INTERVENTIONS FOR ROSACEA

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ABSTRACT

Background
Rosacea is a common chronic skin condition affecting the face, characterised by flushing, redness, pimples, pustules, and dilated blood vessels. The eyes are often involved and thickening of the skin with enlargement (phymas), especially of the nose, can occur in some patients. A range of treatment options are available but it is unclear which are the most effective.

Objective
To assess the evidence for the efficacy and safety of treatments for rosacea.

Criteria for considering studies for this review
In February 2011 we updated our searches of the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (Clinical Trials) in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index, and Ongoing Trials Registers.

Selection criteria
Randomised controlled trials in people with moderate to severe rosacea.

Data collection and analysis
Study selection, data extraction, assessment of risk of bias, and analyses were carried out by two independent review authors.

Main results
Fifty-eight trials, including 27 from the original review, comprising 6633 participants were included in this updated review. Interventions included topical metronidazole, oral antibiotics, topical azelaic cream or gel, topical benzoyl peroxide and/or combined with topical antibiotics, sulphacetamide/sulphur, and others. Only two studies assessed our primary outcome ‘quality of life’.

Authors’ conclusions
Although the majority of included studies were assessed as being at high or unclear risk of bias there was some evidence to support the effectiveness of topical metronidazole, azelaic acid, and doxycycline (40 mg) in the treatment of moderate to severe rosacea, and cyclosporine 0.5% ophthalmic emulsion for ocular rosacea. Further well-designed, adequately-powered randomised controlled trials are required.

PLAIN LANGUAGE SUMMARY

Rosacea is a common skin condition causing flushing, redness, red pimples, and pustules on the face, which should not be confused with acne. It can also cause inflammation of the eyes or eyelids, or both. Some people can develop a thickening of the skin, especially of the nose, which is called rhinophyma. Because rosacea is a chronic disease the effect of treatment on quality of life is very important to the individual. A range of treatment options are available which include several topical and oral antibiotics, azelaic cream, topical and systemic retinoids, and light-based therapies, e.g. laser therapy.
This review found that in 3 clinical trials with 334 participants, topical metronidazole was more effective than placebo. Although most of the studies did not specifically address participants’ satisfaction with treatment, they did nevertheless confirm the effectiveness of some of the treatments, expressed as a reduction in lesion counts, but these evaluations were largely physician-assessed. Three clinical trials involving 778 participants provided some evidence that topical azelaic acid cream was more effective than placebo. Two studies reported that the anti-inflammatory dose of doxycycline (40 mg) was more effective than placebo, confirmed by another study which also reported a lower risk of side-effects with the 40 mg dose rather than the 100 mg dose. Cyclosporine 0.5% ophthalmic emulsion appears to be more effective than artificial tears for rosacea of the eyes.

Future research should aim to provide reliable evidence for people to make informed decisions about whether other widely-available treatments are effective in managing rosacea, i.e. other oral tetracyclines, isotretinoin, and treatments used for rosacea of the eyes, in addition to investigating the potential role of sunscreens and dietary change.

WHAT'S NEW

Last assessed as up-to-date: 8 February 2011.

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BACKGROUND

OBJECTIVES

To assess and summarise the current evidence for the efficacy and safety of treatments for rosacea.

METHODS OF THE REVIEW

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials (RCTs).

Types of participants

People older than 19 years with moderate to severe rosacea (diagnosed clinically).

Types of intervention

Any type of intervention used, either alone or in combination, to treat rosacea, versus placebo or active treatment. We also considered the effects of avoidance of some foodstuffs, e.g. spicy food, as well as the use of certain cosmetics and sunscreens.

Types of outcome measures

Primary outcomes

(a) Impact on quality of life.
(b) Participant-assessed changes in rosacea severity.

Secondary outcomes

(c) Physician-assessed changes in rosacea severity. These included the following.
   i) Physician's global evaluation (improvement defined as greater than, or equal to, 50% change).
   ii) Lesion counts (treatment success defined as greater than 50% reduction in lesion counts).
   iii) Time needed for improvement of the skin lesions per group.
   iii) Duration of remission.
(d) Dropout rates.
(e) Incidence of participants experiencing adverse events.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Search methods for identification of studies

Two authors (EvZ and MG) performed the searches independently. No language restrictions were imposed and each included study was evaluated both for efficacy and for adverse effects.

Electronic searches

ON 9th February 2011 we updated our searches of the following databases:
The Cochrane Skin Group Specialised Register using the search strategy in Appendix 1;
The Cochrane Central Register of Controlled Trials (Clinical Trials) in The Cochrane Library using the search strategy in Appendix 2;
MEDLINE (from 2006 to the present) using the search strategy in Appendix 3, adapted from the strategy in Higgins 2009;
EMBASE (from 2011 to the present) using the search strategy in Appendix 4; and
Science Citation Index (from 1988 to the present) (see Appendix 5).
BIOSIS (was previously searched from 1970 to March 2002) (see Appendix 6).
The UK and US Cochrane Centres have 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 2005 and in EMBASE to 2010. Further searching of these two databases was undertaken for this review by the Cochrane Skin Group to cover the years not searched by the UK and US Cochrane Centres.

Ongoing Trials

We searched the following ongoing trials databases on 9th February 2011.
The metaRegister of Controlled Trials www.controlled-trials.com.
The U.S. National Institutes 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 on www.nottingham.ac.uk/ongoingskintrials.

Searching other resources

References from published studies

The reference lists of all identified RCTs and key review articles were searched.

Unpublished literature

Attempts were made to locate unpublished and ongoing trials through correspondence with authors and pharmaceutical companies (see and ).

Translation

We did not apply any language restrictions and several studies published in the French, Spanish, Italian, Norwegian, and Danish languages were translated by one author (EvZ). Two articles in the French language were translated by Douglas Grindlay.

DATA COLLECTION AND ANALYSIS

Data collection and analysis

Selection of studies

Two review authors (EvZ and MG) independently assessed the abstracts of studies resulting from the searches. We obtained full text copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, and those for which there were insufficient data in the title and abstract to make a clear decision. The two authors then independently assessed the full-text papers and resolved any disagreement on the eligibility of included studies through discussion and consensus, or through a third party (ZF). All irrelevant studies were
excluded and their details and reasons for exclusion were noted in the 'Characteristics of excluded studies' table in RevMan (Revman 2008).

In earlier versions of this review a number of studies were excluded based on their methodological quality. However, following the recommendations in the current Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009), these studies were re-evaluated for possible inclusion and if considered to be eligible their details were entered in the 'Characteristics of included studies' table and they were assessed for risk of bias.

Data extraction and management

Details of eligible trials were extracted and summarised using structured data extraction forms (EvZ, SK, ZF, and MG). Disagreements were resolved by discussion. The data were checked for consistency by three authors (EvZ, SK, and/or ZF). Study details were entered into the 'Characteristics of included studies' table in RevMan (Revman 2008) by one author (EvZ). The review authors only included data if there was an independently reached consensus, and any disagreements were resolved by discussion between the authors.

The following details were extracted:

- **Trial methods** - method of allocation, masking of participants and outcomes assessors, and date and setting of study.
- **Participants** - sample size, age, sex, inclusion and exclusion criteria, if there was ocular involvement, exclusion of participants after randomisation and proportion for losses at follow up.
- **Intervention and comparison** - length of study, type, and dosage.
- **Outcomes** - primary and secondary outcomes reported in the study.
- **Notes** - if our primary outcomes were addressed, and other comments.

Assessment of risk of bias in included studies

The review authors (EvZ, SK, ZF, or BC) independently assessed risk of bias using the Cochrane Collaboration tool for assessing risk of bias as described in Chapter 8, Section 8.5, in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). The following domains were rated for each of the included studies as 'Yes' (low risk of bias), 'No' (high risk of bias), and 'Unclear' (uncertain risk of bias) if the risk of bias was uncertain or unknown.

- (a) the allocation sequence was adequately generated ('sequence generation');
- (b) the allocation was adequately concealed ('allocation concealment');
- (c) knowledge of the allocated interventions was adequately prevented during the study ('blinding');
- (d) incomplete outcome data were adequately addressed;
- (e) reports of the study were free of suggestion of selective outcome reporting; and
- (f) the study was apparently free of other sources of bias that could put it at high risk of bias. This would include adequate study duration, i.e. a minimum of four weeks and that previous oral and topical rosacea therapy was stopped a minimum of four weeks prior to the initial assessment.

These assessments are reported in the 'Risk of bias' table for each individual study. See 'Characteristics of included studies'.

We also categorised and reported the overall risk of bias of each of the included studies according to the following:

- **Low risk of bias** (plausible bias unlikely to seriously alter the results) if all criteria were met;
- **Unclear risk of bias** (plausible bias that raises some doubt about the results) if one or more criteria were assessed as unclear; or
- **High risk of bias** (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

Measures of treatment effect

Two treatment comparisons

We presented continuous outcomes where possible on the original scale as reported in each individual study. In future updates if similar outcomes are reported using different scales these will be standardised by dividing the estimated mean difference by its standard deviation (SD), thereby allowing comparisons to be made between scales. Dichotomous outcomes data were presented as relative risk ratio. All outcomes data were reported with their associated 95% confidence intervals.

More than two treatment comparisons

Multi-arm trials were included in the review if at least one arm constituted a relevant intervention for rosacea, and separate data extraction was carried out for each pair-wise comparison. These studies were included as pair-wise comparisons.

Unit of analysis issues

Cluster randomised trials
We did not identify any cluster randomised trials for inclusion in this review. If in future updates cluster randomised trials, i.e. groups of individuals randomised to intervention or control, are identified in the searches, these will be checked for unit of analysis errors based on the advice provided in Section 16.3.4 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009).

Cross-over studies

Unit of analysis issues can arise in studies where participants have been randomised to multiple treatments in multiple periods or where there has been an inadequate wash-out period. In general, for cross-over studies we only used data from the first treatment period, unless otherwise stated.

Within-patient studies

The analysis of paired data is not possible with Review Manager, so all data from within-patient studies have been entered into tables and summarised. Where possible, a conditional odds ratio (based on the discordant cases only) was calculated and reported in the text (Curtin 2002). When it was not possible to calculate a conditional odds ratio (OR), this was stated in the text. Marginal odds ratios were not calculated, as they are easily misinterpreted.

Dealing with missing data

If data were missing from trials which were less than 10 years old we tried wherever possible to contact the investigators or sponsors of these studies. We re-analysed data according to the intention-to-treat (ITT) principle whenever possible. For dichotomous outcomes, if authors had conducted a per-protocol analysis, we carried out an ITT analysis with imputation setting the missing data to their baseline values, checking the degree of imbalance of the dropout between the arms to determine the potential impact of bias (Section 16.2.2 of the Cochrane Handbook for Systematic Reviews of Interventions). For continuous outcomes a per-protocol analysis was carried out in place of an ITT analysis.

Assessment of heterogeneity

Clinical heterogeneity was assessed by examining the characteristics of the studies, the similarity between the types of participants, the interventions, the comparisons, and the outcomes as were specified in the criteria for included studies. Although there is inevitably a degree of heterogeneity between the studies included in a review, if this could be explained by clinical reasoning and a coherent argument could be made for combining the studies these were entered into a meta-analysis.

The clinical diversity between many of the studies in this review as well as the limited number of studies that could be combined for each intervention only allowed us to make assessments of heterogeneity between the studies in two of the comparisons. We reported heterogeneity as important and at least moderate to substantial by $I^2 > 60\%$ (Higgins 2009).

Assessment of reporting biases

The low number of studies evaluating similar interventions and comparisons did not permit an assessment of publication bias. In future updates if a sufficient number of trials assessing similar effects are identified for inclusion in this review, publication bias will be assessed according to the recommendations on testing for funnel plot asymmetry (Egger 1997) as described in Section 10.4.3.1 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). If asymmetry is identified we will try to assess other possible causes and these will be explored in the discussion if appropriate.

Skewed data

Outcomes data reported as counts, e.g. papules or pustules, were often skewed and frequently inappropriately analysed. We did not enter these types of outcomes data into a meta-analysis but reported them separately as 'Data that cannot be presented graphically in Revman', for comparisons where these data have been provided by investigators.

Data synthesis

Four review authors (EvZ, and/or SK, ZF, BC) analysed the data in RevMan (Revman 2008) and reported them as specified in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). Data synthesis was only carried out if we were able to identify a sufficient number of studies ($n \geq 3$) investigating similar treatments and which reported data that could be pooled (Treadwell 2006). We used a fixed-effect model to combine the results of individual studies in this review. In future updates, and if heterogeneity is identified, random-effects models will be fitted. For comparisons where data synthesis was not feasible this data has been reported separately as 'Data that cannot be presented graphically in Revman' and presented in the review as a narrative summary.

Subgroup analysis and investigation of heterogeneity

In view of the paucity of included studies for any one specific intervention, we did not carry out any subgroup analyses. In future updates we plan to carry out the following subgroup analyses if we identify at least moderate to substantial heterogeneity (as defined above) and if we are able to include at least 10 studies: differences in treatment effect by differing baseline risk, and possible differences in effect by the range of modes of administration of the interventions used, i.e. topical, systemic, and different dosing regimens.

Sensitivity analysis
We did not conduct any sensitivity analyses in this review. If a sufficient number of studies (n = 10) investigating similar interventions had been included, we had planned to conduct sensitivity analyses to assess the robustness of our review results.

METHODOLOGICAL QUALITY

RESULTS

Description of studies

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

Results of the search

The updated searches for this review identified an additional 57 citations to potentially eligible studies. After assessment for eligibility a further 23 studies were included and the remaining 34 were eliminated from further review. We also undertook a re-assessment of the studies which had been excluded in the earlier version of this review, and some of these provided additional studies to be included in this update.

Included studies

Fifty-eight studies were included in this review. In addition to the 27 trials already in this review there were 23 newly included studies and 8 which had been excluded in earlier versions of this review but had been re-evaluated for eligibility. A total of 6633 participants were studied (see 'Characteristics of included studies').

Characteristics of the participants

A majority of the participants in the included studies had papulopustular rosacea. They were between 40 and 50 years of age; there were more women than men. Twenty-eight of the studies were carried out after the year 2000, a further 19 were conducted in the 1990s, 8 in the 1980s, and 3 dated further back. Although the number of participants in the individual studies varied widely - from 13 to 1299 - sample sizes of between 30 and 100 were the most common.

It was agreed between the authors that Thiboutot 2008 should be included but considered as a maintenance study. The investigators enrolled 172 participants in the pilot phase of the study of which only 136 continued into the second phase but consisted of the participants who had already achieved an improvement of > 75% reduction in inflammatory lesions.

Characteristics of the interventions

The trials can be grouped into six categories of interventions: topical metronidazole (28), oral antibiotics (15), topical azelaic cream or gel (11), topical benzoyl peroxide and/or combined with topical antibiotics (4), sulphacetamide/sulphur (3), and other therapies (14). Eighteen trials evaluated comparisons in more than one category, e.g. a topical plus an oral agent, and in seven of the studies the individuals served as their own controls, with active treatment and placebo assigned to either the left or right side of the face (Barnhorst 1996; Blecher 1987; Carmichael 1993; Maddin 1999; Karsai 2008; Mostafa 2009; Neuhaus 2009). The duration of treatment ranged between two and three months, and only two studies addressed interventions for ocular rosacea (Barnhorst 1996; Scheck 2009).

Heterogeneity in study design, skewed data, missing standard deviations, and a mix of different comparators and dosing regimens did not, in general, permit pooling of the data or allow the authors to make accurate and direct comparisons of some of the interventions.

Characteristics of the outcomes

Only 2 of the included studies (Schechter 2009; Weissenbacher 2007) reported assessments of change in 'quality of life' as a result of the interventions, and just half (29) of the remaining studies evaluated participant-assessed changes in rosacea severity; both of which were the primary outcomes for this review. The patient-reported outcomes (PRO) which were reported in the 29 studies, included not only assessments of changes in severity but also, in most instances, the patient-satisfaction associated with these changes.

We evaluated these PROs against the checklist for describing and assessing patient-reported outcomes in clinical trials (See ), which is described in Chapter 17.6.a of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). We found that hardly any of them matched the recommended criteria. In the vast majority of studies the self-assessments were made by way of questionnaires and instruments which evaluated the resolution of symptoms either jointly, or separately, with patient satisfaction related to the treatment. While most of these instruments were based on Likert-type scales a very small number of the studies utilised Visual Analogue Scales (VAS) in their assessments (Neuhaus 2009; Weissenbacher 2007).
There was wide diversity in the format of the questionnaires; many appeared to be unvalidated, used a range of scaling which offered a choice of from three- to seven-point items covering similar outcomes across the different questionnaires (Bitar 1990), and in several of them the physician and participant assessments were combined and expressed as composite scores. In the majority of the questionnaires it was not clear how the ratings correlated with the scaling of the items nor how reliable the interval-level measurements were between the individual items. Additionally, in a number of the patient-satisfaction questionnaires the judgements appeared to have been framed in such a way that only positive responses were possible, which would most likely lead to biased assessments being made (Breneman 1998; Bjerke 1999; Lebwohl 1995; Maddin 1999; Sauder 1997).

The quality of life assessment tools which were utilised in two of the studies had been validated and were internationally recognised. A disease-specific instrument, Ocular Surface Disease Index (OSDI), was used in Schechter 2009 and the generic Dermatology Life Quality Index (DLQI) in the other study (Weissenbacher 2007). In both of these studies the investigators provided citations to reports indicating that the tools had been previously validated as was specified in the PRO checklist ( ).

Most of the studies used clinician-assessed numbers of papules or pustules as an outcome rather than a more patient-relevant measure such as participant assessment of appearance. However, it is recognised that in the everyday clinical setting the decrease in number of lesions, time-to-response, and duration of response may be considered more practical and readily measurable outcomes. Outcomes assessment of erythema and telangiectasia involved the use of proprietary scoring systems which did not permit pooling of data from these studies. Outcomes assessments of ocular disease were only carried out in two of the included studies (Barnhorst 1996; Schechter 2009).

Excluded studies

Sixty-nine studies, 42 of which were newly identified, were excluded from this review. Fifty, out of the total number of studies, were excluded only after evaluation of their full-text copies and this was largely on the basis that they were non-randomised trials (see 'Characteristics of excluded studies').

Risk of bias in included studies

Only three of the studies (Bleichers 1987; Del Rosso 2007a; Del Rosso 2007b) met all of the criteria across all of the domains in The Cochrane Collaboration's tool for assessing the risk of bias, and therefore these studies were considered to be at 'low risk of bias' (plausible bias unlikely to seriously alter the results). Almost half of the studies were categorised as 'unclear risk of bias' (plausible bias that raises some doubt about the results) because one or more criteria were assessed as unclear, and the remaining 25 studies were assessed as 'high risk of bias' (plausible bias that seriouslyweakens confidence in the results) because one or more of the criteria were not met. Further details of these assessments are available in the 'Risk of bias' table corresponding to each study in the 'Characteristics of included studies', and are also presented in the 'Risk of Bias' graph in and the 'Risk of Bias' summary in .

Some of these assessments were to a certain extent based on the inadequate reporting of the criteria that are a prerequisite in the evaluation of methodological rigour, in terms of trial design and conduct. Concealment of the allocation sequence and blinding are key domains in the assessment of risk of bias and most of the studies in this review provided insufficient detail to enable accurate judgements to be made. Protocol deviation, losses to follow up with incomplete data, and subsequent per-protocol analyses were other important sources of potential bias in a number of the included studies (see 'Risk of bias' table in 'Characteristics of included studies').

Allocation

The methods used to generate the allocation sequence and how the sequence was concealed, such that participants and investigators enrolling participants could not foresee the upcoming assignment, are the most important and sensitive indicators that bias has been minimised in a clinical trial (Schulz 1995). In 37 out of the 58 trials in this review the method of sequence generation was not described at all or was at best unclear, and concealment of the allocation sequence was reported adequately in only 13 of the trials (see 'Risk of bias' tables in 'Characteristics of included studies').

Blinding

Blinding of outcome assessment was reported clearly in only 25 of the 58 included studies. In the majority of these, blinding was achieved by the use of unmarked or identically appearing tubes, capsules, or tablets. Some of the interventions were coded left or right for the within-patient studies.

Incomplete outcome data

In slightly more than half of the studies incomplete outcome data appear to have been adequately addressed and any missing outcome data were reasonably well-balanced across intervention groups with similar reasons for missing data across groups. However, in 20 of the 58 studies the reporting of missing outcome data was largely inadequate. Attrition was one of the main causes for incomplete outcome data. The reasons for attrition varied and these were often dependent on the assignment of the participant to one or other particular group, and thus, for example, more dropouts tended to occur in groups receiving active intervention secondary to any side-effects, as opposed to dropouts due to lack of efficacy in the corresponding placebo group.

Selective reporting
The reporting quality in most of the older studies, although not ideal, was consistent with the editorial style and standards existing at the time of publication. Although the protocols were not available for any of the included studies, based on the information in the methods section of the reports, 42 out of the 58 studies appear to have reported all prespecified outcomes and were therefore judged to be free of selective reporting. In the remaining studies, rarely was more than one outcome inadequately addressed, but in some instances these outcomes were reported only as a graph plot without any clearly discernible data.

**Other potential sources of bias**

Twenty-three of the studies appeared to be free of other forms of bias, whereas in 24 studies this domain was judged to be unclear. This judgement was based in part on an assessment of the extent to which funding by the sponsors may have had an impact on the results of a study; or if groups were treated unequally or; in some of the older studies, if there was an inadequate wash-out period before the start of the study. Eleven of the included studies were largely not free of other forms of bias. In some of these studies the investigators received financial compensation, or there was baseline imbalance between the groups, and in one study the investigator was the inventor of the formula used in the intervention.

**Effects of interventions**

Pooling of outcomes data across studies to provide a summary estimate of effect was only possible for two interventions and comparisons; these investigated the effects of topical metronidazole and topical azelaic acid against placebo. Data on the effects of some of the other interventions could not be presented graphically in RevMan, and therefore these have been reported together with relevant comments under each comparison in the Data and analyses section of the review.

A substantial number of the studies included in this review were categorised as 'unclear' or 'high' risk of bias (see and ) and therefore caution is advised in interpretation of their results and in the extrapolation of the effects of interventions.

We have addressed our prespecified outcomes under the following intervention headings

**Topical interventions - Studies with only topical metronidazole (comparisons 1 to 5)**

**Topical interventions - Studies with only topical azelaic acid (comparisons 6 to 8)**

**Topical interventions - Studies with topical metronidazole, azelaic acid, and/or other topical treatments (comparisons 9 to 22)**

**Systemic interventions - Studies with oral antibiotics (comparisons 23 to 30)**

**Systemic interventions - Studies with oral antibiotics combined with topical treatments (comparisons 31 to 33)**

**Systemic interventions - Studies with oral antibiotics compared with topical antibiotics (comparisons 34 to 35)**

**Studies with other systemic treatments (comparisons 36 to 39)**

**Other interventions - Studies with laser-/light-based treatment (comparisons 40 to 41)**

**Topical interventions - Studies with only topical metronidazole**

(1) **Topical metronidazole versus placebo**


**Primary outcomes**

**Quality of life:**

Not assessed.

**Participant-assessed changes in rosacea severity:**

Only three studies reported relevant data and although these could not be pooled for this outcome they provided some evidence that metronidazole was more effective than placebo.

In Bjerke 1989b 43 out of 50 participants in the metronidazole group considered themselves improved compared with 24 out of 47 in the placebo group (RR 1.68, 95% CI 1.25 to 2.28), and similarly in Nielsen 1983a 25 out of 41 (metronidazole group) versus 8 out of 40 (placebo) (RR 3.05, 95% CI 1.57 to 5.94).

A split-face within-patient design was used in Bleicher 1987, and therefore pooling of data with the other two studies was not possible. In this study the majority (28/37) of participants reported a greater improvement on the metronidazole-treated side than on the placebo side (4/37) (conditional OR 7.0, 95% CI 2.5 to 20.0).

**Secondary outcomes**

**Physician-assessed changes in rosacea severity:**
The pooled data from three studies (Bjerke 1989b; Breneman 1998; Nielsen 1983a) indicated an improvement in rosacea severity in the active intervention group which was largely in agreement with the participant-assessed outcomes for this comparison. Topical metronidazole was more effective than placebo and the results were both statistically significant and clinically important (RR 1.95, 95% CI 1.48 to 2.56). Heterogeneity between the studies was assessed as $I^2 = 44\%$. See Analysis 1.1.

Although a different rating scale (one to seven, worst = seven) was used in Bitar 1990, the results were not dissimilar to those in the other three studies. The mean change in severity in the metronidazole group was 2.80 (SD 1.41), and 3.30 (SD 1.41) in the placebo group with a mean difference (MD) of -0.50, (95% CI fixed -1.05 to +0.05). In the split-face study (Bleicher 1987) 29/37 participants were assessed as improved on the metronidazole-treated side, compared with 1/37 on the placebo side (conditional OR 29.0, 95% CI 4.0 to 212.9). See Analysis 1.4.

Lesion counts: In seven of the studies these outcomes were reported as continuous data but without the corresponding standard deviations (SD) and the data were skewed, i.e. not normally distributed. Although the data analysis in these studies was potentially flawed, it does nevertheless provide some supporting evidence of a positive treatment effect of metronidazole over placebo. See Analysis 1.4 (various outcomes).

Only one study assessed ocular rosacea (Barnhorst 1996) but the data as reported were unusable and not amenable to re-analysis. See Analysis 1.4.

Duration of remission: Only one trial (Dahl 1998) addressed this outcome, and demonstrated that continued treatment with metronidazole gel alone can maintain remission (initiated by tetracycline and topical metronidazole) of moderate to severe rosacea. See Analysis 1.4.

Dropouts:

Pooled data from six studies demonstrated that there was no significant difference in the number of dropouts across the intervention groups in these studies (RR 0.93, 95% CI 0.58 to 1.50). See Analysis 1.2.

Adverse events:

The number of participants in the metronidazole compared with the placebo group who experienced adverse events (RR 1.09, 95% CI 0.58 to 2.06) was not significantly different across the five studies and in most instances these adverse events were mild and consisted of pruritus, skin irritation, and dry skin. See Analysis 1.3.

The adverse events reported in the other studies are presented in Analysis 1.4.

(2) Metronidazole and sunscreen SPF 15 versus placebo

Only one study provided data for this comparison (Tan 2002).

Primary outcomes

Quality of life:

Not assessed.

Participant-assessed changes in rosacea severity:

Although the data for this outcome were presented as graph plots and were largely indiscernible, the investigators reported that there was a more noticeable improvement in rosacea severity in the metronidazole combined with SPF 15 group than in the placebo group ($P = 0.002$). See Analysis 2.1.

Secondary outcomes

Physician-assessed changes in rosacea severity:

The mean reduction in erythema at the end of the study, measured on a four-point scale (four = severe) was 0.89 (SD 0.6) in the treatment group and 0.58 (SD 0.1) in the placebo group ($P = 0.02$). However, the data were skewed and these have not been entered into a meta-analysis but reported separately. See Analysis 2.1.

Lesion counts: There was a reduction in the mean number of lesions, 13.6 (SD 15.2), in the active intervention group compared with placebo, 4.6 (SD 12.3) ($P = 0.006$). However the data were incomplete, skewed and inappropriately analysed. See Analysis 2.1.

Dropouts:

There were a large number of dropouts in both groups, 17/61 metronidazole compared with 14/59 in the placebo group, and these were excluded from the efficacy analysis (RR 1.17, 95% CI 0.64 to 2.16). The reasons for exclusion were voluntary withdrawal of one participant in the metronidazole group and two in the placebo group. Additional exclusions due to adverse events were one in the metronidazole group and three in the placebo group. Non-compliance with the study protocol occurred with six participants in the metronidazole and three in the placebo group, and nine participants used prohibited medication in the metronidazole compared with six in the placebo group.
Adverse events:
A small number of participants reported adverse events and these were similar in both groups: 1/61 in the metronidazole group and 3/59 in the placebo (RR 0.32, 95% CI 0.03 to 3.01). There was no statistically significant difference in local tolerance of the intervention between the two groups. See Analysis 2.1.

(3) Metronidazole 0.75% cream versus metronidazole 1% cream

Only one study compared these interventions and provided relevant outcomes data (Dahl 2001).

Primary outcomes
None of the primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity:
There was no statistically significant difference in these assessments between the two groups at the end of the study. Twenty of the 36 participants using the 0.75% metronidazole cream group were clear or nearly clear at the end of the study compared with 13 out of 36 in the 1% cream group (RR 1.54, 95% CI 0.91 to 2.60). The percentage change in the total erythema severity score from baseline to endpoint was comparable (range 25% to 30%) and not statistically significantly different between the two groups. See Analysis 3.1.

Lesion counts: The overall reductions in lesion counts (± 60%) were similar in both groups at the end of the study. See Analysis 3.1.

Dropouts:
There was no statistically significant difference in the number of participants who dropped out in each of the treatment groups (RR 0.57, 95% CI 0.18 to 1.78).

Adverse events:
Adverse events were mild and comparable in both groups (RR 0.93, 95% CI 0.53 to 1.64).

(4) Metronidazole 0.75% gel versus metronidazole 0.75% lotion

A single study compared these interventions (Guillet 1999). Neither of our primary outcomes were reported, but physician-assessed changes demonstrated a similar improvement in rosacea severity of between 55% to 60%, and a reduction in lesion counts by more than 70% in both groups. See Analysis 4.1.

(5) Metronidazole 0.75% cream versus 0.75% gel

The investigators in the single study which compared these two interventions were unable to provide any additional data over and above what had been reported (Dreno 1998). None of our primary outcomes were assessed but the secondary outcome 'physician's global evaluation' was rated as good to excellent in 75% of the participants for both formulations, and the reduction in lesion count was similar (60%) in both the cream and gel groups. See Analysis 5.1.

Topical interventions - Studies with only topical azelaic acid

(6) Azelaic acid versus placebo

This comparison was evaluated by four trials (Bjerke 1999; Carmichael 1993; Thiboutot 2003a; Thiboutot 2003b).

Primary outcomes

Quality of life:
Not assessed.

Participant-assessed changes in rosacea severity:
Three studies provided evidence for the effectiveness of azelaic acid over placebo. Pooled outcomes data from these studies indicated an improvement in rosacea severity and that the rates of complete remission or marked improvement, as assessed by the participants, were 70% to 80% in the azelaic acid group as compared with 50% to 55% in the placebo group (RR 1.52, 95% CI 1.32 to 1.76). Heterogeneity between the studies was assessed as I² = 0%. See Analysis 6.1.

Secondary outcomes
Physician-assessed changes in rosacea severity:

Data for these assessments from three studies illustrated that azelaic acid was more effective than placebo. The rates of complete remission or marked improvement were 60% in the azelaic acid and 40% in the placebo group in both the Thiboutot 2003a and Thiboutot 2003b studies, and correspondingly 80% and 60% in Bjerke 1999 (RR 1.36, 95% CI 1.21 to 1.53). Heterogeneity between the studies was assessed as $I^2 = 0\%$. See Analysis 6.2.

In the single within-patient study (Carmichael 1993), 16/33 of the participants showed an improvement in VAS-score on the azelaic acid-treated side compared with 1/33 on the placebo-treated side. See Analysis 6.5. There was no difference in the assessments between the active treatment and placebo sides in the remaining 16 participants. There was an overall improvement, with complete remission or marked improvement in 30/33 sides treated with azelaic acid compared with 11/33 sides treated with placebo. See Analysis 6.5.

Lesion counts: No standard deviations were reported for these outcomes in Carmichael 1993 and the data were skewed. See Analysis 6.5.

Dropouts:

No dropouts were reported in the Carmichael 1993 study. The pooled results of the other three studies showed no statistically significant difference in the number of dropouts, which were 13.4% in the azelaic acid group compared with 10% in the placebo group (RR 1.46, 95% CI 0.98 to 2.17). See Analysis 6.3. Discontinuation with treatment in the active treatment group was largely as a result of adverse events, whereas in the placebo group lack of effect was the chief reason for dropouts.

Adverse events:

Based on the pooled data from three studies there was no statistically significant difference in the number of adverse events reported by the participants in the azelaic acid group (11%) compared with 5% in the placebo group (RR 1.42, 95% CI 0.92 to 2.19). See Analysis 6.4. In the Carmichael 1993 study, 24/33 participants in the azelaic acid group versus 19/33 in the placebo group reported adverse events. These were considered to be transient and of mild to moderate intensity with burning, stinging, or irritation being the most commonly reported.

(7) Azelaic acid 15% gel once daily versus azelaic acid 15% gel twice daily

A single study compared the safety and effectiveness of azelaic acid 15% gel applied once daily versus twice daily (Thiboutot 2008). No statistically significant differences were reported in any of the efficacy endpoints between the two regimens.

Primary outcomes

None of the primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity:

There was no statistically significant difference between the two treatment regimens; 20 of the 35 participants in the single daily application improved versus 22 of 37 in the twice daily group (RR 0.96, 95% CI 0.65 to 1.42). Treatment success, defined as clear or minimal lesions, was achieved in 13 of 35 in the once-daily, versus 15 of 37 in the twice-daily group (RR 0.92, 95% CI 0.51 to 1.64).

Dropouts:

There were similar numbers (2) of dropouts in both groups (RR 1.06, 95% CI 0.16 to 7.10).

Adverse events:

The number of participants experiencing adverse events was comparable in both groups, i.e. 18 of 45 participants in the once-daily group versus 17 of 47 in the twice-daily group (RR 1.11, 95% CI 0.66 to 1.86). Further data which cannot be presented graphically is reported in Analysis 7.1.

(8) Azelaic acid 15% gel twice daily as maintenance therapy versus vehicle twice daily

Thiboutot 2009 was a two-phase study in which participants, demonstrating a level of treatment effectiveness at week 12, were randomised to receive either azelaic acid gel or its vehicle twice daily as maintenance therapy. We have only included data from the maintenance phase of this study.

Primary outcomes

None of the primary outcomes were assessed.

Secondary outcomes
Physician-assessed changes in rosacea severity:

Success, as determined by an investigator-based global assessment and defined as clear, minimal or mild, was reported for 39 out of 51 participants in the azelaic acid group and for 31 out of 53 in the vehicle-only group (RR 1.30, 95% CI 0.93 to 1.80). There was no statistically significant difference between the groups for this outcome. Cosmetic acceptability was rated good or very good by 56 of the 67 participants in the azelaic acid group and by 53 of the 69 participants in the vehicle group (RR 1.09, 95% CI 0.92 to 1.29). See Analysis 8.1.

Seventeen out of the 67 participants in the azelaic acid group relapsed compared with 24 of 69 in the vehicle-only group (RR 0.73, 95% CI 0.43 to 1.23), with no statistically significant difference between the two groups.

Dropouts:

There were identical numbers of dropouts (7) in both groups (RR 1.03, 95% CI 0.38 to 2.78).

Adverse events:

Adverse events were reported in 22 of the 67 participants using azelaic acid and in 20 of 69 in the vehicle-only group (RR 1.13, 95% CI 0.68 to 1.87).

Topical interventions - Studies with topical metronidazole, azelaic acid, and/or other topical treatments

(9) Topical azelaic acid versus topical metronidazole

Three studies provided data for this comparison: Elewski 2003, Wolf 2006, and Maddin 1999 (which had a within-patient study design, therefore pooling of data with the other two studies was not possible).

Primary outcomes

Quality of life:

Not assessed.

Participant-assessed changes in rosacea severity:

In two of the studies there was no statistically significant difference between the treatment groups for this outcome. In the Elewski 2003 study 50/124 participants in the azelaic acid gel group considered themselves improved versus 43/127 in the metronidazole gel group (RR 1.19, 95% CI 0.68 to 1.65), and in the Wolf 2006 study 75 out of 82 versus 65 of 82 respectively (RR 0.92, 95% CI 0.77 to 1.10). Cosmetic acceptability was assessed as 75% in the azelaic acid gel group versus 82% for the metronidazole gel. See Analysis 9.1.

In the Maddin 1999 study participants considered the 20% azelaic acid cream more effective than the metronidazole 0.75% cream. Severity was rated on a five-point scale (four = worse), the mean score on the azelaic acid-treated side was 1.87 (SD 0.76) compared with 2.33 (SD 0.95) on the metronidazole-treated side (P = 0.02). A majority of participants (92%) said they would use topical azelaic acid gel again compared to 66% for metronidazole gel.

Secondary outcomes

Physician-assessed changes in rosacea severity:

The physician-based assessments appeared to indicate a greater satisfaction with the outcomes by the physicians when compared with the self-assessments made by the participants. Thus, in contrast with the participants' assessments, the physicians in the Elewski 2003 study considered the azelaic acid group significantly more improved than the metronidazole group. In the azelaic acid group 86/124 participants were considered to be improved versus 70/127 in the placebo group (RR 1.26, 95% CI 1.03 to 1.53).

In the Wolf 2006 study 44 out of the 78 participants in the azelaic acid group were considered to be cleared or nearly cleared versus 44 of the 82 in the metronidazole group, with no statistically significant difference between the groups (RR 1.05, 95% CI 0.79 to 1.39). The investigators in the Maddin 1999 study scored Global Improvement in severity of rosacea as one equals complete clearance to six equals exacerbation. At 15 weeks the score for the azelaic acid-treated side was 2.7 (SD 1.0) compared with 3.1 (SD 1.0) on the metronidazole-treated side (P = 0.05), demonstrating limited superiority of azelaic acid over metronidazole.

Lesion counts: The decrease in inflammatory lesion counts reported in Elewski 2003 were 12.9 in the azelaic acid group versus 10.7 in the metronidazole group. In Maddin 1999 the decrease in lesion count was expressed as a percentage, which was 78.5% in the azelaic acid group versus 69.4% in the metronidazole group. In Wolf 2006 this was reported as 80% versus 77% respectively. See Analysis 9.1.

Dropouts:

Elewski 2003 reported 14/124 dropouts in the azelaic acid versus 8/127 in the metronidazole group (RR 1.79, 95% CI 0.78 to 4.12), and 10 out of 78 versus 14 of 82 respectively in Wolf 2006 (RR 0.75, 95% CI 0.35 to 1.59) dropped out or were lost to follow up and these losses were not statistically significant. Three participants dropped out in the Maddin 1999 study, one due to an adverse event not related to treatment and two discontinued for personal
reasons. In Elewski 2003 5 of 14 participants in the azelaic acid group discontinued due to adverse events compared with no dropouts in the metronidazole group, whilst a variety of reasons accounted for the remainder these were comparable across the groups.

The most common reasons for dropouts in Wolf 2006 were protocol violation, a request to discontinue treatment, over and above those participants who were simply lost to follow-up.

**Adverse events:**

The number of participants in Elewski 2003 experiencing adverse events was higher and statistically significant in the azelaic acid group, with 32 of 124 as compared to 9 of 127 in the metronidazole group (RR 3.64, 95% CI 1.81 to 7.31). There was no statistically significant difference in adverse events between the groups in Wolf 2006; 29 of 78 versus 41 of 82 (RR 0.74, 95% CI 0.52 to 1.07). The adverse events reported in both Elewski 2003 and Wolf 2006 were mild to moderate and mostly transient, with skin dryness, scaling, stinging, and burning being the most frequent. In Maddin 1999 only one participant reported an adverse event, i.e. stinging, on the side of the face which had been treated with azelaic acid cream.

(10) Azelaic acid 20% versus metronidazole 0.75% versus permethrin 5%

Only one study compared these interventions (Mostafa 2009).

**Primary outcomes**

None of the primary outcomes were assessed.

**Secondary outcomes**

Azelaic acid 20%, metronidazole 0.75%, and permethrin 5% all appeared to demonstrate effectiveness for erythema and in reducing lesion counts. However, the investigators conclusions were based on the analysis of skewed data. Recurrence of inflammatory lesions was also addressed at the six-month follow-up. See Analysis 10.1.

(11) Topical permethrin versus topical metronidazole

One study (Koçak 2002) reported data for this comparison.

**Primary outcomes**

None of the primary outcomes were assessed.

**Secondary outcomes**

**Physician-assessed changes in rosacea severity:**

The mean change in erythema score (scale 0 to 3, 3 = severe) from baseline to day 60 was 1.30 (SD 0.76) in the permethrin group versus 1.45 (SD 0.69, P = 0.66) in the metronidazole 0.75% group. Neither treatment was shown to be more effective than the other for rhinophyma or telangiectasia.

Lesion counts: The mean difference in number of papules was 4.30 (SD 5.51) in the permethrin group versus 5.10 (SD 5.44, P = 0.13) in the metronidazole group. The mean difference in pustules was 1.78 (SD 3.74) for the permethrin group, and 3.5 (SD 3.55, P = 0.029) in the metronidazole group.

Most of the data that were reported were skewed, but the authors concluded that permethrin 5% cream showed comparable effectiveness to metronidazole on both erythema and papules, but indicated this did not apply to pustules.

**Dropouts:**

No dropouts were reported.

**Adverse events:**

No adverse events were reported in either intervention group. Additional data are reported in Analysis 11.1.

(12) Benzoyl peroxide acetone versus placebo

Only one study provided data for this comparison (Montes 1983), but complete data were only reported for the first four weeks.

**Primary outcomes**

None of the primary outcomes were assessed.
Secondary outcomes

Physician-assessed changes in rosacea severity:

At four weeks 19/31 (benzoyl peroxide 5%) and 9/27 (placebo) participants were considered improved (RR 1.84, 95% CI 1.01 to 3.36). Based on these assessments benzoyl peroxide appeared to be nearly twice as effective as placebo. The overall response score, rated on a scale of zero to four (four = worst), was 2.69 (benzoyl peroxide) versus 3.71 (placebo).

Lesion counts: These were rated on a scale of zero to three (three = worst) and the improvement in scores appeared to favour benzoyl peroxide. The papule scores were 0.89 (benzoyl peroxide) compared with 1.91 (placebo), and pustules scores of 0.46 (benzoyl peroxide) versus 1.31 in the placebo group (P < 0.05). See Analysis 12.1.

Dropouts:

There was no statistically significant difference in the number of dropouts between the groups. In the benzoyl peroxide-treated group 2/31 participants dropped out, versus 4/27 in the placebo group (RR 0.44, 95% CI 0.09 to 2.19).

Adverse events:

There was also no statistically significant difference between the two groups in the number of participants reporting adverse events: 26/31 in the benzoyl peroxide group versus 18/27 in the placebo group (RR 1.26, 95% CI 0.92 to 1.71). Irritation and burning were the most frequently reported side-effects in both groups. The rate of adverse events was high in both groups, which the authors indicated could be attributed to the vehicle, in that the benzoyl peroxide gel may have a greater dehydrating effect than the newer aqueous gels.

(13) Benzoyl peroxide 5% with clindamycin 1% gel versus placebo

Two studies (Breneman 2004; Leyden 2004 - see the reference under Breneman 2004) reported different outcome measures for the same study and, therefore, the outcomes in Leyden 2004 are discussed jointly with those in Breneman 2004. In the first of these studies both participant and physician assessments were reported and the second study described a photographic comparison.

Primary outcomes

Quality of life:

Not assessed.

Participant-assessed changes in rosacea severity:

The mean scores, rated as one to four (four = worst), at the end of the study were 1.54 in the benzoyl peroxide with clindamycin group versus 2.50 in the placebo group. See Analysis 13.1.

Secondary outcomes

Physician-assessed changes in rosacea severity:

The mean scores, rated zero to five (five = worst), at the end of the study were 1.85 - which was equivalent to a marked improvement in the active treatment group - versus 2.96, indicating minimal improvement in the placebo group. See Analysis 13.1. In the benzoyl peroxide with clindamycin group 6 of the 27 participants compared with 1/26 in the placebo group were considered to have a marked improvement which extended up to complete clearance (RR 5.78, CI 95% 0.75 to 44.76).

Global photographic improvement was assessed on a seven-point scale (−2 to +4, four = best) in Leyden 2004. The investigators reported a mean Global photographic comparison rating of 1.6 (SD 1.04) in the active intervention group versus 0.7 (SD 1.02) in the placebo group (P value < 0.001 author reported). Although the standard deviations were not reported these were estimated from the graph plots.

Lesion counts: The reduction in lesion counts in the treatment group was 71.3% (SD 25.3) versus 19.3% (SD 89.6) in the placebo group (Breneman 2004). Papule counts decreased from 15.6 (SD 7.8) to 3.9 (SD 3.6) in the benzoyl peroxide with clindamycin group, versus a decrease from 16.8 (SD 10) to 13.4 (SD 14.6) in the placebo group, and the pustule counts decreased from 2.5 (SD 3.8) to 0.8 (SD 2.4) versus from 2.5 (SD 4.0) to 2.0 (SD 4.5) respectively. The investigators in this study also concluded that a treatment effect, i.e. a reduction in the number of lesions, was demonstrated in the benzoyl peroxide and clindamycin group, which we were unable to confirm because the data as reported were skewed.

Dropouts:

The dropout rate in Breneman 2004 was comparable for both groups, which was 3/27 in the treatment group versus 2/26 in the placebo group (RR 1.44, CI 95% 0.26 to 7.96).
Adverse events:

There was no statistically significant difference in the number of participants between the groups reporting adverse events. There were 7 out of 27 participants in the benzoyl peroxide with clindamycin group who reported adverse events, versus 4/26 in the placebo group (RR 1.69, 95% CI 0.56 to 5.08). Treatment-related adverse events included localised burning and itching, which are both well known side-effects of benzoyl peroxide.

(14) Sodium sulphacetamide 10% and sulphur 5% versus placebo

Only one study evaluated these interventions but the overall reporting quality was inadequate: the number of participants in each treatment arm was not reported, improvement as an outcome was ill-defined, and the data reported as continuous outcomes were skewed and largely unusable (Sauder 1997). This study was categorised as at 'high risk of bias'. For further details see the 'risk of bias' tables in 'Characteristics of included studies'.

Primary outcomes

Quality of life:

Not assessed.

Participant-assessed changes in rosacea severity:

A larger percentage of participants (90%) in the active treatment group considered themselves improved as compared with the placebo group (58%). See Analysis 14.1.

Secondary outcomes

Physician-assessed changes in rosacea severity:

Based on these assessments, 98% in the active treatment group versus 68% of the participants in the placebo group demonstrated an improvement, and the mean lesion count reductions were reported as 78% versus 36% respectively. See Analysis 14.1 for further details.

Dropouts:

Although it was unclear how many participants in each group were entered into the study, two participants in the treatment group withdrew prematurely due to adverse events, versus one in the placebo group which was due to localised burning and pruritus.

Adverse events:

Adverse events were reported as 38% in the active versus 29% in the placebo group. Application site reactions such as dryness, erythema, and pruritus were the most commonly reported adverse events.

(15) Sodium sulphacetamide 10% and sulphur 5% versus metronidazole 0.75%

Two studies which we assessed as 'uncertain to high risk of bias' reported data this comparison (Lebwohl 1995; Torok 2005).

Primary outcomes

None of the primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity:

These assessments indicated that there was some evidence that sodium sulphacetamide 10% with sulphur 5% was more effective than metronidazole 0.75% gel. In Torok 2005 59 of the 75 participants were considered to be improved in the sulphacetamide plus sulphur group versus 45 of the 77 in the metronidazole gel group (RR 1.35, 95% CI 1.08 to 1.68). Further data for Lebwohl 1995 are reported in Analysis 15.1.

Lesion counts: There was no statistically significant difference in decrease of papule count (MD -1.10, 95% CI -3.19 to 0.99) for these interventions in Lebwohl 1995. However, there was a statistically significant difference in decrease in the pustule count in favour of sodium sulphacetamide plus sulphur (MD -1.90, 95% CI -3.01 to -0.79). Data for lesion counts in Torok 2005 are reported in Analysis 15.1.

Dropouts:

Whilst the dropout rates might appear to be higher in the sodium sulphacetamide plus sulphur group compared to the placebo group, 5 of 31 versus 1 of 32 for Lebwohl 1995, this is unsupported by the wide confidence intervals (RR 5.16, 95% CI 0.64 to 41.71). In contrast, in the Torok 2005 study there were more than twice as many dropouts.
in the sulphacetamide plus sulphur group (10 of 75) than in the metronidazole group (4 of 77) (RR 2.57, 95% CI 0.84 to 7.83).

**Adverse events:**

Fewer participants experienced adverse events in the metronidazole group but the difference between groups was not statistically significant. In *Lebwohl 1995* 5 out of 31 versus 3 out of 32 (RR 1.72, 95% CI 0.45 to 6.59), and in *Torok 2005* 48 of 75 versus 41 of 77 (RR 1.20, 95% CI 0.92 to 1.57) reported adverse events.

**16) Pimecrolimus 1% versus placebo**

Twice daily applications of pimecrolimus 1% were compared with placebo (vehicle) in *Weissenbacher 2007*.

**Primary outcomes**

**Quality of life:**

The "quality of life impairment" (Dermatology Life Quality Index, score 0 to 30, higher score = more impairment) showed a reduction of the mean absolute value from 5.50 to 3.10 for the pimecrolimus group versus of 6.70 to 3.70 for the vehicle group (authors state P = 0.75).

**Participant-assessed changes in rosacea severity:**

The subjective severity score (visual analogue scale, 0 to 100 mm, higher = worse) indicated an improvement of mean absolute value from 53.45 to 48.95 for the pimecrolimus group and from 64.75 to 43.35 for the vehicle group (author reported value P = 0.48).

Although the data reported in this study were sparse, no statistically significant differences in efficacy could be demonstrated between treatment arms for any of the outcomes. See for other outcomes Analysis 16.1.

**17) Metronidazole 1% cream versus pimecrolimus cream**

One study compared these interventions (*Koca 2010*) but there was an appreciable baseline imbalance at enrolment, i.e. an increased duration and severity of disease in the pimecrolimus arm as compared with the metronidazole arm. The conclusions reached by the investigators did not appear to plausibly reflect the data that were reported. See Analysis 17.1.

**Primary outcomes**

None of the primary outcomes were assessed.

**Secondary outcomes**

**Physician-assessed changes in rosacea severity:**

There was no statistically significant difference in global improvement between the two groups. In the metronidazole group all (25/25) of the participants showed a measure of improvement as compared with 22 out of 25 participants in the pimecrolimus group (RR 1.13, 95% CI 0.96 to 1.33). See Analysis 17.1.

**Dropouts:**

Only one participant dropped out in the pimecrolimus group and there were no losses to follow up in the metronidazole group (RR 0.35, 95% CI 0.01 to 8.12).

**Adverse events:**

Very few of the participants in either of the groups reported experiencing any adverse events (RR 2.08, 95% CI 0.42 to 10.34).

**18) Erythromycin 2% gel versus metronidazole 0.75% gel**

Only one study compared these two interventions (*Verea Hernando 1992*). Baseline imbalance in severity of the disease at enrolment placed the study at a serious risk of bias.

**Primary outcomes**

**Quality of life:**

Not assessed.

**Participant-assessed changes in rosacea severity:**
There was no statistically significant difference between the two groups for this outcome; 16 of the 22 participants considered themselves improved with erythromycin gel versus 17 of 18 in the metronidazole gel group (RR 0.77, 95% CI 0.58 to 1.02).

**Secondary outcomes**

**Physician-assessed changes in rosacea severity:**

The physicians' assessments were largely in agreement with the participants' assessments (RR 0.77, 95% CI 0.58 to 1.02).

Lesion counts: Baseline imbalance with respect to the number of papules and pustules placed the study at a serious risk of bias. See Analysis 18.1.

**Dropouts:**

There were proportionately more dropouts in the erythromycin group, 5 of 22 participants compared with 1 of 18 in the metronidazole group (RR 4.09, 95% CI 0.52 to 31.93).

**Adverse events:**

These were inadequately reported and we have not included them in this review.

(19) **Topical cyclosporine ophthalmic emulsion 0.05% versus artificial tears for the treatment of ocular rosacea**

One study examined this comparison (Schechter 2009).

**Primary outcomes**

**Quality of life:**

Assessment of changes in Quality of life were carried out with the Ocular Surface Disease Index (OSDI) (scale 0 to 100, 100 = worst). Baseline scores were 19.1 (SD 13.9) in the topical cyclosporine group and 16.9 (SD 15.8) in the artificial tears group. The difference between the change scores at completion of the study was 8.6 in favour of topical cyclosporine (P = 0.022, 95% CI 1.78 to 15.42), which equates to a moderate improvement in quality of life.

**Participant-assessed changes in rosacea severity:**

Not assessed.

**Secondary outcomes**

**Physician-assessed changes in rosacea severity:**

The data from these assessments provide evidence for the effectiveness of topical cyclosporine in the treatment of ocular rosacea. At baseline the mean Schirmer scores were 9.7 mm (SD 5.1) in the cyclosporine group compared with 10.2 mm (SD 5.8) in the artificial tears group. The difference in change scores between the groups at the end of the study was 4.1 (P = 0.001, 95% CI 1.66 to 6.54), which points to a significant improvement in the cyclosporine group. Furthermore, the change score of 3.6 in the tear break-up time (P < 0.001, 95% CI 2.59 to 4.61) provides an indication of the role played by topical cyclosporine in increasing tear production. This is also supported by a difference between the groups in corneal staining of -1.1 (P < 0.012, 95% CI -1.57 to -0.63) and in the number of unoccluded expressible meibomian glands of 2.69 (P < 0.001, 95% CI 1.33 to 4.05) due to a reduction in inflammation attributed to cyclosporine. For other data see Analysis 19.1 (various outcomes).

**Dropouts:**

Two participants out of 21 in the topical cyclosporine group dropped out compared with 1 out of 16 in the artificial tears group (RR 1.52, 95% CI 0.15 to 15.36).

**Adverse events:**

Only one participant in the topical cyclosporine group reported an adverse event, which consisted of stinging (RR 2.32, 95% CI 0.10 to 53.42).

(20) **4-Ethoxybenzaldehyde 1% versus placebo**

The anti-inflammatory effect of this intervention in reducing facial erythema was evaluated in only one study (Draelos 2005b).

**Primary outcomes**
Secondary outcomes

Physician-assessed changes in rosacea severity:

These assessments illustrated significant improvements which had occurred in the active intervention group for; erythema ($P < 0.01$); desquamation ($P < 0.05$); uneven skin tone ($P < 0.01$); and overall severity ($P < 0.01$); but not in any of the measured outcomes in the vehicle treated group. However, the differences between groups were only statistically significant for uneven skin tone and overall severity ($P < 0.05$). See Analysis 20.1.

Dropouts:

Two dropouts were reported but it was unclear from which group and for what reasons.

Adverse events:

There were no adverse events reported in either group.

(21) Assessment of adjunctive benefits of PHA skin regimen in combination with azelaic acid 15% gel versus non standardised skin care and azelaic acid 15% gel

A single study, albeit inadequately reported, compared these interventions (Draelos 2006). It was unclear how many participants were randomised to each intervention and because very limited outcomes data were reported no reliable conclusions could be drawn. See Analysis 21.1 (various outcomes).

(22) Cream containing 1% extract of a flavonoid-rich plant-Chrysanthellum indicum versus placebo

One trial (Rigopoulos 2005) reported data for this comparison.

Primary outcomes

Quality of life:

Not assessed.

Participant-assessed changes in rosacea severity:

A large number of participants in both the active intervention and placebo cream groups reported improvement in rosacea severity, 98 of 125 participants with the flavonoid cream and 92 of 121 in the placebo arm (RR 1.03, 95% CI 0.90 to 1.18).

Secondary outcomes

Physician-assessed changes in rosacea severity:

Based on these assessments which were comparable to the participant-assessed outcomes, 68 of 125 participants in the active treatment group showed improvement versus 54 out of 121 in the placebo group (RR 1.22, 95% CI 0.94 to 1.57). The difference in mean change in rosacea severity score (scale 0 to 3.5, higher = worse) from baseline showed a reduction of 0.34 and favoured the flavonoid-rich cream (fixed 95% CI 0.18 to 0.50).

Dropouts:

There was no statistically significant difference between the groups in the number of dropouts, such that there were 11 dropouts from 125 in the treatment group compared with 6 of 121 in the placebo group (RR 1.77, 95% CI 0.68 to 4.65).

Adverse events:

There was also no statistically significant difference in the number of participants experiencing adverse events; 13 of the 125 in the flavonoid cream group experienced adverse events and 8 out of 121 in the placebo group (RR 1.57, 95% CI 0.68 to 3.66).

Systemic interventions - Studies with oral antibiotics

(23) Tetracycline versus placebo

Two trials were included (Marks 1971; Sneddon 1966).

Primary outcomes

Quality of life:
Participant-assessed changes in rosacea severity:

Only one of the studies provided data for this outcome (Marks 1971). Based on these participant-assessed outcomes there was insufficient evidence to demonstrate that tetracycline was more effective than placebo (14/20 in the tetracycline group versus 9/19 in the placebo group) (RR 1.48, 95% CI 0.85 to 2.57).

Secondary outcomes

Physician-assessed changes in rosacea severity:

In contrast with the participant-assessed changes these assessments indicated that tetracyclines appeared to be significantly more effective than placebo in the treatment of rosacea. In the Marks 1971 study 17 out of 20 participants in the tetracycline group were considered to be improved versus 4 of 19 in the placebo group (RR 4.04, 95% CI 1.66 to 9.83). In Sneddon 1966 28 of 36 participants in the tetracycline group improved versus 19 of 42 in placebo (RR 1.72, 95% CI 1.18 to 2.50). For other data (various outcomes) see Analysis 23.1.

Dropouts:

The reporting of dropouts was unclear in both studies, and although Sneddon 1966 indicated seven participants had dropped out they did not clarify from which group.

Adverse events:

Marks 1971 reported one adverse event in each group, diarrhoea in the tetracycline group and the other was unspecified. Data on adverse events were not clearly reported in Sneddon 1966.

(24) Anti-inflammatory dose doxycycline 40 mg versus placebo

Study duration in Del Rosso 2007a and Del Rosso 2007b was 16 weeks, but in Del Rosso 2007b the participants were re-evaluated at 20 weeks and therefore only the data from the 16 week-assessment was analysed for this review.

Primary outcomes

None of the primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity:

The data from the Investigator’s Global Assessment (IGA) in Del Rosso 2007a indicated that doxycycline 40 mg was more effective than placebo. Fifty-eight participants out of the 127 in the doxycycline 40 mg group achieved a two-point or greater improvement in IGA score compared with 32 out of 124 in the placebo group (RR 1.77, 95% CI 1.24 to 2.52). Thirty-nine participants in the doxycycline group achieved an IGA score of 0 (clear) or 1 (near clear) versus 24 in the placebo group (RR 1.59, 95% CI 1.02 to 2.47).

In Del Rosso 2007b there was no statistically significant difference in IGA; 32 participants of the 142 in the doxycycline 40 mg group had achieved a two-point or greater improvement in IGA score compared with 23 of 144 in the placebo group (RR 1.41, 95% CI 0.87 to 2.29). However, more than twice as many participants achieved an IGA score of 0 (clear) or 1 (near clear) in the doxycycline group; 21 participants in the doxycycline group achieved an IGA score of 0 or 1 versus 9 in the placebo group (RR 2.37, 95% CI 1.12 to 4.99). For other data see Analysis 24.1 (various outcomes).

Lesion counts: The weighted mean difference between the groups for the change in inflammatory lesions from baseline was -5.9 (95% CI fixed -9.37 to -2.43) in Del Rosso 2007a and -5.20 (95% CI fixed -8.27 to -2.13) for Del Rosso 2007b, and which was statistically significant and in favour of doxycycline 40 mg.

Time needed to improvement: The data were presented in the reports as graph plots which did not permit accurate data to be extracted. However the steepest changes in the graph plots occurred within the first three weeks in the doxycycline group which provided an indication of the time needed to improvement of inflammatory lesions relative to placebo.

Dropouts:

The dropout rate was comparable between both groups in each of the studies. In Del Rosso 2007a 26 of 127 in the doxycycline 40 mg group versus 21 of 124 in the placebo group (RR 1.21, 95% CI 0.72 to 2.03). In Del Rosso 2007b 27 of 142 in the doxycycline group dropped out versus 26 of 144 (RR 1.05, 95% CI 0.65 to 1.71) in the placebo group.

Adverse events:

The number of participants reporting adverse events was 56 in the doxycycline group versus 48 in the placebo...
group (RR 1.14, 95% CI 0.85 to 1.53) in Del Rosso 2007a, and 93 versus 74 respectively in Del Rosso 2007b (RR 1.27, 95% CI 1.04 to 1.55).

(25) Anti-inflammatory dose doxycycline 40 mg versus doxycycline 100 mg

Only one study evaluated these interventions (Del Rosso 2008).

Primary outcomes

None of the primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity:

These assessments indicated that there was no evidence of a difference in efficacy between the two doses for this outcome. See Analysis 25.1 (various outcomes).

Adverse events:

Four times as many adverse events were reported in the higher dose group compared with the 40 mg dose group. Six of the 44 participants treated with the anti-inflammatory dose of 40 mg had adverse events versus 26 of 47 participants in the 100 mg group (RR 0.25, 95% CI 0.11 to 0.54). The majority of these adverse events were gastrointestinal complaints.

(26) Clarithromycin and omeprazole versus placebo in Helicobacter pylori positive patients with rosacea

The data from the Bamford 1999 study were skewed, had large SDs, and were considered to be unusable (see Analysis 26.1). There were 22 participants in the clarithromycin/omeprazole group and 22 in the placebo group.

Primary outcomes

None of the primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity:

Mean pustule counts were 6.2 (SD 8.3) in the treatment group versus 12.6 (SD 19.3) in the placebo group (P = 0.18).

Dropouts:

Two participants dropped out in the treatment group compared with none in the control group (RR 5.00, 95% CI 0.25 to 98.52).

Adverse events:

One participant in the treatment group reported headaches during treatment, but no adverse events were reported in the placebo group (RR 3.00, 95% CI 0.13 to 69.87).

(27) Azithromycin versus doxycycline

Only one study addressed this comparison (Akhyani 2008).

Primary outcomes

Quality of life:

Not assessed.

Participant-assessed changes in rosacea severity:

Although there was no measurable difference in change in severity between the two treatment groups, 29 out of 37 in the azithromycin group considered themselves improved versus 24 of 30 in the doxycycline group (RR 0.98, 95% CI 0.77 to 1.25).

Secondary outcomes

Physician-assessed changes in rosacea severity:
Lesion counts: The lesion counts were 19.24 ± 9.67 at baseline in the azithromycin group and 1.90 ± 3.28 at 3 months, and similarly in the doxycycline group 18.86 ± 8.95 and 2.34 ± 3.47 at 3 months. See Analysis 27.1 (various outcomes). However, in addition to having large SDs these data were skewed.

Dropouts:

Five out of 37 participants in the azithromycin group dropped out compared with 4 of 30 in the doxycycline group (RR 1.01, 95% CI 0.30 to 3.44).

Adverse events:

Diarrhoea was reported in 4 of the 37 participants in the azithromycin group, and 2 out of 30 in the doxycycline group experienced epigastric burning (RR 1.62, 95% CI 0.32 to 8.26).

(28) Ampicillin versus placebo

One study provided data for this comparison (Marks 1971).

Primary outcomes

Quality of life:

Not assessed.

Participant-assessed changes in rosacea severity:

These assessments demonstrated significant improvements which were in favour of ampicillin over placebo, such that 14 out of 17 participants treated with ampicillin versus 9/19 in the placebo group (RR 1.74, 95% CI 1.03 to 2.93) considered themselves improved.

Secondary outcomes

Physician-assessed changes in rosacea severity:

These were generally in-line with the participant-assessed changes but there was no statistically significant difference between the groups. Nine of 17 participants treated with ampicillin reported improvement compared with 4/19 in the placebo group (RR 2.51, 95% CI 0.94 to 6.70).

Lesion counts: End of study lesion counts were reported as 9.53 (SD 8.79) in the ampicillin group versus 16.63 (SD 12.81) in the placebo group, but these had large SDs and skewed data.

Dropouts:

These were not clearly reported.

Adverse events:

Participants in the ampicillin group were at least three times more likely to develop adverse events than those in the placebo group. Three of the 17 participants treated with ampicillin reported adverse events versus 1/19 in the placebo group (RR 3.35, 95% CI 0.38 to 29.26). The adverse events were mild and transient, and one participant in the ampicillin group experienced diarrhoea.

29) Oral tetracycline versus ampicillin

Only one study provided data for this comparison (Marks 1971).

Primary outcomes

Quality of life:

Not assessed.

Participant-assessed changes in rosacea severity:

These assessments did not indicate any difference in efficacy between the two interventions; 14 of 20 participants treated with tetracycline considered themselves improved versus 14 of 17 in the ampicillin group (RR 0.85, 95% CI 0.59 to 1.22).

Secondary outcomes
Physician-assessed changes in rosacea severity:

These were in-line with the participant-assessed changes, 17 of 20 in the tetracycline group reported they had improved versus 9/17 in the ampicillin group (RR 1.61, 95% CI 0.99 to 2.61).

Lesion counts: End of study lesion counts were 4.60 (SD 6.20) in the tetracycline group versus 9.53 (8.79) in the ampicillin group, with large standard deviations and skewed data.

Dropouts:

These were not clearly reported in the study.

Adverse events:

Most side-effects were mild and transient, 3/17 participants in the ampicillin group reported adverse events compared with 1/20 in the tetracycline group (RR 0.28, 95% CI 0.03 to 2.48).

(30) Oral metronidazole versus oral oxytetracycline

Only one study provided data for this comparison (Saihan 1980).

Primary outcomes

Quality of life:

Not assessed.

Participant-assessed changes in rosacea severity:

These were combined with the physician assessments and reported as unified scores.

Secondary outcomes

Physician-assessed changes in rosacea severity:

The combined scores of participants and physicians demonstrated that there was no statistically significant difference between the two groups in rosacea severity at the completion of the study. The mean severity scores (scale -1 to 3, 3 = much improved) were 2.30 (SD 1.00) in the metronidazole group versus 2.60 (SD 0.70) in the tetracycline group, -0.30 (95% CI -0.83 to +0.23). See Analysis 30.1.

Dropouts:

Two participants in the metronidazole group failed to attend for follow-up (RR 5.0, 95% CI 0.26 to 98.00).

Adverse events:

No adverse events were reported in either group, but data reporting was generally somewhat unclear in this study.

Systemic interventions - Studies with oral antibiotics combined with topical treatments

(31) Oral metronidazole and topical hydrocortisone 1% cream versus oral placebo and topical hydrocortisone 1% cream

Only one study (Pye 1976) provided outcomes data for these interventions.

Primary outcomes

None of the primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity:

Although the study was inadequately reported, the data available for this outcome indicated that oral metronidazole appeared to be almost four times more effective than placebo. Ten of the 15 participants treated with oral metronidazole plus hydrocortisone showed an improvement in severity scores compared with only 2 of the 14 participants in the placebo plus hydrocortisone group (RR 4.64, 95% CI 1.23 to 17.68).

Dropouts:

Headache was reported as the cause of one dropout which occurred in each of the groups (RR 0.93, 95% CI 0.06 to 13.54).
Adverse events:

Adverse events were confined to two participants in the metronidazole plus hydrocortisone group and one participant in the placebo group (RR 1.87, 95% CI 0.19 to 18.38). See Analysis 31.1.

(32) Combined effect of anti-inflammatory dose doxycycline + metronidazole gel versus metronidazole gel alone

Only one study (Sanchez 2005) provided data for this comparison.

Primary outcomes

None of the primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity:

The relative difference in the mean change from baseline in Clinician's Global Severity Score at week 12 was -1.01 in favour of the doxycycline group (P < 0.05, 95% CI -2.00 to -0.02). Numeric data were not provided and both of these outcome measures had to be estimated from figures from the report. This also holds true for the changes in Clinical Erythema Assessment scale. See Analysis 32.1 (various outcomes).

Lesion counts: The relative difference in mean change from baseline in total inflammatory lesion count was -7.70 at week 12 for the doxycycline plus metronidazole group compared to the metronidazole-alone group (P < 0.01, 95% CI -13.59 to -1.81). See Analysis 32.1.

Dropouts:

There were no dropouts reported among the 20 participants in the doxycycline plus metronidazole group which compared with 5 out of the 20 in the metronidazole gel group (RR 0.09, 95% CI 0.01 to 1.54).

Adverse events:

Adverse events were reported in 14 of the 20 participants in the doxycycline plus metronidazole group versus 19 of 20 in the metronidazole gel-alone group (RR 0.74, 95% CI 0.54 to 1.00).

(33) Doxycycline 40 mg combined with topical metronidazole 1% gel twice daily versus placebo capsules combined with topical metronidazole 1% gel twice daily

A single study was included but provided very limited outcomes data for this comparison (Fowler 2007).

Primary outcomes

None of the primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity:

Data for these assessments are presented in Analysis 33.1 (various outcomes), but without the corresponding SDs which were not reported by the investigators.

Lesion counts: These data are presented in Analysis 33.1 but without the SDs, which were unreported.

Dropouts:

Six participants out of 36 dropped out in the doxycycline group compared with 2 in the placebo group (RR 3.0, 95% CI 0.65 to 13.88).

Adverse events:

Participants in the doxycycline group reported 39 adverse events compared with 23 in the placebo group, however the report was unclear how many of the participants experienced these adverse events.

Systemic interventions - Studies with oral antibiotics compared with topical antibiotics

(34) Topical metronidazole versus oral (oxy)tetracycline

Four studies were included in this comparison. Nielsen 1983b investigated the effects of metronidazole 1% cream versus oral oxytetracycline for the treatment of rosacea. The other two studies, Veien 1986 and Schachter 1991, utilised tetracycline instead of oxytetracycline, and in Monk 1991 metronidazole gel 0.75% was compared with oxytetracycline.
Although the quality of reporting of these studies was generally poor they indicated that there was no statistically significant difference in effectiveness between metronidazole cream and oxytetracycline. See Analysis 34.1 (various outcomes). The Schachter 1991 study was assessed as being at high risk of bias and is reported in Analysis 34.1.

**Primary outcomes**

**Quality of life:**

Not assessed.

**Participant-assessed changes in rosacea severity:**

Based on these assessments no statistically significant difference in efficacy could be demonstrated. In Monk 1991 eight of the 16 participants in the topical metronidazole group considered themselves improved versus 12 of 17 in the oxytetracycline group (RR 0.71, 95% CI 0.40 to 1.26). Correspondingly, in Nielsen 1983b there was no statistically significant difference in the assessments between the interventions, in that 24/22 participants in the metronidazole group considered themselves improved versus 24/26 in the oxytetracycline group (RR 0.99, 95% CI 0.84 to 1.17).

**Secondary outcomes**

**Physician-assessed changes in rosacea severity:**

These were in agreement with the participants assessments and showed no statistically significant difference between the two interventions. In Monk 1991 9 out of 16 in the metronidazole group were improved versus 12 of 17 in the oxytetracycline group (RR 0.80, 95% CI 0.47 to 1.35), and 24 of 25 versus 25 of 26 respectively in Nielsen 1983b (RR 1.0, 95% CI 0.78 to 1.12).

**Dropouts:**

In the Nielsen 1983b study there were no dropouts in the metronidazole group but three occurred in the oxytetracycline group. The investigators in Veien 1986 reported that one participant dropped out but it was unclear from which group. In Monk 1991 four participants dropped out in the metronidazole group compared with two in the oxytetracycline group.

**Adverse events:**

No adverse events were reported in Nielsen 1983b, and these were incompletely reported in Veien 1986; four participants in the cream group reported skin dryness, and two participants in both groups complained of a stinging sensation. In both groups in Monk 1991 two participants reported flaking of the skin and two participants experienced gastrointestinal problems. See Analysis 34.1.

(35) **Topical clindamycin versus oral tetracycline**

One study investigated this comparison (Wilkin 1993) but as the report did not provide essential details, such as how many participants were randomised to the interventions, the remaining data were considered largely unusable. See Analysis 35.1 (various outcomes).

**Studies with other systemic treatments**

(36) **Rilmenidine versus placebo**

Only one study examined this comparison (Grosshans 1997).

**Primary outcomes**

**Quality of life:**

Not assessed.

**Participant-assessed changes in rosacea severity:**

Six out of 15 participants in the rilmenidine group considered their rosacea improved compared with 6/19 in the placebo group (RR 1.27, 95% CI 0.51 to 3.14). Based on these data rilmenidine appeared to be ineffective.

**Secondary outcomes**

**Physician-assessed changes in rosacea severity:**

The physicians reported that 5/15 in the rilmenidine group versus 1/19 in the placebo group showed improvement (RR 6.33, 95% CI 0.83 to 48.59), and in-line with the participants' assessments rilmenidine was not considered to be effective. There was a tendency towards fewer flushing episodes in the rilmenidine group. The mean decrease in
number of flushes was 13 versus 5 (respectively rilmenidine and placebo). No standard deviations were reported in
this study.

Lesion counts: The number of participants with at least a 50% reduction in lesion count was 10/15 in the rilmenidine
group versus 11/19 in placebo. See Analysis 36.1.

Dropouts:
There was no statistically significant difference in dropout rates between the rilmenidine group (2/15) and placebo
(3/19) (RR 0.84, 95% CI 0.16 to 4.42).

Adverse events:
Although only mild adverse events were reported, there was no statistically significant difference in the number of
participants experiencing adverse events, i.e. 8/15 (rilmenidine) versus 8/19 (placebo) (RR 1.27, 95% CI 0.62 to
2.57).

(37) Dark sulphonated shale oil versus placebo
One study evaluated the effectiveness of this intervention but it was only available as an abstract which provided
very limited and unusable data (Koch 1999). See Analysis 37.1.

(38) Zinc sulphate versus placebo
One study provided data for this comparison but the data were largely unusable because only the baseline standard
deviations were reported (Sharquie 2006). See Analysis 38.1 (various outcomes).

(39) Nadolol versus placebo
Only one study (Wilkin 1989) investigated the effect of nadolol on flushing. There was no difference between
nadolol and placebo pretreatments for flushing. However, the sample size was small (three to four participants per
group) and no statistical analyses were undertaken by the investigators. See Analysis 39.1.

Other interventions - Studies with laser-/light-based treatment

(40) Dual-Wavelength laser system (595 + 1064 nm) versus 595 nm PDL or Nd:YAG laser
One study (Karsai 2008) evaluated the efficacy of these treatment for telangiectasia on the nose.

Primary outcomes
None of the primary outcomes were assessed.

Secondary outcomes
Physician-assessed changes in rosacea severity: Treatment with dual wavelength laser resulted in an improvement
in 18 of the 20 sites on the nose versus 2 of the 10 sites treated with PDL and 2 of the 10 face sites treated with
Nd:YAG. For a descriptive analysis see other data in Analysis 40.1 (various outcomes).

Dropouts:
None.

Adverse events: The number of adverse events was not reported but these were described as transient purpura and
immediate post-treatment erythema.

(41) Pulsed Dye Laser versus Intense Pulsed Light therapy versus control
Very limited and largely unusable data were reported in the single study which addressed these interventions (Neuhaus 2009). The data are summarised in Analysis 41.1 (various outcomes).

DISCUSSION

Discussion

Summary of main results
Fifty-eight studies were included in the updated version of this review. It was somewhat disappointing to see that our
principal outcome, ‘quality of life’, was assessed in only two of the studies (Schechter 2009; Weissenbacher 2007) and
that only half of the studies addressed participants’ assessments of improvement in rosacea severity, which was
the other primary outcome in this review.

The majority of studies focused on the number of papules and pustules which although they may provide a
quantifiable, objective, and more readily intelligible outcome, are generally considered to be clinician-centred rather than patient-preferred. Rosacea is a chronic skin disease and the importance of self-assessments by the participants of the effectiveness of the interventions should not be underestimated.

In day-to-day clinical practice clinicians and patients need to know how rapidly lesions will respond to treatment and, once an optimal response has been achieved, how long this will last. Although these would appear to be key issues in clinical decision-making, the time to response, which was one of our secondary outcomes, was not addressed by most of the studies and duration of remission was also only assessed in one of the studies (Dahl 1998).

Two of the studies (Marks 1971; Elewski 2003) illustrated the level of disagreement in the assessments made by the investigators and participants, such that in both of these reports the investigators were apparently more satisfied with the outcomes than the participants. It is conceivable that the physicians may have been more permissive in terms of what they considered to be improvement than perhaps the participants.

Pooling of data was not feasible for most of the treatment options, and was only possible for several outcomes in the trials which evaluated topical metronidazole and azelaic acid.

Overall completeness and applicability of evidence

Study duration was less than eight weeks in Bamford 1999, Draelos 2005b, Koch 1999, Marks 1971, Pye 1976, Sneddon 1966, Weissenbacher 2007, and Wilkin 1989 which is most likely to be an inadequate period of time to demonstrate an optimal treatment effect for some of the interventions. Because rosacea is a chronic disease there is a pressing need for more studies that evaluate strategies focused on therapies that are capable of maintaining remission. Consequently the evidence was noticeably incomplete for some of these interventions, such as for, example, patient education and avoidance measures for trigger factors, i.e. certain foods, exposure to heat and sunlight, or the use of non-irritating cosmetics. The review also failed to identify any eligible studies addressing dietary manipulation, sun protective measures, or the use of topical NADH (the reduced form of β-nicotinamide adenine dinucleotide) for the treatment of rosacea.

Treatments for subtype I, erythematotelangiectatic rosacea

A substantial majority, up to 75%, of the included studies assessed the effects of interventions on erythema and/or telangiectasia although they were not explicitly stated as outcomes for this review are nevertheless important participant-preferred outcomes and are also integral to the physician-assessed changes of rosacea severity. These outcomes have been reported in the Data and analyses section of this review.

A quarter (16) of the total number of included studies demonstrated a reduction in erythema but in general not of telangiectasia, and in view of the potential impact of these reductions on the quality of life in people with rosacea, future updates of this review should place increased emphasis on the effects of interventions on both erythema and telangiectasia.

The use of different scoring systems to assess improvement on erythema and telangiectasia, and the paucity and variability of evidence on the effects of interventions on this subtype of rosacea did not in most cases permit firm conclusions to be made.

Topical treatments

Based on the data reported in Dahl 2001, Elewski 2003, Koçak 2002, Monk 1991, Nielsen 1983a, and Torok 2005 topical metronidazole appears to be effective in reducing erythema. Azelaic acid (Elewski 2003; Thiboutot 2003a; Thiboutot 2003b) and sulphacetamide/sulphur (Sauder 1997; Torok 2005) are also equally effective in reducing erythema. One study provided some evidence for the effectiveness of permethrin on erythema (Koçak 2002), however further research is still required.

Oral treatment

Oral doxycycline (Del Rosso 2007a; Del Rosso 2008; Fowler 2007), and oral zinc sulphate (Sharquie 2006) appeared to be effective for reducing erythema, but further research of their effect on erythema is needed to confirm these findings.

Laser and light therapies

Lasers and light therapies would appear to have a major clinical role to play in the treatment of erythematotelangiectatic rosacea but these treatment modalities are still largely under researched. There was some evidence that pulsed dye laser and intense pulsed light therapy are capable of reducing erythema and telangiectasia on the face (Neuhaus 2009). The effects of laser therapy for rosacea on the nose were investigated in only one study (Karsai 2008). Because clearance of the redness and telangiectasia occurring on the rest of the face is highly desirable, can be a source of personal embarrassment and may lead to low self esteem, further studies of laser and light-based therapies should be considered a priority (Menezes 2009).

Treatments for subtype 2, papulopustular rosacea

Topical treatments

Pooled data for topical metronidazole (Bjerke 1999b; Breneman 1998; Nielsen 1983a) and azelaic acid (Bjerke 1999; Thiboutot 2003a; Thiboutot 2003b) indicate that both are effective treatments for rosacea. However, based
on physicians’ assessments in Elewski 2003, and both physician and participant assessments in Maddin 1999, azelaic acid would appear to be more effective than metronidazole albeit with more side-effects and, therefore, further supporting evidence is required.

No statistically significant difference in effect was reported between the two concentrations of topical metronidazole or when different vehicles were compared (Dahl 2001; Dreno 1998; Guillet 1999). Topical metronidazole was also shown to be effective in maintaining remission (Dahl 1998).

A single daily dose of azelaic acid appears to be as effective as the twice daily dose and is also likely to result in improved compliance (Thiboutot 2008). This comparison warrants further investigation.

The results of Thiboutot 2009 illustrate that there is insufficient evidence to conclude that azelaic acid is either effective or ineffective for maintenance treatment. Rosacea is a chronic disease, and therefore randomised controlled trials investigating the effectiveness of azelaic acid and metronidazole used in maintenance therapy are still required.

The effectiveness or otherwise of benzoyl peroxide in the treatment of papulopustular rosacea is unclear, inadequate study design coupled with a short study duration of four weeks did not enable any definite conclusions to be drawn from the one included study (Montes 1982). Benzoyl peroxide combined with clindamycin was investigated in Breneman 2004 but the data were incomplete, no standard deviations were reported, and the data were skewed, which did not permit firm conclusions to be made about the efficacy of this combined intervention.

Although a number of studies which examined the use of azithromycin were retrieved in our searches, they were excluded from this review because they were not randomised controlled trials (Bakar 2004; Bakar 2006; Bakar 2009; Dereli 2005), and only Akhyani 2008 which compared azithromycin with doxycycline was included but the data were skewed, and consequently more research is required on the effects of this intervention.

No eligible studies were identified for dapsone or topical tretinoin although these treatments are still in fairly common use in the treatment of rosacea (Jansen 1997; Thiboutot 2000; Wilkin 1994).

**Oral treatments**

Two studies (Sneddon 1966; Marks 1971) evaluated the effects of tetracycline. In both of these the physicians’ assessments indicated an improvement in severity but only Marks 1971 provided data on the participants’ assessments of treatment. In contrast, although the six-week study duration may appear to have been too short, the assessments of the participants failed nevertheless to provide any evidence of a difference in effectiveness between tetracycline and placebo. Tetracyclines are used extensively for the treatment of rosacea and although their efficacy may be widely-accepted by clinicians, this is currently not substantiated by high-level evidence from robust and methodologically-sound clinical trials.

Whilst a number of studies included in this review (Del Rosso 2007a; Del Rosso 2007b; Fowler 2007; Sanchez 2005) demonstrated the efficacy of an anti-inflammatory dose of doxycycline as a reduction in physician-assessed lesion counts, quite significantly, the participants' views and satisfaction with the effects of this intervention were not assessed. Furthermore, while there has been a measurable decrease in lesion counts as a result of the intervention, it was unclear if these counts were continuing to decrease or had stabilised by the time the studies were completed.

Although a number of studies have shown that anti-inflammatory doses of doxycycline do not have an antimicrobial effect on skin flora, nor do they lead to an increase in the number or severity of resistant organisms, studies with a longer duration and which are capable of providing conclusive evidence of the efficacy of an anti-inflammatory dose of doxycycline are still required (Bikowski 2007; Fowler 2007; Korting 2009; Sloan 2008). There is evidence from these trials that the 40 mg dose is at least as effective as the 100 mg dose, has a correspondingly lower risk of adverse effects (Del Rosso 2008), and that, albeit these events may be mild to moderate, more were reported with the 100 mg of doxycycline than the 40 mg dose. Therefore, because anti-inflammatory doses of antibiotics represent a novel approach in the management of rosacea, further trials evaluating the effects of such dosing regimens of other antibiotics should be encouraged (Bikowski 2007; Fowler 2007).

Although a number of studies which examined the use of azithromycin were retrieved in our searches, they were excluded from this review because they were not randomised controlled trials (Bakar 2004; Bakar 2006; Bakar 2009; Dereli 2005), and only Akhyani 2008 which compared azithromycin with doxycycline was included but the data were skewed, and consequently more research is required on the effects of this intervention.

Several studies examined other interventions such as rilmenidine and ampicillin (Grosshans 1997; Marks 1971) and although the latter showed some evidence of effectiveness, neither of these are now considered as treatment options by clinicians.
Treatments for subtype 3, phymatous rosacea

Surgical therapies as well as ablative laser therapies have been used with reportedly good results for this subtype of rosacea, but no eligible randomised controlled trials were identified for this systematic review.

Treatments for subtype 4, ocular rosacea

The symptoms of ocular rosacea are often mild but can also be severe and debilitating, and although ocular involvement occurs in 60% of people with rosacea, only two trials included in this review examined the treatment of ocular rosacea (Barnhorst 1996; Schechter 2009).

Topical treatments

Although there was insufficient evidence to support the efficacy of topical metronidazole for ocular rosacea (Barnhorst 1996), there was some evidence of a consistent improvement in all outcomes and that cyclosporine 0.5% ophthalmic emulsion was more effective than artificial tears in the treatment of ocular rosacea (Schechter 2009).

Adverse events

The adverse events reported were mostly mild and transient and comprised of skin irritation, pruritus, and stinging/burning or dry skin. In most of the studies the number and type of adverse events did not differ significantly between active treatment and the placebo groups, however, these were not always reported adequately and completely.

Quality of the evidence

Limitations in study design and implementation

Although the overall clinical design of the included studies appeared to be adequate, our assessments of risk of bias revealed the limitations in the quality of the studies covering most of the interventions.

There was considerable variation in how well the studies were reported and in particular the methods used to generate the sequence, to conceal the allocation, and the measures taken to blind investigators and participants. These factors, compounded with unsuccessful attempts to contact many of the investigators for additional information, created difficulties in making accurate assessments of the risk of bias in some of the included studies.

A significant proportion of the outcome data was not normally distributed (skewed). Standard deviations were frequently missing from study reports, which meant that the continuous data could not be entered in a meta-analysis. For most treatment comparators it was not possible to pool data relating to the various studies, and it was only possible to pool the data for several outcome measures in the trials involving topical metronidazole and azelaic acid.

However, whilst recognising these limitations the authors consider that the body of evidence summarised in this review is sufficient to allow certain conclusions to be drawn about the effectiveness of several of the interventions used in the treatment of rosacea.

Indirectness of the evidence

Patient-relevant primary outcomes are a pre-requisite for informing evidence-based clinical decision making, but the importance of patient-reported outcomes (PRO) and specifically those used in evaluating the impact of interventions on quality of life appears to have been underestimated by the investigators in most of the included studies. Improvement in symptoms may not necessarily equate with or translate into measurably significant changes in quality of life in the individual, and therefore whilst a moderate change in some of the physical symptoms, i.e. erythema, may be interpreted by clinicians as evidence of effective treatment it does little to address the wider psychological distress or physical disfigurement that may occur in those with chronic rosacea. Thus, although the majority of reports appeared to recognise the importance of patient-assessment of symptoms, in reality, greater emphasis was placed on the reporting of lesion counts as primary outcomes whereas self-assessments were almost always considered as secondary outcomes.

Over half of the studies included in this review were placebo-controlled trials which may only provide limited evidence on the advantages or disadvantages of new-relative-to existing interventions. To fill the evidence gap clinicians need to have access to not only the risk and benefits of individual interventions but also the comparative efficacy of these interventions and thus head-to-head trials are more likely to have provided evidence that is both relevant and direct.

Inconsistency of results

Although a diverse range of interventions were considered in this systematic review, the majority of participants in the included studies had subtype I and II rosacea and the results for specific outcomes were fairly consistent across the very limited number of studies and interventions where pooling of data was feasible.

Imprecision of results

The rather limited number of studies (albeit of adequate sample size and duration and examining similar
interventions) that were included in this review did not permit any substantive assessment of the degree of precision of effect.

Publication bias

A large number of abstracts to conference proceedings were identified, some of which were published in full but a number were not otherwise available. There is a possibility that a number of reports, in particular those which conclude with negative outcomes, involve serious adverse effects or a lack of effect, and may have been sponsored by parties with potentially vested interests, remain unpublished.

Potential biases in the review process

Previous versions of the review used an overall numerical score of methodological quality as a basis on which to include or exclude studies. In this version of the review, all of the previously excluded studies were re-assessed for inclusion if they met the a priori specified inclusion criteria and were then subjected to a detailed 'Risk of bias' assessment.

Strident attempts were made to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies. The authors' independent assessments of eligibility of studies for inclusion in this review and the extraction of data minimised the potential for additional bias beyond that detailed in the 'Risk of bias' tables.

Agreements and disagreements with other studies or reviews

We are not aware of any other reviews that have covered this research question. There are no disagreements with earlier versions of this review. However, as new studies have been added to this review, additional information is included.

AUTHORS' CONCLUSIONS

Implications for practice

Based on only those studies which are most likely to have provided reliable results, i.e. reproducible, repeatable - and therefore valid -, and selecting the most rigorously described and conducted studies, we have made several conclusions. Evidence of treatment effect could be demonstrated for only a limited number of the interventions studied.

There is insufficient evidence to support either the effectiveness or lack of effectiveness of interventions for the management of erythematotelangiectatic rosacea (subtype 1).

For subtype 2, papulopustular rosacea, topical metronidazole, azelaic acid, and anti-inflammatory dose doxycycline (40 mg) appear to be effective and safe for short-term use. There is evidence that 40 mg is at least as effective as 100 mg with evidence of less adverse effects. There is some evidence that tetracycline is effective. There is no clear evidence that any one of these treatments, or any combination of treatments, has a particular advantage in terms of higher remission rates and/or fewer adverse effects.

No studies could be included that addressed treatment of phymatous rosacea (subtype 3).

For ocular rosacea cyclosporine 0.5% ophthalmic emulsion showed some evidence of benefit over artificial tears.

Clinical decision making on the choice of intervention for rosacea should be based on high-level evidence if it is available, but in the absence of such evidence for any specific intervention these decisions should continue to be guided by clinical experience and patients' individual characteristics and preferences until further evidence becomes available.

Implications for research

There is an urgent need for high-quality, well-designed, and rigorously-reported studies of the more widely-used treatments for rosacea, i.e. tetracycline, minocycline, azithromycin, isotretinoin, topical retinoids, and light-based therapies. Clearing of the "redness of the face" in those with rosacea can have a significant impact on their quality of life but the evidence for the efficacy of light-based therapies, which are commonly used for erythematotelangiectatic rosacea, is lacking and further studies addressing the efficacy of these treatment modalities are warranted.

The impact of available treatment on ocular rosacea warrants further examination and this might include the removal of Meibomian cysts. Less direct interventions, such as dietary adjustments, avoidance measures for trigger factors, the use of sunscreens, and patient education in addition to trials investigating which is the most effective treatment for phymatous rosacea are further areas of much-needed research. Conceivably, some of the studies listed in the 'Characteristics of ongoing studies' section of this review will be able to provide answers to these remaining questions in the future.

There was wide variability in not only the conduct but also in the quality of reporting of many of the trials. A major area for improvement would be in the standardisation of outcome reporting in any future research. The use of proprietary severity scales, and non-standardised erythema scales significantly hampered our ability to combine study results for a meta-analysis. Outcomes collected in future trials should be primarily based on a standardised scale of the participant's assessment of the treatment efficacy and also have a greater emphasis on changes in quality of life as a result of the interventions. Standardised and uniform scales should be developed and used for
physicians' assessments, and these should reliably reflect global evaluation, lesion counts, and assessment of telangiectasia.

Time needed to response and response duration should be addressed more completely and reporting of adverse events reported more rigorously. Furthermore, to ensure improved clinical decision-making, future research should place a greater emphasis on the management and treatment of rosacea based on the staging pattern of the disease.

Future randomised controlled trials must be well-designed, well-conducted, and adequately delivered with subsequent reporting, including high-quality descriptions of all aspects of methodology. Rigorous reporting needs to conform to the Consolidated Standards of Reporting Trials (CONSORT) statement and this will enable appraisal and interpretation of results, and accurate judgements to be made about the risk of bias, and the overall quality of the evidence. Although it is uncertain whether reported quality mirrors actual study conduct, it is noteworthy that studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995). Adherence to guidelines, such as the CONSORT statement, would help ensure complete reporting.

**Acknowledgements**

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**NOTES**

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Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

### Topical metronidazole versus placebo

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tbody>
<tr>
<td>1 Physician’s global evaluation of improvement</td>
<td>3</td>
<td>334</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.95 [1.48, 2.56]</td>
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<tr>
<td>2 Dropout rate</td>
<td>6</td>
<td>563</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.93 [0.58, 1.50]</td>
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<td>3 Adverse events</td>
<td>5</td>
<td>474</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.09 [0.58, 2.06]</td>
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### Metronidazole and sunscreen SPF 15 versus placebo

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### Metronidazole 0.75% cream versus metronidazole 1% cream

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### Metronidazole 0.75% cream versus metronidazole 0.75% gel

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### Topical azelaic acid versus placebo

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<tr>
<td>1 Participant-assessed improvement of rosacea</td>
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<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
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<td>2 Physician's global evaluation of improvement</td>
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<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.36 [1.21, 1.53]</td>
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<td>3 Dropout rate</td>
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<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
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### Azelaic acid 15% gel once daily versus azelaic acid 15% gel twice daily

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### Azelaic acid 15% gel twice daily as maintenance therapy versus vehicle twice daily

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### Azelaic acid 20% versus metronidazole 0.75% versus permethrin 5%

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### Topical permethrin versus topical metronidazole

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### Benzoyl peroxide acetone versus placebo

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### Benzoyl peroxide 5% with clindamycin 1% gel versus placebo

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<td>Assessment of adjunctive benefits of PHA skin regimen in combination with azelaic acid 15% gel versus non standardised skin care and azelaic acid 15% gel</td>
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<td><strong>Oral metronidazole and topical hydrocortisone 1% cream versus oral placebo and hydrocortisone 1% cream</strong></td>
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<td><strong>Combined effect of anti-inflammatory dose doxycycline (40 mg) + metronidazole gel versus metronidazole gel alone</strong></td>
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### Nadolol versus placebo

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### Dual-Wavelength laser system (595 + 1064 nm) versus 595 nm PDL or Nd:YAG laser

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### Pulsed Dye Laser versus Intense Pulsed Light therapy versus control

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**COVER SHEET**

**Interventions for rosacea**

**Reviewer(s)**
van Zuuren Esther J, Kramer Sharon, Carter Ben, Graber Mark A, Fedorowicz Zbys

**Contribution of Reviewer(s)**

**Issue protocol first published**
2001 issue 4

**Issue review first published**
2004 issue 1

**Date of last minor amendment**
Information not supplied by reviewer

**Date of last substantive amendment**
Information not supplied by reviewer

**Most recent changes**

**Date new studies sought but none found**
Information not supplied by reviewer

**Date new studies found but not yet included/excluded**
Information not supplied by reviewer

**Date new studies found and included/excluded**
Information not supplied by reviewer

**Date reviewers' conclusions section amended**
Information not supplied by reviewer

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Editorial group  Cochrane Skin Group
Editorial group code  HM-SKIN

KEYWORDS
Humans; Dermatologic Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Rosacea [*drug therapy]

HISTORY
History
Review first published: Issue 1, 2004

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<tr>
<th>Date</th>
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<tr>
<td>7 September 2008</td>
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