly, in Francisco-Diaz 2004, the physician-assessed MASI for the Gigawhite-treated side was not significantly different to placebo, but colorimeter analysis showed significantly lighter melasma on the side treated with Gigawhite. The clinical benefit of improvement on objective measures only without taking into account improvement noted subjectively by the participants or physicians is questionable.

For the other comparisons (six studies) the results for the interventions studied were not significantly different and maybe equally effective.

Implications for research

Melasma affects many people around the world, yet there is a paucity of well-conducted RCTs. Most of the trials conducted were of poor methodological quality and short duration. Melasma is a chronic and relapsing disorder. We therefore recommend that trials should have an intervention period of at least 6 months and there should be long-term follow up for at least 12 months following the intervention to assess the maintenance of response. Future trials should clearly define participants at baseline. Variation in participant features such as age, duration, or type of melasma are important considerations in assessing the differing response to the interventions and should be provided for each group. Well-designed RCTs investigating the benefit of sunscreen are needed. If sunscreen is recommended as a co-intervention there should be details on the SPF, frequency of application and ideally, the sunscreen should be provided along with the study products. In poorer countries, adequate application of a sunscreen may be costly and if not equal between the groups could lead to confounding.

Participant perception of the severity of disease and degree of improvement can be different to the clinical trial investigators, and participant-assessed outcomes should be incorporated into the study design. There is also a need for trials to include quality of life measures in view of the considerable effect that melasma has on sufferers. The inclusion of the quality of life measures such as the Dermatology Quality of Life Index or the new melasma specific MELASQOL developed for women with melasma would improve relevance of trials and allow comparison between trials using different interventions. Trial investigators should avoid individual made-up scores to assess response and instead use uniform outcome measures such as the subjective measures of MASI

or the melasma severity scale as well as objective measures, e.g. reflectance spectroscopy or corneomelametry. Finally, trials should include a more systematic approach to adverse event reporting including grading of the severity of the adverse event by participants and it should be noted whether the adverse event is related to the study product.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Baliña 1991b

Methods	Parallel group randomised study
Participants	**Included**: women with epidermal or mixed melasma **Excluded**: pregnant or nursing mothers **Setting**: multicentre. Dermatology departments in Brazil, Peru, Uruguay, Venezuela, and Argentina **Age**: 18 to 57 years **Randomised**: 329 **Male/Female**: 0/329 **Evaluable**: 243 **Epidermal/Dermal/Mixed**: 177/0/66 **Skin type**: not stated **Duration of melasma**: median 4 years (mean not provided)
Interventions	A: 4% hydroquinone cream BD for 24 weeks. B: 20% azelaic acid cream BD for 24 weeks. Co-intervention in both groups: 'use of a broad spectrum sunscreen was mandatory'.
Outcomes	1. Physician-subjective evaluation of improvement 2. Physician-assessed reduction in lesion size 3. Physician-assessed reduction in pigmentary intensity 4. Adverse events
Notes	Sp: The study was conducted in association with Schering AG, Berlin Germany. Not stated if they are the manufacturers of the study creams.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described, similar baseline.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	No	Loss to follow up: 86 withdrawals (74 poor compliance, 12 adverse events) (26%), the study did not address ITT (intention-to-treat).
Free of selective reporting?	Unclear	Insufficient information provided.

Baliña 1991b (*Continued*)

Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions clear, no SPF/frequency of sunscreen co-intervention, subjective evaluation by physician and objective measure.
Reliable outcome measure?	Unclear	Authors own scoring system, objective measure of lesion size reduction.

Chan 2008

Methods	Parallel group randomised study
Participants	**Included**: moderate to severe facial melasma > 3 months; epidermal, dermal, and mixed **Excluded**: pregnancy, allergy to products used, atrophic lesions, previous radiation, post-inflammatory pigmentation, other facial inflammatory dermatosis **Setting**: multicentre. Hospital outpatients in Korea, the Philippines, Singapore, and Hong Kong **Age**: 29 to 70 (45) years **Randomised**: 260 **Male/Female**: 12/248 **Evaluable**: 260 **Epidermal/Dermal/Mixed**: 152/10/98 **Skin type**: 2 type II, 71 type III, 168 type IV, 19 type V **Duration of melasma**: not stated
Interventions	A: triple-combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) cream OD for 8 weeks. B: hydroquinone 4% cream BD for 8 weeks. Co-intervention in both groups: 'provided Anthelios SPF-60 sunscreen and use recommended in case of exposure to sunlight'.
Outcomes	1. Physician-subjective evaluation of improvement 2. Participant subjective evaluation of improvement 3. Participant-assessed satisfaction with treatment 4. Adverse events
Notes	Sp: The study was funded by Galderma, France, the manufacturers of the triple-combination cream. The physicians received payments for the study.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Blocked randomisation to form the allocation lists for the 2 arms, similar baseline.
Allocation concealment?	Unclear	No details provided.

Chan 2008 (*Continued*)

Blinding? All outcomes	Yes	Outcome assessor-blinded.
Incomplete outcome data addressed? All outcomes	Yes	Loss to follow up: 13/260 withdrawals (6 subject request, 4 loss to follow up, 2 protocol violation, 1 adverse event) (5%). Missing data was imputed appropriately.
Free of selective reporting?	Yes	-
Compliance to treatment assessed?	Yes	Stated as done but not described.
Aims/interventions and outcomes clear?	Yes	Aims clear, interventions clear, subjective evaluation by participant and physician and participant satisfaction questionnaire.
Reliable outcome measure?	Yes	Subjective measures of MASI and melasma severity score.

Ejaz 2008

Methods	Parallel group randomised study
Participants	**Included**: epidermal melasma assessed by Wood's lamp **Excluded**: those unable to avoid excessive daytime activities, pregnant or lactating women, those with a history of liver disease, those using contraceptive pills or hormonal therapy, those taking systemic medication or topical treatment for melasma **Setting**: dermatology department of a military hospital in Karachi, Pakistan **Age**: 17 to 44 (30.4) years **Randomised**: 60 **Male/Female**: 7/53 **Evaluable**: 57 at 12 weeks and 46 at 24 weeks **Epidermal/Dermal/Mixed**: 60 E/0D/0M **Skin type**: 2 type III, 11 type IV, 47 type V **Duration of melasma**: not stated
Interventions	A: peel with Jessners (14% salicylic acid, 14% lactic acid, 14% resorcinol in alcohol) solution 5 minutes every 2 weeks for 12 weeks. B: peel with 30% salicylic acid for 5 minutes every 2 weeks for 12 weeks. Co-intervention in both groups: 2 weeks of priming with nightly application of 0.05% tretinoin and daytime sunscreen SPF-60, moisturiser was provided whereas sunscreen was purchased.
Outcomes	1. Physician-subjective evaluation of improvement 2. Adverse events

Ejaz 2008 (*Continued*)

Notes	Sp: No sponsorship was declared. There was a 12-week extension period during which sunscreen use in the morning was continued.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random numbers table, similar baseline.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 3 withdrawals at 12 weeks all due to crusting and 14 withdrawals at 24 weeks (23.2%) . The study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Yes	Yes - returned medication assessed.
Aims/interventions and outcomes clear?	Yes	Aims clear, interventions clear, subjective evaluation by physician.
Reliable outcome measure?	Yes	Subjective measure of MASI.

Ennes 2000

Methods	Parallel group randomised study
Participants	**Included**: participants with melasma, participants had to agree to employ a 'safe contraceptive' **Excluded**: use of other topical bleaching agents, alcoholic or abrasive cleaning agents, UV treatment, peeling agents within last 2 weeks, history of alcohol or drug abuse, emotional problems affecting participation, hypersensitivity to study products, burns or irritation in area to be treated, participation in any other study within last month, pregnant or nursing women **Setting**: dermatology department in Sao Paulo, Brazil **Age**: 19 to 55 (no mean given) **Randomised**: 48 **Male/Female**: 4/44 **Evaluable**: 45 **Epidermal/Dermal/Mixed**: not stated **Skin type**: not stated **Duration of melasma**: 5 to 336 months

Ennes 2000 (*Continued*)

Interventions	A: cream containing 4% hydroquinone and 2 sunscreens (SPF-15) BD for 12 weeks. B: cream containing 2 sunscreens (SPF-15) BD for 12 weeks. Co-intervention in both groups: participants were instructed to apply SPF-30 sunscreen every morning.
Outcomes	1. Physician-subjective evaluation of improvement 2. Adverse events
Notes	Sp: No sponsorship was declared.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised in blocks, baseline stated to be similar, though no separate data presented.
Allocation concealment?	Yes	Randomisation done by the supplies department.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 3 withdrawals (2 adverse events and 1 contact dermatitis all in hydroquinone and sunscreen group) (6%). The study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Yes	Yes - returned medication counted.
Aims/interventions and outcomes clear?	Yes	Aims clear, interventions clear, subjective evaluation by physician.
Reliable outcome measure?	Unclear	Subjective measures according to authors own scale.

Espinal-Perez 2004

Methods	Randomised right/left study
Participants	**Included**: bilateral and symmetrical melasma **Excluded**: pregnancy, miscarriage, recent delivery, use of hormones or other topical treatment for 2 months **Setting**: dermatology department in Mexico **Age**: 23 to 43 (36) yrs **Randomised**: 16 **Male/Female**: 0/16

Espinal-Perez 2004 (*Continued*)

	Evaluable: 14 **Epidermal/Dermal/Mixed**: 8/0/8 **Skin type**: 8 type IV, 8 type V **Duration of melasma**: 8 months to 23 (8.2) years
Interventions	A: 4% hydroquinone emulsion OD for 16 weeks. B: 5% L-ascorbic acid cream OD for 16 weeks. Co-intervention in both groups: all participants were instructed to apply a sunscreen (UVA and UVB range) every 3 hours each morning.
Outcomes	1. Participant-subjective evaluation of improvement 2. Objective evaluation of improvement with colorimeter 3. Adverse events
Notes	Sp: None stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Yes	Loss to follow up: 2 withdrawals (1 irritation from hydroquinone, 1 excellent response to both hydroquinone and ascorbic acid) (12.5%), no missing outcome data.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions clear, no SPF of sunscreen co-intervention, subjective evaluation by participant and objective evaluation.
Reliable outcome measure?	Yes	Subjective measure of percentage improvement and objective colorimetric assessment of melanin index difference.

Francisco-Diaz 2004

Methods	Randomised right/left study
Participants	**Included**: epidermal or mixed melasma **Excluded**: if applying depigmenting creams, benzoyl peroxide or chemical peels (wash-out period required), dermal melasma, pregnant and lactating mothers, those on oral contraceptive, tranquilliser or photosensitising drugs, hyperpigmentation due to metabolic or endocrine disorders or facial surgery in last year, psychiatric disease or if in another trial **Setting**: dermatology department in the Philippines **Age**: 18 to 60 **Randomised**: 28 **Male/Female**: 4/22 **Evaluable**: 26 **Epidermal/ Dermal/ Mixed**: 0/0/26 **Skin type**: II to V **Duration of melasma**: mean 3.75 years
Interventions	A: Gigawhite 5% solution BD for 12 weeks. B: placebo solution BD for 12 weeks. Co-intervention in both groups: Sunscreen SPF-60 was applied over the 2 test drugs.
Outcomes	1. Participant-subjective evaluation of improvement 2. Physician-subjective evaluation of improvement 3. Objective evaluation with colorimeter 4. Adverse events
Notes	Sp: None stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation code.
Allocation concealment?	Yes	Third party, e.g. non-investigator from the skin sciences lab investigation (SSLI).
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 2 withdrawals (moved away) (7%), the study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Yes	Aims clear; interventions clear; physician and participant subjective evaluation and objective evaluation.

Reliable outcome measure?	Yes	Subjective measure of MASI and percentage improvement; objective measure of colorimeter and lesion area.

Griffiths 1993

Methods	Parallel group randomised study
Participants	**Included**: caucasian women with clinical diagnosis of facial melasma **Excluded**: use of systemic or topical retinoids for 6 months and 1 month respectively, pregnant or nursing mothers, use of tanning salons or those taking frequent sunny holidays **Setting**: cermatology department in Michigan, USA **Age**: 28 to 59 (42) years **Randomised**: 50 **Male/Female**: 0/50 **Evaluable**: 38 **Epidermal/Dermal/Mixed**: 94%/4%/2% **Skin type**: not stated **Duration of melasma**: 1 to 35 (12) years
Interventions	A: 0.1% tretinoin cream OD for 40 weeks. B: colour-matched placebo cream OD for 40 weeks. Co-intervention in both groups: Use of emollients was encouraged and a sunscreen of at least SPF-15 was worn outdoors.
Outcomes	1. Physician-subjective evaluation of improvement 2. Objective evaluation of improvement using colorimeter and histology 3. Adverse events
Notes	Sp: Sponsored by RW Johnson Pharmaceutical research institute (but it states that they took no part in design, conduct, analysis, or interpretation) and Babcock dermatologic endowment.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation code. No baseline characteristics provided for each group.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	No	Loss to follow up:12 withdrawals (6 non compliance, 3 side-effects, 2 pregnancy, 1 worsening melasma) (24%). The study did not address ITT.

Griffiths 1993 (*Continued*)

Free of selective reporting?	Yes	-
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions clear, no frequency of sunscreen co-intervention, subjective and objective evaluation by physician.
Reliable outcome measure?	Yes	Objective assessment with colorimeter and histology, subjective measure of 'much worse to much improved'.

Guevara 2003

Methods	Parallel group randomised study
Participants	**Included**: healthy Hispanic women, aged 18 to 50 years, Fitzpatrick skin type III to V with moderate to severe bilateral and symmetrical epidermal melasma noticeable at a distance of 3 feet and confirmed on Wood's lamp **Excluded**: dermal melasma, use of tanning parlours or intense sun exposure, pregnancy, use of hydroquinone, treatment with topical of systemic vitamin A in the last 3 months or laser, chemical or microdermabrasion within last 9 months or the use of topical or alpha-hydroxy acid products on the face in the last 1 month **Setting**: dermatology department in Texas, USA **Age**: 28 to 42 (38) years **Randomised**: 39 **Male/Female**: 0/39 **Evaluable**: 35 **Epidermal/Dermal/Mixed**: 39/0/0 **Skin type**: 15 type III, 18 type IV, 2 type V **Duration of melasma**: 3 to 14 (9) years
Interventions	A: combination cream (4% hydroquinone, 10% buffered glycolic acid, vitamin C and E, sunscreen) BD for 12 weeks. B: sunscreen BD for 12 weeks. Co-intervention in both groups: nil.
Outcomes	1. Objective evaluation of improvement with mexameter 2. Physician and participant subjective evaluation of improvement 3. Adverse events evaluated by participant and physician
Notes	Sp: ICN pharmaceuticals the manufacturer of the combination cream. 1 of the authors is a speaker for ICN pharmaceuticals and has received research support.

Risk of bias

Item	**Authors' judgement**	**Description**

Guevara 2003 (*Continued*)

Adequate sequence generation?	Yes	Computer-generated randomisation code. No baseline characteristics provided for each group.
Allocation concealment?	Yes	Third party at manufacturing facility.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 4 withdrawals (no reasons for withdrawal given) (10.2%). The study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions not clear, no SPF of sunscreen in study product or if similar to control, subjective evaluation by participant and physician-objective evaluation.
Reliable outcome measure?	Yes	Subjective measure of MASI and objective assessment with mexameter.

Huh 2003

Methods	Randomised right/left study
Participants	**Included**: healthy women with melasma who had not received any melasma treatment in the last 4 weeks, difference in Luminance value between melasma and normal skin > 2 measured by colorimeter **Excluded**: pregnancy, lactating mothers, pacemaker or wounds on face **Setting**: dermatology department in Seoul, Korea **Age**: mean 37 years **Randomised**: 29 **Male/Female**: 0/29 **Evaluable**: uncertain likely 26 **Epidermal/Dermal/Mixed**: not stated **Skin type**: not stated **Duration of melasma**: not stated
Interventions	A: vitamin C iontophoresis 8 minutes twice a week for 12 weeks. B: distilled water iontophoresis 8 minutes twice a week for 12 weeks. Co-intervention in both groups: All participants were allowed to use a sunscreen which was applied twice a day to both sides of the face.

Huh 2003 (*Continued*)

Outcomes	1. Participant-subjective evaluation of improvement 2. Objective evaluation of improvement with colorimeter 3. Adverse events
Notes	Sp: Not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Table of random sampling numbers.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Unclear what loss to follow up was - possibly 10%. Likely 3 withdrawals (readings on 26/29 participants, likely that 3 were lost to follow up, no reasons or reference to participants lost to follow up was made).
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions clear, no SPF of sunscreen co-intervention, objective evaluation, participant evaluation of improvement.
Reliable outcome measure?	Yes	Objective measure using colorimeter and subjective measure percentage improvement,

Hurley 2002

Methods	Randomised right/left study
Participants	**Included**: Hispanic women, aged 18 to 65 years, Fitzpatrick skin type IV and V with moderate to severe bilateral and symmetrical epidermal and mixed melasma confirmed on Wood's lamp **Excluded**: pregnancy, use of hydroquinone within 3 months of the study, use of chemical peels, microdermabrasion or facial lasers within 9 months, introduction of oral contraceptives during study period, dermal melasma **Setting**: dermatology department in Texas, USA. **Age**: 22 to 6 (40) years **Randomised**: 21 **Male/Female**: 0/21

	Evaluable: 18 **Epidermal/Dermal/Mixed**: 16/0/2 **Skin type**: 9 type IV, 9 type V **Duration of melasma**: 2 to 26 (11) years
Interventions	A: 4% hydroquinone cream BD for 8 weeks. B: 4% hydroquinone cream BD for 8 weeks in addition to 20% glycolic acid peels every 2 weeks for 4 weeks, then 30% glycolic acid peels every 2 weeks for 4 weeks. Co-intervention in both groups: Participants were given a supply of moisturiser to apply BD 45 minutes after applying hydroquinone cream and SPF 25 UV-B sunscreen to apply OD 15 minutes after hydroquinone cream.
Outcomes	1. Objective evaluation of improvement with mexameter 2. Physician-subjective evaluation of improvement 3. Participants subjective evaluation of improvement
Notes	Sp: ICN pharmaceuticals the manufacturer of the peels and hydroquinone cream. Limited data on adverse events.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation code.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Outcome assessor-blinded.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 3 withdrawals (2 participants did not follow the protocol, 1 equipment malfunction)(14%). The study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Yes	Stated to be done but not described.
Aims/interventions and outcomes clear?	Yes	Aims clear, interventions clear, subjective evaluation by participant and physician and objective evaluation.
Reliable outcome measure?	Yes	Subjective measure of MASI and objective assessment with mexameter.

Khemis 2007

Methods	Randomised right/left study
Participants	**Included**: women aged 18 to 50 years, with skin type III to V and moderate to severe melasma **Excluded**: pregnant or nursing mothers, on hormone or corticosteroid therapy, history of endocrine disorders or allergies, depigmenting cream in previous 2 weeks, product containing tretinoin in previous 3 months or product containing hydroquinone in previous 6 months **Setting**: dermatology department in Nice, France **Age**: mean 40 years **Randomised**: 32 **Male/Female**: 0/32 **Evaluable**: 28 **Epidermal/Dermal/Mixed**: 17/0/13 **Skin type**: 11 type III, 10 type IV, 11 type V **Duration of melasma**: not stated
Interventions	A: rucinol serum BD for 12 weeks. B: vehicle serum BD for 12 weeks. Co-intervention in both groups: provided a broad spectrum sunscreen (SPF 60) to use for the duration of the study.
Outcomes	1. Physician-subjective evaluation of improvement 2. Objective evaluation of improvement using colorimeter 3. Participant-subjective evaluation of improvement and effects on quality of life 4. Adverse events
Notes	Sp: Merck Medication Famialiale, Lyon, France the manufacturers of rucinol sponsored the study. Notes: Participant self-assessment and quality of life evaluation was undertaken only in phase 2 (open label extension for further 3 months) and these results excluded.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random list.
Allocation concealment?	Yes	Third party biostatistician.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 4 withdrawals (no reasons stated) (12.5%). The study did not address ITT.
Free of selective reporting?	No	Not all prespecified outcomes reported, e.g. participant and assessor global assessment of improvement, and effects on quality of life.

Khemis 2007 (*Continued*)

Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions clear, no frequency of sunscreen co-intervention, physician- and participant-subjective and objective evaluation.
Reliable outcome measure?	Unclear	Subjective measure authors own scoring system and objective assessment with colorimeter.

Kimbrough-Green 1994

Methods	Parallel group randomised study
Participants	**Included**: black participants with moderate to severe facial melasma **Excluded**: use of topical steroids or other agents within 2 last 2 weeks, hydroquione or oral steroids for last 4 weeks, use of topical tretinoin for last 6 months, keloids, UV light therapy, pregnant or nursing mothers **Setting**: dermatology department in Michigan, USA. **Age**: 22 to 70 (53) years **Randomised**: 30 **Male/Female**: 1/29 **Evaluable**: 28 **Epidermal/Dermal/Mixed**: 13/11/6 **Skin type**: not stated **Duration of melasma**: 1 to 40 (12) years
Interventions	A: 0.1% tretinoin cream OD for 40 weeks. B: colour-matched placebo cream OD for 40 weeks. Co-intervention in both groups: A sunscreen with SPF-15 was supplied to all participants to be used before exposure to sun light. An emollient and soap was also provided.
Outcomes	1. Physician-subjective evaluation of improvement 2. Objective evaluation of improvement using colorimeter and histology 3. Adverse events
Notes	Sp: RW Johnson Pharmaceutical research institute (but states that took no part in design, conduct, analysis or interpretation) and Babcock dermatologic endowment.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random list, similar baseline.
Allocation concealment?	Unclear	Identical coded containers but no further detail.

Kimbrough-Green 1994 (*Continued*)

Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 2 withdrawals (2 non compliance from placebo group) (6.6%). The study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Yes	Aims clear, interventions clear, physician-subjective, and objective evaluation.
Reliable outcome measure?	Yes	Objective assessment with colorimeter and histology, subjective measure of MASI.

Leenutaphong 1999

Methods	Parallel group randomised study
Participants	**Included**: Thai participants with moderate to severe facial melasma, women off a child bearing age using 'an approved method of contraception' **Excluded**: use of systemic retinoids within the last 6 months or topical retinoids within last 1 month, topical steroids or other agents within last 2 weeks, pregnant and nursing women **Setting**: dermatology department in Bangkok, Thailand **Age**: mean 39 years **Randomised**: 30 **Male/Female**: 4/26 **Evaluable**: 23 **Epidermal/Dermal/Mixed**: 2/2/26 **Skin type**: not stated **Duration of melasma**: mean 7 years
Interventions	A: 0.05% isotretinoin gel BD for 40 weeks. B: colour-matched placebo BD for 40 weeks. Co-intervention in both groups: Broad spectrum sunscreen SPF-28 (Butyl methoxydibenzoylmethane 2%, padimate O 8%, oxybenzone 3%, titanium dioxide 2%) was supplied to all participants to be used daily and before exposure to sunlight.
Outcomes	1. Physician-subjective evaluation of improvement 2. Objective evaluation of improvement using colorimeter 3. Adverse events
Notes	Sp: Stiefel laboratories supplied study creams.

Leenutaphong 1999 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation code, similar baseline.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	No	Loss to follow up: 7 withdrawals (6 non compliance, 1 pregnancy) (23%). The study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions clear, physician-subjective and objective evaluation, women of a child bearing age had to use an approved method of contraception and it is unclear what this is.
Reliable outcome measure?	Yes	Subjective measure of MASI and objective outcome with colorimeter.

Lim 1997

Methods	Randomised right/left study
Participants	Included: Asian women skin type IV and V with moderate to severe facial melasma **Excluded**: pregnant or nursing women, hypersensitivity to the formulation, concurrent therapy or illness, topical steroids or bleaching agents in last 2 weeks or systemic steroids in last 4 weeks **Setting**: dermatology hospital in Singapore **Age**: 36 to 58 (43) years **Randomised**: 10 **Male/Female**: 0/10 **Evaluable**: 10 **Epidermal/Dermal/Mixed**: 10/0/0 **Skin type**: type IV and V **Duration of melasma**: at least 2 years (no mean provided)
Interventions	A: pre-treatment with 8% AHA cream BD for 2 weeks then 2% hydroquinone, 10% glycolic acid gel BD, and 20% to 70% glycolic acid peel every 3 weeks for 24 weeks. B: pre-treatment with 8% AHA cream BD for 2 weeks then 2% hydroquinone, 10% glycolic acid gel BD for 24 weeks.

Lim 1997 (*Continued*)

	Co-intervention in both groups: Participants had to use a sunscreen SPF-15.
Outcomes	1. Physician-subjective evaluation of improvement 2. Participants subjective evaluation of improvement 3. Adverse events
Notes	Sp: Neostrata company Inc manufacturers of the study products sponsored the trial.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated randomisation code.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Blinded to assessor.
Incomplete outcome data addressed? All outcomes	Yes	Loss to follow up 0%. No missing outcome data.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions clear, no frequency of sunscreen co-intervention, all subjective measures of improvement by physician and participant.
Reliable outcome measure?	Unclear	Munsell colour chart to assess participants at baseline but not at follow-up, subjective measure of % improvement.

Lim 1999

Methods	Randomised right/left study
Participants	**Included**: Chinese women with epidermal melasma confirmed on Wood's light **Excluded**: dermal melasma, mixed melasma, Naevus of Ota, oral contraceptive pill, hormone replacement therapy, regular outdoor activity or treatment for melasma in prior 4 weeks to study **Setting**: dermatology hospital in Singapore **Age**: 32 to 58 (42.5) years **Randomised**: 43 **Male/Female**: 0/43 **Evaluable**: 40 **Epidermal/Dermal/Mixed**: 43/0/0 **Skin type**: not stated

Lim 1999 (*Continued*)

	Duration of melasma: 2 to 10 years (no mean provided)
Interventions	A: 2% hydroquinone, 10% glycolic acid, 2% kojic acid gel BD for 12 weeks. B: 2% hydroquinone, 10% glycolic acid gel BD for 12 weeks. Co-intervention in both groups: Participants had to use a physical sunscreen containing titanium dioxide SPF-15 over the gels daily.
Outcomes	1. Physician-subjective evaluation of improvement 2. Participants subjective evaluation of improvement 3. Adverse events
Notes	Sp: None stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 3 withdrawals (redness and peeling both sides) (7%). The study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Yes	Aims clear, interventions clear, subjective measures of improvement by participant and physician.
Reliable outcome measure?	Unclear	Subjective measure of % improvement.

Sivayathorn 1995

Methods	Parallel group randomised study
Participants	**Included**: participants with epidermal or mixed melasma **Excluded**: pregnant or nursing women, no oral contraceptives six weeks prior to study, dermal melasma **Setting**: Multicentre; 5 dermatology units in Thailand and Philippines **Age**: 20 to 59 (no mean given) **Randomised**: 340 **Male/Female**: 17/323

Sivayathorn 1995 (*Continued*)

	Evaluable: 300 **Epidermal/Dermal/Mixed**: 225/0/111 **Skin type**: 1 type I, 7 type II, 108 type III, 169 type IV, 49 type V **Duration of melasma**: median 4.5 and 4 years
Interventions	A: 2% hydroquinone cream BD for 24 weeks. B: 20% azelaic acid cream BD for 24 weeks. Co-intervention in both groups: Broad spectrum sunscreen UVB SPF-10 and UVA SPF-7 was used.
Outcomes	1. Physician-subjective evaluation of improvement 2. Physician-assessed reduction in lesion size 3. Physician-assessed reduction in pigmentary intensity 4. Adverse events
Notes	Sp: None stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described, similar baseline.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 40 withdrawals (25 lost to follow up, 8 non-compliance, 7 adverse events) (11.8%). The study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions clear, no frequency of sunscreen co-intervention, subjective and objective evaluation by physician.
Reliable outcome measure?	Unclear	Subjective measure authors own scale and percentage improvement, objective measure of lesion size reduction.

Taylor 2003

Methods	Parallel group randomised study (4 groups)
Participants	**Included**: stable hyperpigmentation on the face for 3 months duration, macular lesions that were neither depressed nor atrophic, melasma severity score of at least 2 **Excluded**: atrophic or depressed lesions, severity score of less than 2 **Setting**: Multicentre; 13 dermatology departments in USA **Age**: 21 to 75 yrs **Randomised**: 641 **Male/Female**: predominantly women, no other data given **Evaluable**: 641 **Epidermal/Dermal/Mixed**: not stated **Skin type**: predominantly white women skin type I through IV **Duration of melasma**: at least 3 months no other data given
Interventions	A: triple-combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) cream OD for 8 weeks. B: dual-combination (hydroquinone 4%, tretinoin 0.05%) cream OD for 8 weeks. C: dual-combination (fluocinolone acetonide 0.01%, tretinoin 0.05%) cream OD for 8 weeks. D: dual-combination (fluocinolone acetonide 0.01%, hydroquinone 4%) cream OD for 8 weeks. Co-intervention in both groups: Nil else.
Outcomes	1. Physician-subjective evaluation of improvement 2. Adverse events
Notes	Sp: Educational grant from Galderma laboratories and 3 authors had either received grants or were speakers for Galderma.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described, baseline stated to be similar, though no separate data presented.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Outcome assessor-blinded
Incomplete outcome data addressed? All outcomes	Yes	Loss to follow up 0%. No missing outcome data.
Free of selective reporting?	No	Global improvement from baseline using an 8 point scale was stated to be done but was not reported.
Compliance to treatment assessed?	Unclear	Not mentioned.

Taylor 2003 (*Continued*)

Aims/interventions and outcomes clear?	Yes	Aims clear, interventions clear, all subjective measures of improvement by physician.
Reliable outcome measure?	Yes	Subjective measures using melasma severity scale.

Thirion 2006

Methods	Parallel group randomised study
Participants	**Included**: women with melasma on the forehead for at least 6 months (unclear if this is a subset of participants with centrofacial melasma and if participants were excluded if they had melasma elsewhere) **Excluded**: not stated **Setting**: dermatology department Belgium **Age**: 27 to 38 years **Randomised**: 27 **Male/Female**: 0/27 **Evaluable**: 27 **Epidermal/Dermal/Mixed**: not stated **Skin type**: 27 type III **Duration of melasma**: at least 6 months
Interventions	A: whitening formulation Thiospot intensive cream (ethyl linoleate, thioctic acid, octadecanedioic acid, lactic acid, and ethylhexylmethoxycinnamate) BD for 3 months. B: non-whitening skin care Eucerin cream BD for 3 months. Co-intervention in both groups: Nil else.
Outcomes	1. Physician-subjective evaluation of improvement 2. Objective evaluation of improvement using mexameter and corneomelametry and video recorded ultraviolet light reflection
Notes	Sp: None stated. Also states all volunteers were under oral contraception and it is unclear if this was introduced during study.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described, no baseline characteristics provided for each group.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	Yes	Double-blind.

Thirion 2006 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Loss to follow up 0%. No missing outcome data.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions clear, unclear if co-intervention of oral contraceptive was introduced, physician-subjective and objective evaluation of improvement.
Reliable outcome measure?	Unclear	Subjective measures authors own scale, objective measure using mexameter, video recorded ultraviolet light reflection and corneomelametry.

Vázquez 1983

Methods	Parallel group randomised study
Participants	**Included**: participants with melasma **Excluded**: pregnant or taking oral contraceptives **Setting**: dermatology department Puerto Rico **Age**: not stated **Randomised**: 59 **Male/Female**: 0/59 **Evaluable**: 53 **Epidermal/Dermal/Mixed**: not stated **Skin type**: not stated **Duration of melasma**: 2 to 25 years
Interventions	A: 3% hydroquinone solution BD and placebo cream OD for 12 weeks. B: 3% hydroquinone solution BD and broad spectrum sunscreen OD for 12 weeks. Co-intervention in both groups: Nil.
Outcomes	1. Physician-subjective evaluation of improvement 2. Participant-subjective evaluation of improvement 3. Adverse events
Notes	Sp: Neutrogena Corporation supplied the hydroquinone solution and Herbert Laboratories supplied sunscreen.

Risk of bias

Item	**Authors' judgement**	**Description**

Vázquez 1983 (*Continued*)

Adequate sequence generation?	Yes	Random number list, no baseline characteristics provided for each group.
Allocation concealment?	Unclear	Identical coded containers but no further detail.
Blinding? All outcomes	Yes	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 6 withdrawals (all due to poor compliance, unclear which group) (10%). The study did not address ITT.
Free of selective reporting?	No	Participants were stated to be evaluated at 4 and 8 weeks and this data was not available.
Compliance to treatment assessed?	Yes	-
Aims/interventions and outcomes clear?	Unclear	Aims clear, interventions not adequately described, sunscreen SPF not stated, physician- and participant-subjective evaluation.
Reliable outcome measure?	Unclear	Subjective measures authors own scale.

Wang 2004

Methods	Parallel group randomised study
Participants	**Included**: women with melasma unresponsive to hydroquinone cream for at least 3 months **Excluded**: pregnancy, lactating mothers, oral pills, hormone replacement therapy, major outdoor activities **Setting**: dermatology department Taipei, Taiwan **Age**: mean 46 years **Randomised**: 33 **Male/Female**: 0/33 **Evaluable**: 31 **Epidermal/Dermal/Mixed**: 0/0/33 **Skin type**: 6 type III, 27 type IV **Duration of melasma**: mean 10.4 yrs
Interventions	A: 4% hydroquinone cream for 16 weeks. B: 4% hydroquinone cream and intense pulsed light - 4 sessions at 4 weekly intervals for 16 weeks. Co-intervention in both groups: Broad spectrum sunscreens were used throughout the study.
Outcomes	1. Objective evaluation of improvement with mexameter 2. Participant-subjective evaluation of improvement

Wang 2004 (*Continued*)

Notes	Sp: None stated. Also measured outcome for group B) at 36 weeks but not measured for group A) and this was excluded.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described, similar baseline.
Allocation concealment?	Unclear	No details provided.
Blinding? All outcomes	No	Unblinded.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up: 2 withdrawals (2 poor compliance both hydroquinone only group) (6.1%). The study did not address ITT.
Free of selective reporting?	Unclear	Insufficient information provided.
Compliance to treatment assessed?	Unclear	Not mentioned.
Aims/interventions and outcomes clear?	Unclear	Aims clear, methodology of using hydroquinone in the control and treatment arm where inclusion criteria was refractory melasma previously unresponsive to hydroquinone for at least 3 months was not appropriate for the stated aims. Interventions not clear, no frequency of hydroquinone or if similar between groups, no SPF/frequency of sunscreen co-intervention, subjective evaluation by participants and objective evaluation.
Reliable outcome measure?	Yes	Participant satisfaction, objective assessment using mexameter.

n/s = not stated
OD = once daily
BD = twice daily
SPF = sun protection factor
Sp = sponsorship
ITT = intention-to-treat analyses
Y = yes
N = No

Characteristics of excluded studies *[ordered by study ID]*

Abarca 1987	Not an RCT.
Astaneh 2005	Crucial information lacking, there is also a disparity of whether 32 or 64 participants took part in this study.
Baliña 1991a	The same participants were included in the multicentre trial Baliña 1991b.
Bari 2002	Placebo use was possible but not used and the study was not blinded.
Bissett 2007	Study participants had pigmentary disorders other than melasma.
Cestari 2007a	Not an RCT.
Cestari 2007b	Placebo use was possible but not used and the study was not blinded.
Dogra 2002	Placebo use was possible but not used and the study was not blinded.
Erbil 2007	Important information is lacking, not clear what intervention was used in the control group and whether this intervention was consistent across the group.
Ertam 2008	Quasi-randomisation.
Garg 2008	Quasi-randomisation.
Graupe 1996	Placebo use was possible but not used and the study was not blinded.
Grimes 2007	Not an RCT, participants were not randomised to the 2 arms of the study.
Kakita 1998	Study participants had pigmentary disorders other than melasma.
Lee 2002	Quasi-randomisation.
Li 2007	Placebo use was possible but not used and the study was not blinded.
Lowe 1998	Study participants had pigmentary disorders other than melasma.
Mateus 2007	Lacking detail on interventions, participant selection, randomisation, and method of assessment.
Nanda 2004	Cases were matched according to age, gender, skin type, and nature and severity of melasma, equal numbers achieved in each arm unlikely to be an RCT.
Njoo 1997	Not an RCT.
Nouri 1999	Pilot study on 8 participants to gain information of safety, only treated test patches, outcomes not of relevance to the review.
Pathak 1986	Not an RCT.

(*Continued*)

Piquero MartÍn 1988	Same participants appear to be included in the multitrial Baliña 1991b; the participants, interventions, outcomes are all identical.
Shi 1998	Placebo use was possible but not used and the study was not blinded.
Shi 2007	Placebo use was possible but not used and the study was not blinded.
Su 2004	Placebo use was possible but not used and the study was not blinded.
Sánchez 1982	Crucial information lacking; it is not clear how many participants were in each group or from which groups dropouts occurred from.
Valkova 2005	Placebo use was possible but not used and the study was not blinded.
Verallo-Rowell 1989	The same participants were included in the multicentre trial Sivayathorn 1995.
Yan 2000	Placebo use was possible but not used and the study was not blinded, abstract with limited information.

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Azzam 2009

Methods	Randomised controlled trial
Participants	**Included**: patients with melasma **Setting**: n/s **Age**: n/s **Randomised**: 45 **Male/Female**: n/s **Evaluable**: n/s **Epidermal/Dermal/Mixed**: n/s **Skin type**: n/s **Duration of melasma**: n/s
Interventions	A: Jessner's solution peel. B: 20% trichloracetic acid peel. C: 2% hydroquinone and kojic acid.
Outcomes	1. Clinical evaluation with MASI score at baseline and 16 weeks 2. Photographic evaluation at baseline and 16 weeks
Notes	-

Baliña 1992

Methods	Multicentre, double-blind, controlled study
Participants	**Included**: women **Setting**: multicentre, dermatology departments India **Age**: n/s **Randomised**: 243 **Male/Female**: 0/243 **Evaluable**: n/s **Epidermal/Dermal/Mixed**: n/s **Skin type**: n/s **Duration of melasma**: n/s
Interventions	A: 20% azelaic acid given for 24 weeks. B: 4% hydroquinone cream. Co-intervention in both groups: Broad spectrum sunscreen.
Outcomes	1. Planimetric measurement of melasma size 2. Subjective assessment of melasma intensity 3. Subjective assessment of overall response rate
Notes	Sp: n/s ITT: n/s Withdrawal: n/s

Chen 2007

Methods	Randomised controlled trial
Participants	**Included**: n/s **Age**: n/s **Randomised**: 96 **Male/Female**: n/s **Evaluable**: 96 **Epidermal/Dermal/Mixed**: n/s **Skin type**: n/s **Duration of melasma**: n/s
Interventions	A: treated with acupuncture and intensive pulsed light irradiation B: treated with acupuncture only
Outcomes	1. n/s
Notes	-

Haddad 2003

Methods	2-arm randomised right/left study
Participants	**Included**: age 38 to 56 years, Fitzpatrick skin type III to V, no previous treatment for 6 months **Excluded**: active dermatologic diseases, sensitivity to clarifying agents or sunscreens, recent treatment, pregnant or breast feeding women, history of endocrinopathies, oral retinoid treatment in last 12 months **Setting**: dermatology department in Sao Paulo, Brazil **Age**: 38 to 56 years **Randomised**: 30 **Male/Female**: n/s **Evaluable**: 25 **Epidermal/Dermal/Mixed**: n/s **Skin type**: III to V **Duration of melasma**: n/s
Interventions	A: 4% hydroquinone, or B: placebo solution to right or left side of face OD for 12 weeks. C: skin-whitening complex extract of uva-ursi, *Aspergillus*, grapefruit extract, rice extract, or d: placebo to right or left side of face OD for 12 weeks. Co-intervention in both groups: Standardised sunscreen SPF-25 was used during the day.
Outcomes	1. Physician-subjective evaluation of improvement 2. Participant-satisfaction 3. Adverse events
Notes	Sp: None stated. ITT: None stated. Withdrawal: 5 withdrawals (no reasons provided). Notes: There is a discrepancy between the table and text regarding the number of participants completing treatment in each group.

Handog 2009

Methods	Randomised, double-blind, placebo-controlled trial
Participants	**Included**: adult, women, bilateral epidermal melasma **Setting**: single institution **Age**: n/s **Randomised**: 60 **Male/Female**: 0/60 **Evaluable**: 56 **Epidermal/Dermal/Mixed**: all epidermal **Skin type**: types III to V **Duration of melasma**: n/s
Interventions	A: oral procyanidin & Vitamins A, C, & E taken twice daily with meals. B: placebo taken twice daily with meals.
Outcomes	1. Mexameter 2. MASI score 3. Global evaluation by patient

	4. Global evaluation by investigator
Notes	-

Hantash 2009

Methods	Split face, randomised, double-blind, placebo-controlled pilot study
Participants	**Included**: moderate, recalcitrant melasma **Setting**: n/s **Age**: n/s **Randomised**: 5 **Male/Female**: 0/5 **Evaluable**: 5 **Epidermal/Dermal/Mixed**: n/s **Skin type**: 5 type IV **Duration of melasma**: n/s
Interventions	A: twice-daily application of propriety oligopeptide to 1 half of the face B: n/s
Outcomes	1. Physician-subjective evaluation using a 10-point grading scale 2. Patient satisfaction using a 5-point grading scale
Notes	-

Huh 2010

Methods	Randomised, double-blind, vehicle-controlled, split face comparison study
Participants	**Included**: n/s **Setting**: n/s **Age**: n/s **Randomised**: 23 **Male/Female**: n/s **Evaluable**: 23 **Epidermal/Dermal/Mixed**: n/s **Skin type**: n/s **Duration of melasma**: n/s
Interventions	A: liposome-encapsulated 4-n-butylresorcinol 0.1% cream was applied to 1 half of the face twice daily for 8 weeks. B: placebo vehicle was applied twice daily to the other half of the face for 8 weeks.
Outcomes	1. Mexameter at baseline, 4 and 8 weeks 2. Clinical evaluation at baseline, 4 and 8 weeks 3. Photographic evaluation at baseline, 4 and 8 weeks 4. Patient satisfaction at baseline, 4 and 8 weeks 5. Side-effects at baseline, 4 and 8 weeks

Huh 2010 (*Continued*)

Notes	-

Ilknur 2010

Methods	Single-blind, randomised right/left comparison study
Participants	**Included**: bilateral epidermal melasma **Excluded**: dermal and mixed melasma, pregnancy, breast feeding, recent delivery, oral contraceptive and hormone replacement therapies at the time of the study or in the previous 6 months, a history of recurrent herpes simplex on the face, keloidal tendency, topical treatment within the previous 3 months, use of tanning parlours or intense sun exposure, and a history of chemical peeling, microdermabrasion, or laser treatment **Setting**: n/s **Age**:18 years or older **Randomised**: 31 **Male/Female**: not stated **Evaluable**: 24 **Skin type**: 4 type II, 19 type III, 1 type IV **Duration of melasma**: 0 to 20 years
Interventions	A: 12 serial glycolic acid peels at 12 week intervals for a total of 6 months to one half of the face. B: 12 serial amino fruit acid peels at 12 week intervals for a total of 6 months to the other half of the face.
Outcomes	1. Clinical evaluation based on MASI scores at 3 and 6 months
Notes	-

Poli 1997

Methods	Randomised right/left study
Participants	**Included**: women, Fitzpatrick skin type I to V, bilateral symmetrical facial melasma > 6 months **Excluded**: pregnant, nursing mothers, treatment with photosensitisers, intense exposure to light or artificial UV, treatment of heliodermatitis or depigmenting agents for 1 month and contraception or hormone replacement therapy for 3 months **Setting**: multicentre, dermatology departments France, Tunisia, and Morroco **Age**: n/s **Randomised**: 38 **Male/Female**: 0/38 **Evaluable**: 35 **Epidermal/Dermal/Mixed**: n/s **Skin type**: 13 type IV, 13 type V **Duration of melasma**: 0 to 10 years
Interventions	A: Trio-D (2% HQ, 12% AHA and a 1% polypeptide ascorbate complex and titanium oxyd) BD for 8 weeks. B: placebo containing titanium oxyd BD for 8 weeks. Co-intervention in both groups: 'Moisturising cream Ictyane'.

Outcomes	1. Physician-objective evaluation 2. Physician-subjective evaluation 3. Participant self-assessment of improvement 4. Adverse events
Notes	Sp: None stated. ITT: None stated. Withdrawal: 3 withdrawals The percentage improvement concluded did not correspond to the values presented in the table and clarification has been requested.

Verallo-Rowell 2002

Methods	Randomised right/left study
Participants	**Included**: age 20 to 50 years with epidermal or dermo-epidermal melasma **Excluded**: dermal melasma, pregnant and lactating mothers,use of oral contraceptive pills or depigmenting creams within 2 weeks of the study, endocrine and metabolic illness causing hyperpigmentation, sensitivity to study products **Setting**: dermatology department in Makati, Philippines **Randomised**: 60 **Male/Female**: 3/57 **Evaluable**: 50 **Epidermal/Dermal/Mixed**: 51/0/9 **Skin type**: 51 type IV, 9 type V **Duration of melasma**: 2 to 5 years
Interventions	A: Melfade- a bio-ingredient, standardised extract of *Bearberry Ursi* and glycolic acid 10% BD for 6 months B: hydroquinone 4% and glycolic acid 10% BD for 6 months. Co-intervention in both groups: All participants received a sunscreen SPF-45 to be applied twice daily.
Outcomes	1. Physician-objective evaluation 2. Physician-subjective evaluation 3. Participant self-assessment of improvement 4. Adverse events
Notes	Sp: None stated. ITT: None stated. Withdrawal: 10 withdrawals (3 irritation both sides, 3 poor compliance, 3 moved away, 1 pregnant). Outcome values did not appear different for the 2 sides though concluded as significantly different, there were more outcomes than participants in the table presented and authors asked for clarification.

Wattanakrai 2010

Methods	Randomised right/left study
Participants	**Included**: n/s **Setting**: n/s

	Age: n/s **Randomised**: 22 **Male/Female**: n/s **Evaluable**: 35 **Epidermal/Dermal/Mixed**: dermal & mixed **Skin type**: n/s **Duration of melasma**: n/s
Interventions	A: QS-Nd: YAG laser to 1 half of the face, 5 sessions at 1 week intervals. B: 2% hydroquinone to the other side of the face.
Outcomes	1. Colorimeter 2. Modified MASI
Notes	-

n/s = not stated
OD = once daily
BD = twice daily
Sp = sponsorship
ITT = intention-to-treat analyses
Y = yes
N = no

Characteristics of ongoing studies *[ordered by study ID]*

IRCT138809212840N1

Trial name or title	Randomized comparative clinical trial of hydroquinone 2% and Melfade for the treatment of melasma
Methods	Randomised, single-blind, parallel
Participants	1. Clinical diagnosis of melasma 2. women
Interventions	A: Melfade cream once daily to the affected area B: 2% Hydroquinone cream once daily to the affected area
Outcomes	1. 'Faint coloured of scar' at 12 weeks
Starting date	March 2008
Contact information	Dr. Roksana Yaghmaee Dermatology clinic Besat Hospital Keshavarz St Sanandaj

IRCT138809212840N1 (*Continued*)

	Iran ryaghmaee@muk.ac.ir
Notes	Recruitment complete

ISRCTN84133969

Trial name or title	Fractional photothermolysis versus triple therapy for the treatment of melasma: A randomised controlled trial
Methods	Randomised, controlled, parallel group, observer blinded trial
Participants	1. Adult participants with melasma 2. Skin phototype II - V 3. Subjects attending the outpatient department of the Netherlands Institute for Pigment Disorders 4. Aged at least 18 years 5. Subjects willing and able to give written informed consent
Interventions	A: Triple-therapy (bleaching cream [hydroquinone 5%, tretinoin 0.05%, and triamcinolone acetonide 0.1% in cremor lanette II]) B: Fractional photothermolysis using the Fraxel laser
Outcomes	1. Observer blinded MASI score, measured before treatment and at 3, 12, and 24 weeks of follow up 2. Objective colour measurement by reflectance spectroscopy, measured before treatment and during 3, 12, and 24 weeks of follow up 3. Visual assessment of side-effects and quality of life measurements (SKINDEX-16) 4. Fraxel laser group: after laser treatment and during follow up (3, 12, 24 weeks) 5. Triple group: during follow up (3, 12, 24 weeks) 6. Registration of side-effects noticed by the participant 7. Fraxel group: after laser treatment and during follow up 8. Triple group: after 3 weeks of treatment by telephone
Starting date	September 2007
Contact information	A Wolkerstorfer Academic Medical Centre (AMC) Netherlands a.wolkerstorfer@amc.uva.nl
Notes	Study completed May 2008

NCT00467233

Trial name or title	Study of acid peel and laser for the treatment of melasma
Methods	Randomised, single-blind (outcomes assessor), active control, single group assignment, safety/efficacy study

NCT00467233 (*Continued*)

Participants	1. Diagnosis of melasma lesion measuring at least 4 square centimetres 2. Age 18 to 75 years 3. Good health 4. Willingness and ability to understand and provide informed consent for participation in the study 5. Ability to communicate with the investigator 6. Willing to forgo other treatment options for melasma during the course of the study
Interventions	A: Experimental laser treatment B: Experimental acid peel
Outcomes	1. MASI at 20 weeks 2. Safety at 20 weeks
Starting date	May 2007
Contact information	Murad Alam, MD Northwestern University, USA j-sorrell@northwestern.edu
Notes	Study ongoing

NCT00500162

Trial name or title	Comparison of two Tri-Luma® maintenance regimens in the treatment of melasma (CLARA)
Methods	Treatment, randomised, single-blind (investigator), active control, parallel assignment, safety/efficacy study
Participants	1. Subjects with a clinical diagnosis of moderate to severe melasma 2. Subjects with a Fitzpatrick skin type between I and V
Interventions	Comparison of 2 Tri-Luma® maintenance regimens in the treatment of melasma
Outcomes	1. Time to relapse during the maintenance phase 2. Subject's Quality of Life questionnaire (MelasQol) at the end of each treatment phase/early termination
Starting date	November 2006
Contact information	Karime Hassun UNIFESP - Universidade Federal de São Paulo Brazil
Notes	Completed October 2008, sponsored by Galderma

NCT00509977

Trial name or title	Study of light treatment and laser treatment for melasma
Methods	Treatment, randomised, single-blind (outcomes assessor), active control, single group assignment, safety/efficacy study
Participants	1. Diagnosis of melasma lesion measuring at least 4 square centimetres. 2. Age 18 to 75 years 3. Good health 4. Willingness and ability to understand and provide informed consent for participation in the study 5. Ability to communicate with the investigator 6. Must be willing to forgo other treatment options for melasma during the course of the study
Interventions	A: Light treatment applied to half of the face at each study visit B: Laser treatment applied to half of the face at each study visit
Outcomes	1. MASI at 20 weeks 2. Safety at 20 weeks
Starting date	April 2007
Contact information	Jennifer Sorrell Northwestern University Dermatology Department Chicago, Illinois, USA j-sorrell@northwestern.edu
Notes	Study ongoing

NCT00616239

Trial name or title	The efficacy of salicylic acid peels combined with 4% hydroquinone cream versus 4% hydroquinone cream alone in the treatment of Hispanic women with moderate to severe melasma
Methods	Treatment, randomised, single-blind (investigator), active control, single group assignment, safety/efficacy study
Participants	Hispanic women ages 18 to 65 years of age with moderate to severe melasma
Interventions	A: Subjects randomised to have the right side of the face peeled with salicylic acid every 2 weeks for a total of 4 peels (first 2 at 20% and last 2 at 30%). Subjects will apply 4% hydroquinone cream to affected areas on entire face for 14 weeks B: subjects randomised to have the left side of the face peeled with salicylic acid every 2 weeks for a total of 4 peels (first 2 at 20% and last 2 at 30%). Subjects will apply 4% hydroquinone cream to affected areas on entire face for 14 weeks
Outcomes	1. Improvement of melasma based on mexameter readings at 14 weeks 2. Improvement of melasma based on MASI scores, melasma severity assessment, and physician and participant global improvement compared with the opposite side

NCT00616239 (*Continued*)

Starting date	January 2008
Contact information	Amit Pandya UT Southwestern Medical Center Department of Dermatology Dallas, USA
Notes	Completed June 2008

NCT00717652

Trial name or title	Efficiency and safety of association arbutin, triamcinolone and tretinoin in the treatment of facial melasma, taking as reference the product Triluma ® (hydroquinone, fluoncinolone and tretinoin)
Methods	Treatment, randomised, double-blind (subject, investigator), active control, parallel assignment, safety/efficacy study
Participants	1. Women aged more than 18 years 2. Participants with mild and moderate melasma (epidermal) of the face 3. Participants who have not had any treatment for melasma for 3 months preceding the study 4. Participants with good mental and physical health
Interventions	A: Arbutin, tretinoin, triamcinolone B: Triluma
Outcomes	Evaluating the clinical activity of the association (tretinoin, arbutin, and triamcinolone) in the treatment of epidermal melasma
Starting date	July 2008
Contact information	Alexandre Frederico Lal Clinica Pesquisa E Desenvolvimento Ltda Valinhos, S, Brazil dr.alexandre@alclinica.com.br
Notes	Study ongoing

NCT00848458

Trial name or title	Azelaic acid iontophoresis versus topical azelaic acid cream in the treatment of melasma - an open randomised, controlled, prospective, single-blinded clinical trial
Methods	Treatment, randomised, single-blind (investigator), active control, parallel assignment, safety/ efficacy study
Participants	1. Women 2. MASI - Score over 6 3. Age: over 18 years 4. Skin Type: III, IV, V

NCT00848458 (*Continued*)

Interventions	A: Iontophoresis with 15% azelaic acid gel twice weekly B: Topical treatment with 20% azelaic acid cream twice daily
Outcomes	1. Change in colorimetric measurement of skin colour and MASI score after 12 weeks of treatment 2. Physician global assessment 3. Participant global assessment 4. Overall response assessment
Starting date	January 2009
Contact information	Oliver Schanab Medical University Vienna Depatment of Dermatology Vienna, Austria oliver.schanab@meduniwien.ac.at
Notes	Ongoing study

NCT00863278

Trial name or title	Treatment of melasma with stabilized Kligman preparation associated or not with pulsed dye laser; a comparative prospective study
Methods	Treatment, randomised, single-blind (outcome assessor), active control, parallel assignment, safety/ efficacy study
Participants	1. Pregnant women or breastfeeding 2. Skin type V or VI
Interventions	A: Participants will be treated by stabilised Kligman's trio with daily application during 4 months, after 1 month, the left side of the face will be treated with pulsed dye laser weekly for 3 weeks, the hemiface treated without laser and the hemiface treated with the laser will be compared B: Participants will be treated by stabilised Kligman's trio with daily application during 4 months, after 1 month, the side of the right face will be treated by pulsed dye laser every 3 weeks for 9 weeks, the cheek treated without laser and the cheek treated with the laser will be compared
Outcomes	1. MASI 2. Safety
Starting date	March 2009
Contact information	Thierry Passeron CHU de Nice - 4 avenue Reine Victoria - Hôpital de Cimiez Recruiting Nice Alpes-Maritimes France passeron.t@chu-nice.fr

NCT00863278 (*Continued*)

Notes	Ongoing study

NCT01001624

Trial name or title	Efficacy of Melanil in the Treatment of Melasma
Methods	Randomised, controlled, double blind, open label, parallel assignment
Participants	1. 18 to 75 years 2. Men and women 3. Clinical diagnosis of melasma 4. Skin types I to IV 5. Signed informed consent 6. Agrees to use physical barriers for UV protection
Interventions	A: Melanil facial cream (Topical use), twice a day, for 8 weeks B: Hydroquinone 2% cream (Topical use), twice a day, for 8 weeks
Outcomes	1. MASI score at baseline, 4, 8, 12, and 52 weeks 2. Adverse events at baseline, 4, 8, 12, and 52 weeks 3. Photographs at baseline, 4, 8, 12, and 52 weeks
Starting date	October 2009
Contact information	Alfredo Abreu Daniel Clinical-Surgical-Docent Hospital Havana City Havana Cuba 10400
Notes	Not recruiting patients, estimated completion October 2010

NCT01092884

Trial name or title	Polypodium leucotomos extract as an adjunct to sunscreen for the treatment of melasma
Methods	Randomised, placebo-controlled
Participants	1. Hispanic women with moderate to severe facial melasma 2. Over 18 years
Interventions	A: Oral supplementation with Polypodium leucotomos extract 240 mg 3 times per day and topical sunscreen B: Placebo capsule taken 3 times per day and topical sunscreen
Outcomes	1. Mexameter scores at 12 weeks 2. MASI score at 12 weeks 3. Melasma-Related Quality of Life questionnaire at 12 weeks

NCT01092884 (*Continued*)

Starting date	March 2010
Contact information	Texas UT Southwestern Medical Center Dallas, Texas United States 75390
Notes	Enrolling participants by invitation only

MASI = Melasma area and severity index

DATA AND ANALYSES

Comparison 1. Triple-combination cream (TC) versus hydroquinone (HQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant assessed improvement: number with score 0 or 1 (clear or minor hyperpigmentation)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of participants achieving score 0 or 1 (none or mild melasma)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Adverse events (AE)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. 20% Azelaic acid (AzA) vs 4% hydroquinone (HQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with good or excellent response	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Adverse events (AE)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. 20% Azelaic acid (AzA) vs 2% hydroquinone (HQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with >50% improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Adverse events (AE)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Tretinoin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants rated as 'improved' or 'much improved'	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Melasma severity assessed by Woods lamp at 40 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Increase in Luminance (L value)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Adverse events (AE)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Isotretinoin gel versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction in MASI from baseline	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 6. Combination cream (hydroquinone and sunscreen) versus sunscreen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events (AE)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 7. Triple-combination cream (TC) vs dual-combination cream (tretinoin and hydroquinone)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with complete clearing of melasma	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 8. Triple-combination cream (TC) vs dual-combination cream (tretinoin and fluocinolone acetonide (FA))

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with complete clearing of melasma	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 9. Triple-combination cream (TC) vs dual-combination cream (hydroquinone and fluocinolone acetonide) (HQ&FA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with complete clearing of melasma	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 10. Combination cream (hydroquinone, glycolic acid, vitamin C, E and sunscreen) versus sunscreen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mild adverse events (AE) (dryness)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Mild adverse events (AE) (erythema)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Mild adverse events (burning)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Moderate adverse events (AE) (peeling)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 11. Jessner's peel with tretinoin priming versus salicylic acid peel with tretinoin priming

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction in MASI at 12 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Mean reduction in MASI at 24 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Adverse events (AE)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 12. Cosmetic whitening formulation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean melanin index at 3 months	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Triple-combination cream (TC) versus hydroquinone (HQ), Outcome 1 Participant assessed improvement: number with score 0 or 1 (clear or minor hyperpigmentation).

Review: Interventions for melasma

Comparison: 1 Triple-combination cream (TC) versus hydroquinone (HQ)

Outcome: 1 Participant assessed improvement: number with score 0 or 1 (clear or minor hyperpigmentation)

Study or subgroup	TC cream n/N	HQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Chan 2008	87/125	57/129		1.58 [1.26, 1.97]

Analysis 1.2. Comparison 1 Triple-combination cream (TC) versus hydroquinone (HQ), Outcome 2 Number of participants achieving score 0 or 1 (none or mild melasma).

Review: Interventions for melasma

Comparison: 1 Triple-combination cream (TC) versus hydroquinone (HQ)

Outcome: 2 Number of participants achieving score 0 or 1 (none or mild melasma)

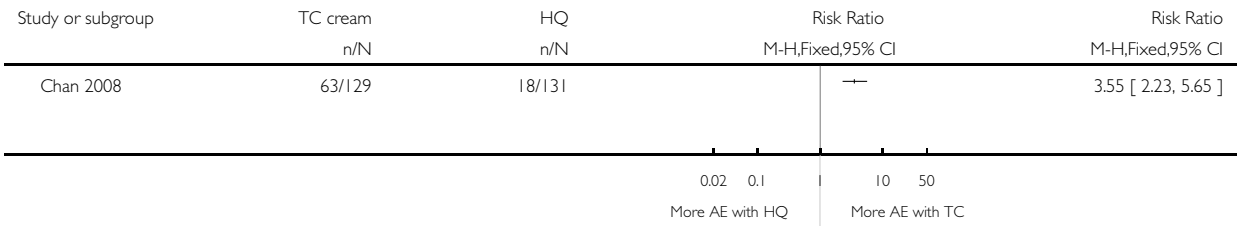
Study or subgroup	TC cream n/N	HQ n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Chan 2008	77/129	48/131		1.63 [1.25, 2.13]

Analysis 1.3. Comparison 1 Triple-combination cream (TC) versus hydroquinone (HQ), Outcome 3 Adverse events (AE).

Review: Interventions for melasma

Comparison: 1 Triple-combination cream (TC) versus hydroquinone (HQ)

Outcome: 3 Adverse events (AE)

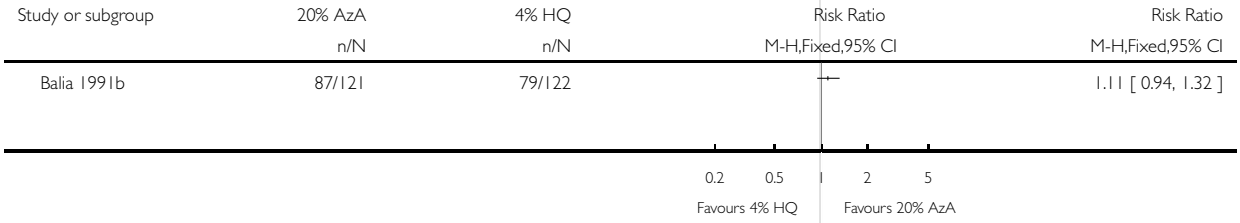


Analysis 2.1. Comparison 2 20% Azelaic acid (AzA) vs 4% hydroquinone (HQ), Outcome 1 Participants with good or excellent response.

Review: Interventions for melasma

Comparison: 2 20% Azelaic acid (AzA) vs 4% hydroquinone (HQ)

Outcome: 1 Participants with good or excellent response

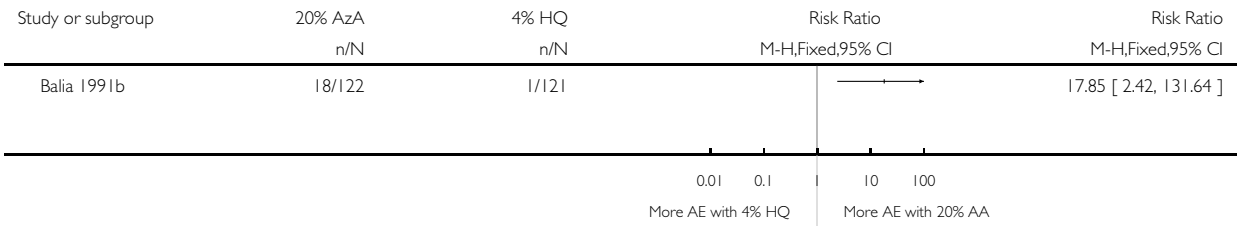


Analysis 2.2. Comparison 2 20% Azelaic acid (AzA) vs 4% hydroquinone (HQ), Outcome 2 Adverse events (AE).

Review: Interventions for melasma

Comparison: 2 20% Azelaic acid (AzA) vs 4% hydroquinone (HQ)

Outcome: 2 Adverse events (AE)

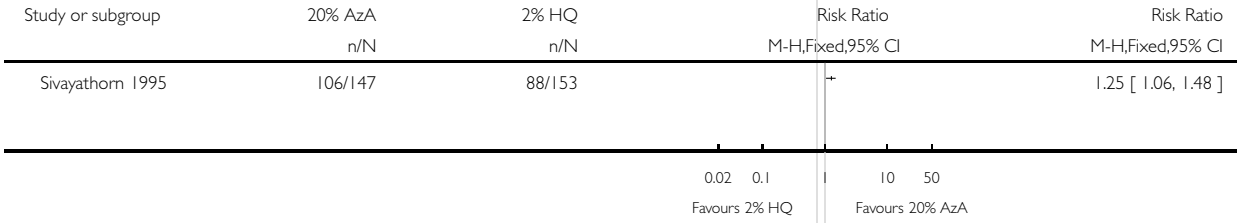


Analysis 3.1. Comparison 3 20% Azelaic acid (AzA) vs 2% hydroquinone (HQ), Outcome 1 Number of participants with >50% improvement.

Review: Interventions for melasma

Comparison: 3 20% Azelaic acid (AzA) vs 2% hydroquinone (HQ)

Outcome: 1 Number of participants with >50% improvement

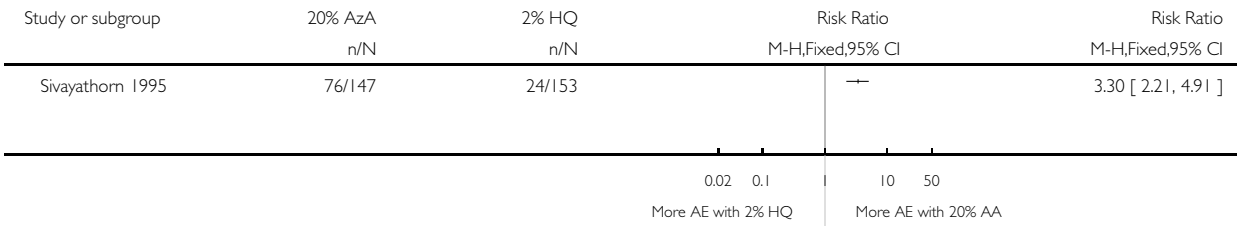


Analysis 3.2. Comparison 3 20% Azelaic acid (AzA) vs 2% hydroquinone (HQ), Outcome 2 Adverse events (AE).

Review: Interventions for melasma

Comparison: 3 20% Azelaic acid (AzA) vs 2% hydroquinone (HQ)

Outcome: 2 Adverse events (AE)

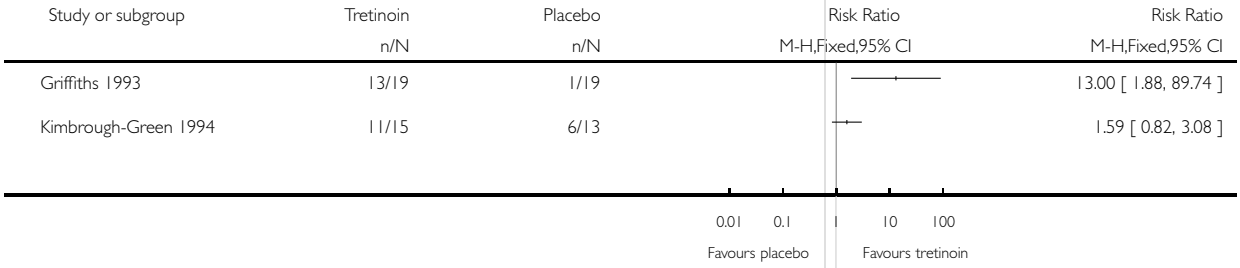


Analysis 4.1. Comparison 4 Tretinoin versus placebo, Outcome 1 Number of participants rated as 'improved' or 'much improved'.

Review: Interventions for melasma

Comparison: 4 Tretinoin versus placebo

Outcome: 1 Number of participants rated as 'improved' or 'much improved'



Analysis 4.2. Comparison 4 Tretinoin versus placebo, Outcome 2 Melasma severity assessed by Woods lamp at 40 weeks.

Review: Interventions for melasma

Comparison: 4 Tretinoin versus placebo

Outcome: 2 Melasma severity assessed by Woods lamp at 40 weeks

Study or subgroup	Tretinoin N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Griffiths 1993	19	4.3 (2.6)	19	6.2 (1.7)		-0.85 [-1.51, -0.18]

Analysis 4.3. Comparison 4 Tretinoin versus placebo, Outcome 3 Increase in Luminance (L value).

Review: Interventions for melasma

Comparison: 4 Tretinoin versus placebo

Outcome: 3 Increase in Luminance (L value)

Study or subgroup	Tretinoin N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Kimbrough-Green 1994	15	3.2 (3.5)	13	0.3 (3.24)		0.83 [0.05, 1.61]

Analysis 4.4. Comparison 4 Tretinoin versus placebo, Outcome 4 Adverse events (AE).

Review: Interventions for melasma

Comparison: 4 Tretinoin versus placebo

Outcome: 4 Adverse events (AE)

Study or subgroup	Tretinoin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Kimbrough-Green 1994	10/15	1/15		10.00 [1.46, 68.69]

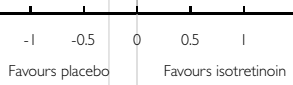
Analysis 5.1. Comparison 5 Isotretinoin gel versus placebo, Outcome 1 Mean reduction in MASI from baseline.

Review: Interventions for melasma

Comparison: 5 Isotretinoin gel versus placebo

Outcome: 1 Mean reduction in MASI from baseline

Study or subgroup	Isotretinoin gel N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Leenutaphong 1999	11	5.84 (7.13)	12	5.33 (6.89)		0.07 [-0.75, 0.89]

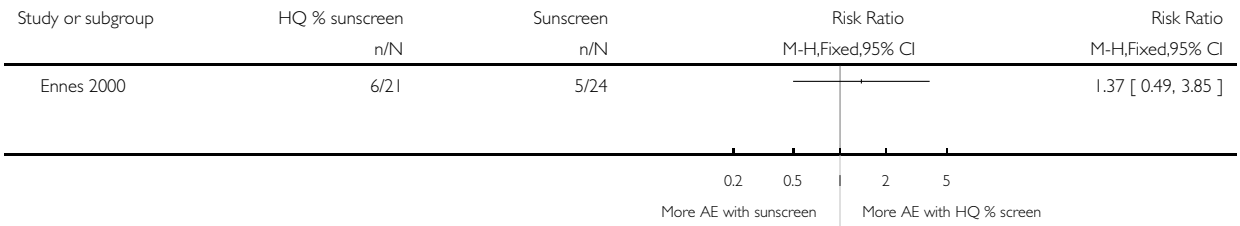


Analysis 6.1. Comparison 6 Combination cream (hydroquinone and sunscreen) versus sunscreen, Outcome 1 Adverse events (AE).

Review: Interventions for melasma

Comparison: 6 Combination cream (hydroquinone and sunscreen) versus sunscreen

Outcome: 1 Adverse events (AE)

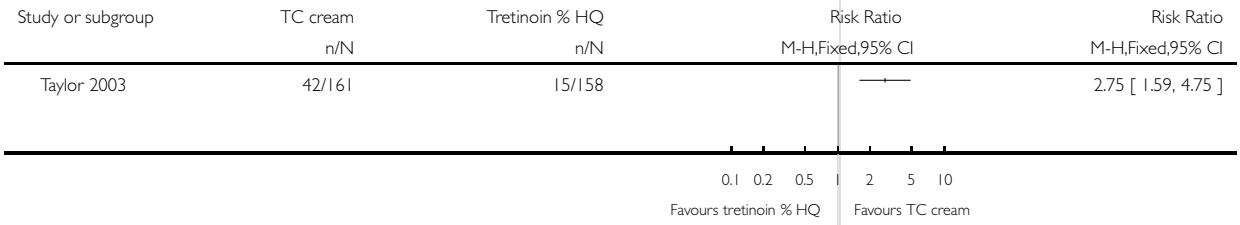


Analysis 7.1. Comparison 7 Triple-combination cream (TC) vs dual-combination cream (tretinoin and hydroquinone), Outcome 1 Number of participants with complete clearing of melasma.

Review: Interventions for melasma

Comparison: 7 Triple-combination cream (TC) vs dual-combination cream (tretinoin and hydroquinone)

Outcome: 1 Number of participants with complete clearing of melasma



Analysis 8.1. Comparison 8 Triple-combination cream (TC) vs dual-combination cream (tretinoin and fluocinolone acetonide (FA)), Outcome 1 Number of participants with complete clearing of melasma.

Review: Interventions for melasma

Comparison: 8 Triple-combination cream (TC) vs dual-combination cream (tretinoin and fluocinolone acetonide (FA))

Outcome: 1 Number of participants with complete clearing of melasma

Study or subgroup	TC cream n/N	Tretinoin % FA n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Taylor 2003	42/161	3/161		14.00 [4.43, 44.25]

Analysis 9.1. Comparison 9 Triple-combination cream (TC) vs dual-combination cream (hydroquinone and fluocinolone acetonide) (HQ&FA), Outcome 1 Number of participants with complete clearing of melasma.

Review: Interventions for melasma

Comparison: 9 Triple-combination cream (TC) vs dual-combination cream (hydroquinone and fluocinolone acetonide) (HQ%FA)

Outcome: 1 Number of participants with complete clearing of melasma

Study or subgroup	TC cream n/N	HQ % FA n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Taylor 2003	42/161	4/161		10.50 [3.85, 28.60]

Analysis 10.1. Comparison 10 Combination cream (hydroquinone, glycolic acid, vitamin C, E and sunscreen) versus sunscreen, Outcome 1 Mild adverse events (AE) (dryness).

Review: Interventions for melasma

Comparison: 10 Combination cream (hydroquinone, glycolic acid, vitamin C, E and sunscreen) versus sunscreen

Outcome: 1 Mild adverse events (AE) (dryness)

Study or subgroup	Combn cream n/N	Sunscreen n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Guevara 2003	12/20	0/15		19.05 [1.22, 298.21]

Analysis 10.2. Comparison 10 Combination cream (hydroquinone, glycolic acid, vitamin C, E and sunscreen) versus sunscreen, Outcome 2 Mild adverse events (AE) (erythema).

Review: Interventions for melasma

Comparison: 10 Combination cream (hydroquinone, glycolic acid, vitamin C, E and sunscreen) versus sunscreen

Outcome: 2 Mild adverse events (AE) (erythema)

Study or subgroup	Combn cream n/N	Sunscreen n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Guevara 2003	11/20	1/15		8.25 [1.19, 57.10]

Analysis 10.3. Comparison 10 Combination cream (hydroquinone, glycolic acid, vitamin C, E and sunscreen) versus sunscreen, Outcome 3 Mild adverse events (burning).

Review: Interventions for melasma

Comparison: 10 Combination cream (hydroquinone, glycolic acid, vitamin C, E and sunscreen) versus sunscreen

Outcome: 3 Mild adverse events (burning)

Study or subgroup	Combn cream n/N	Sunscreen n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Guevara 2003	7/20	3/15		1.75 [0.54, 5.67]

Analysis 10.4. Comparison 10 Combination cream (hydroquinone, glycolic acid, vitamin C, E and sunscreen) versus sunscreen, Outcome 4 Moderate adverse events (AE) (peeling).

Review: Interventions for melasma

Comparison: 10 Combination cream (hydroquinone, glycolic acid, vitamin C, E and sunscreen) versus sunscreen

Outcome: 4 Moderate adverse events (AE) (peeling)

Study or subgroup	Combn cream n/N	Sunscreen n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Guevara 2003	6/20	0/15		9.90 [0.60, 163.20]

Analysis 11.1. Comparison 11 Jessner's peel with tretinoin priming versus salicylic acid peel with tretinoin priming, Outcome 1 Mean reduction in MASI at 12 weeks.

Review: Interventions for melasma

Comparison: 11 Jessner's peel with tretinoin priming versus salicylic acid peel with tretinoin priming

Outcome: 1 Mean reduction in MASI at 12 weeks

Study or subgroup	Salicylic acid peel N	Mean(SD)	Jessner's peel N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Ejaz 2008	25	3.8 (2.29)	32	3.6 (2.43)		0.08 [-0.44, 0.61]

Analysis 11.2. Comparison 11 Jessner's peel with tretinoin priming versus salicylic acid peel with tretinoin priming, Outcome 2 Mean reduction in MASI at 24 weeks.

Review: Interventions for melasma

Comparison: 11 Jessner's peel with tretinoin priming versus salicylic acid peel with tretinoin priming

Outcome: 2 Mean reduction in MASI at 24 weeks

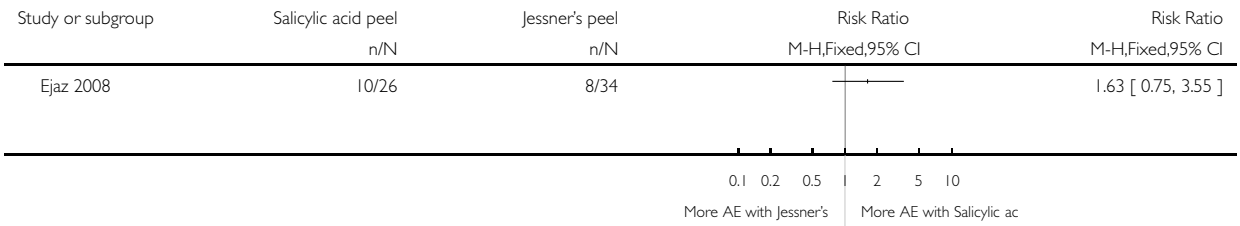
Study or subgroup	Salicylic acid peel N	Mean(SD)	Jessner's peel N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Ejaz 2008	20	2.7 (2.91)	21	3 (3.34)		-0.09 [-0.71, 0.52]

Analysis 11.3. Comparison 11 Jessner's peel with tretinoin priming versus salicylic acid peel with tretinoin priming, Outcome 3 Adverse events (AE).

Review: Interventions for melasma

Comparison: 11 Jessner's peel with tretinoin priming versus salicylic acid peel with tretinoin priming

Outcome: 3 Adverse events (AE)

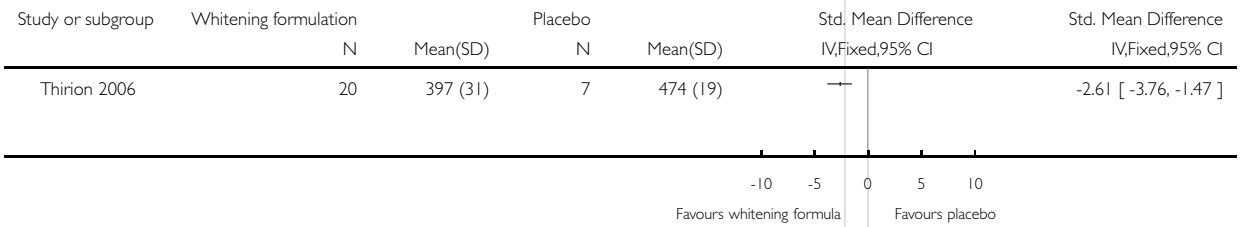


Analysis 12.1. Comparison 12 Cosmetic whitening formulation versus placebo, Outcome 1 Mean melanin index at 3 months.

Review: Interventions for melasma

Comparison: 12 Cosmetic whitening formulation versus placebo

Outcome: 1 Mean melanin index at 3 months



APPENDICES

Appendix 1. Cochrane Library search strategy

#1(melasma) or (chloasma) or (mask NEAR/2 pregnanc*)
#2MeSH descriptor Melanosis explode all trees
#3(#1 OR #2)
#4SR-SKIN
#5(#3 AND NOT #4)

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (human and animals)).sh.
10. 8 not 9
11. (mask adj2 pregnancy).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. melasma$.mp. or exp Melanosis/
13. chloasma$.mp.
14. 11 or 13 or 12
15. 10 and 14

Appendix 3. EMBASE search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. melasma$.mp. or exp Chloasma/
15. chloasma$.mp.
16. melanosis.mp. or exp Melanosis/
17. (mask adj2 pregnancy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
18. 16 or 17 or 15 or 14
19. 13 and 18

Appendix 4. LILACS search strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Palavras] and melasma or chloasma or cloasma or melanosis or (mask and pregnancy) [Palavras]

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 7, 2010

6 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Link with editorial base and coordinate contributions from co-reviewers (RR)

Draft protocol (AS, MRP, LGC, JAT, SV, RR)

Run search (RR)

Identify relevant titles and abstracts from searches e.g. broad screen (RR, JH, AS)

Obtain copies of trials (RR, JH)

Select which trials to include (RR, JH, with AS as arbitrator when necessary)

Extract data from trials (RR, JH)

Enter data into RevMan (RR)

Carry out analysis (RR, JH, CE)

Interpret analysis (RR, CE)

Draft final review (RR, JH, AS, CE)

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- All work done in the authors' own time, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are several changes compared to the published protocol:

In the Methods section, under the subheading 'Criteria for considering studies for this review' > 'Types of studies' we included trials that were open label even if placebo use was possible as long as they were assessor-blinded. This is a change from the protocol in which the plan was to exclude open label trials if placebo use was possible. We felt that the original criteria of excluding all open label trials where placebo use was possible was too stringent. By ensuring there was a blind assessment of outcome, observer bias is likely to have been limited.

Under the section 'Types of interventions' we had planned to categorise treatments according to categories such as sunscreens, treatments which decrease inflammation, skin-lightening agents etc. However, as each trial had a unique set of interventions and as most had active comparisons it did not make sense to categorise treatments in this manner as most trials would come under one or two categories.

Under the section 'Types of outcome measures' we defined our outcome measures more clearly by stratifying the outcomes of greatest interest as the primary outcomes and other measures as secondary outcomes. In view of the significant impact melasma has on sufferers, the two primary outcomes were the participant-assessed changes in severity and quality of life measures. We felt it was necessary to define these outcomes separately as quality of life measures focus on how people feel about their skin appearance and the impact the melasma has on their life whilst the participant-assessed improvement focused on the change in severity of pigmentation following treatment.

The other outcomes of interest: physician evaluation, adverse events, and long-term improvement were our secondary outcomes. In terms of physician-assessed changes we divided this into subjective and objective evaluation techniques. After extracting the data we found most trials assessed outcomes according to either method and this may allow more accurate comparisons between trials. The subjective measures are the clinically relevant changes in pigmentation whilst the objective techniques aim to measure skin colour in an accurate reproducible manner. The MASI score, whilst attempting to standardise the evaluation of pigmentation, was included in the subjective rather than objective measures as set out in the protocol as the components of darkness, area, and homogeneity which make up the score are assessed subjectively.

We added two further outcomes, the time to improvement of melasma and the long-term remission rate. The rapidity of action of a test substance may affect adherence to treatment and overall satisfaction with treatment and this was measured by time to improvement of melasma. Long-term remission rate is defined as improvement in pigmentation lasting more than 12 months and was used to identify potential relapses following cessation of treatment.

In the 'Data collection and analysis' section under 'Measure of treatment effect' we changed the effect estimate from odds ratio (OR) stated in the protocol, to risk ratio (RR) and 95% confidence intervals (CI) for dichotomous outcomes.