BJD
British Journal of Dermatology

Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review

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Summary

Rosacea is a common chronic skin disease affecting the face. There are numerous treatment options, but it is unclear which are the most effective. The aim of this review was to assess the evidence for the efficacy and safety of treatments for rosacea. Searches included the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index, and Ongoing Trials Registers (updated February 2011). Randomized controlled trials in people with moderate to severe rosacea were included. 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. There was some evidence that topical metronidazole and azelaic acid were more effective than placebo. Two trials indicated that doxycycline 40 mg was more effective than placebo. There was no statistically significant difference in effectiveness between doxycycline 40 mg and 100 mg but there were fewer adverse effects. One study reported that ciclosporin ophthalmic emulsion was significantly more effective than artificial tears for treating ocular rosacea. 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 ciclosporin 0·05% ophthalmic emulsion for ocular rosacea. Further well-designed, adequately powered randomized controlled trials are required.

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Accepted for publication
3 June 2011

Funding sources
No external funding.

Conflicts of interest
None declared.

Footnote
This paper is based on a Cochrane review published in Issue 3, March 2011 of The Cochrane Library 2011 (see http://www.CochraneLibrary.net for further information). Cochrane reviews are regularly updated as new evidence emerges and in response to comments and criticisms. The Cochrane Library should be consulted for the most recent version of this review.

DOI 10.1111/j.1365-2133.2011.10473.x

Rosacea is a chronic skin disease that can affect the cheeks, nose, eyes, chin and forehead. It is characterized by recurrent episodes of flushing, erythema, papules, pustules and telangiectasia.[1–3] Although there is no standard clinical definition of the condition, rosacea is generally classified into four subtypes and one variant.[4,5]

Subtype 1 Erythematotelangiectatic rosacea. The clinical features include flushing and persistent central facial erythema with or without telangiectasia.

Subtype 2 Papulopustular rosacea. This is characterized by persistent central facial erythema with transient, central face papules or pustules, or both.

Subtype 3 Phymatous rosacea. This may occur on the nose (rhinophyma), chin, forehead, cheeks or ears.

Subtype 4 Ocular rosacea. It may be found in up to 58% of cases, but it is frequently undiagnosed.

Variant Granulomatous rosacea. This is noninflammatory and characterized by hard, brown, yellow or red cutaneous papules, or nodules of uniform size.

Progression from one subtype to another is possible; however, each individual characteristic may change from absent to severe.[1,3,5]

As with most chronic skin diseases, rosacea requires long-term treatment, therapies are numerous, and their use is frequently based on anecdotal evidence.[2,3,6] Management strategies for people with rosacea can often be tailored to the specific subtype of rosacea, but because rosacea can have a significant impact on quality of life, these strategies should also

be directed towards achieving improvement in general well-being.[3,7–10]

This is a summary of a Cochrane systematic review that was conducted to examine the different management options and determine the most effective strategy in the treatment of rosacea. Systematic reviews, which represent the uppermost level of reliability in the hierarchy of evidence, are a valuable source of information for healthcare providers, consumers, researchers and policymakers. They provide one of the best opportunities for clinicians to understand and translate the current best evidence of the effects of healthcare interventions into their daily clinical practice. Cochrane reviews are internationally recognized for their high quality and are updated regularly.

Methods

A systematic review of randomized controlled trials (RCTs) was conducted following a prespecified protocol.[11]

Search strategies

We searched 11 electronic databases and trial registers (Table 1) from inception to February 2011 for relevant studies. We scanned the bibliographies of included studies, published reviews and articles that cited the included studies. Attempts were made to locate unpublished and ongoing trials through correspondence with authors and pharmaceutical companies. No language restrictions were imposed and several studies were translated. Two reviewers (E.J.v.Z. and M.A.G.) independently reviewed all studies from searches for eligible RCTs.

Inclusion criteria

We included RCTs that compared any type of intervention used to treat rosacea, either as stand-alone or as a combined intervention, vs. placebo or active treatment. We also considered the effects of avoidance of some foods, e.g. spicy food, as well as the use of certain cosmetics and sunscreens.

Table 1 Electronic databases and trial registers searched

Electronic databases
The Cochrane Skin Group Specialised Register
The Cochrane Central Register of Controlled Trials
MEDLINE
EMBASE
Science Citation Index
BIOSIS
Trial registers
The metaRegister of Controlled Trials, http://www.controlled-trials.com
The U.S. National Institutes of Health Ongoing Trials Register, http://www.clinicaltrials.gov
The Australian and New Zealand Clinical Trials Registry, http://www.anzctr.org.au
The World Health Organization International Clinical Trials Registry platform, http://www.who.int/trialsearch
The Ongoing Skin Trials Register, http://www.nottingham.ac.uk/ongoingskintrials

Outcome measures

Our two primary outcomes were (i) impact on quality of life and (ii) participant-assessed changes in rosacea severity. Secondary outcomes were physician-assessed changes in rosacea severity, drop-out rates and adverse events.

Data extraction and synthesis

Details of eligible trials were extracted and summarized using a structured data extraction form (E.J.v.Z., S.F.K., Z.F.). Disagreements were resolved by discussion. The review authors (E.J.v.Z., S.F.K., Z.F. or B.R.C.) independently assessed risk of bias in the included studies using the Cochrane Collaboration's domain-based evaluation tool as described in Chapter 8, Section 8.5, in the *Cochrane Handbook for Systematic Reviews of Interventions*.[12] We presented continuous outcomes where possible on the original scale as reported in each individual study. Dichotomous outcomes were presented as relative risk ratios. All outcomes were reported with their associated 95% confidence intervals. A meta-analysis was carried out if we identified a sufficient number of studies ($n \geq 3$) investigating similar treatments that reported data that were amenable to pooling.[13] In view of a lack of demonstrable statistical heterogeneity between the studies ($I^2 > 60\%$), a fixed-effect model was used to combine the results of individual studies in this review.

Results

Description of the included studies

The results of the literature search are shown in Figure 1. Of the 5434 references retrieved from the searches, 58 studies met our inclusion criteria (see Table 2 for characteristics of included studies).[11] The trials were grouped into six categories

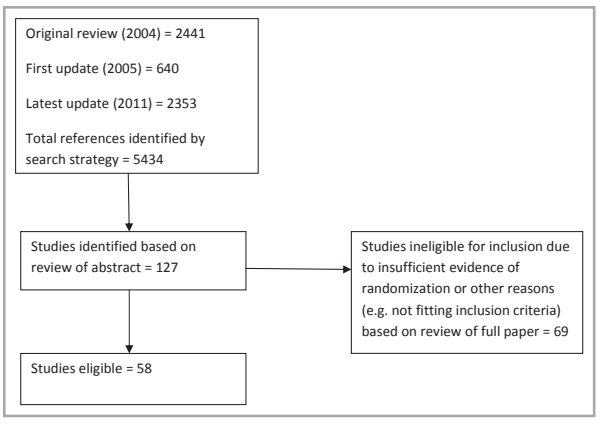

Fig 1. Search results.

of interventions: topical metronidazole (n = 28), oral antibiotics (n = 15), topical azelaic cream or gel (n = 11), topical benzoyl peroxide and/or combined with topical antibiotics (n = 4), sulphacetamide/sulphur (n = 3), and other therapies (n = 14). Eighteen trials evaluated comparisons in more than one category, e.g. a topical plus an oral agent. The duration of treatment ranged between 2 and 3 months, and only two studies addressed interventions for ocular rosacea.[14,15] Diversity in study design, skewed data, missing standard deviations, and a mix of different comparators and dosing regimens did not permit pooling of the data or allow the authors to make accurate and direct comparisons of some of the interventions. Only two of the included studies[15,16] reported assessments of change in 'quality of life' as a result of the interventions, and half (29) of the remaining studies evaluated participant-assessed changes in rosacea severity, both of which were the primary outcomes for this review. Most of the studies gave preference to clinician-assessed numbers of papules or pustules as outcomes rather than patient reported outcomes.

Risk of bias of included studies

Only three of the studies 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).[17,18] Thirty studies were categorized as 'unclear risk of bias' (plausible bias that raises some doubt about the results) because one or more criteria were assessed as unclear, while the remaining 25 studies were assessed as 'high risk of bias' (plausible bias that seriously weakens confidence in the results) because one or more of the criteria were not met.

Effects of interventions

A summary of the most important results is provided in Table 3.

Studies with only topical metronidazole

Fourteen trials provided data on the effectiveness of topical metronidazole.[14,17,19–30] Data from three studies could be pooled (see Fig. 2).[21,22,29] Topical metronidazole was more effective than placebo and the results were both statistically significant [relative risk (RR) 1·95, 95% confidence interval (CI) 1·48–2·56] and clinically important. The pooled data from these studies was largely in agreement with the participant-assessed outcomes for this comparison and were confirmed and supported by the other studies.[14,17,19,20,23–28,30] There were no statistically significant differences between the two concentrations of topical metronidazole (0·75% and 1%), or comparisons using different vehicles and topical metronidazole was also shown to be effective in maintaining remission.[23–26] There were no significant differences in the number of drop-outs and adverse events across the intervention groups in these studies.

Studies with only azelaic acid

Six studies evaluated the effect of azelaic acid out of which three studies compared the effectiveness of azelaic acid vs. placebo.[31–35] Pooled participant-assessed data from these studies indicated an improvement in rosacea severity rate of complete remission or marked improvement of 70–80% in the azelaic acid group compared with 50–55% in the placebo group (RR 1·52, 95% CI 1·32–1·76, see Fig. 3).[31,33] These results were largely in agreement with the physician-assessed outcomes in these studies. A single daily dose of azelaic acid appears to be as effective as the twice daily dose.[34] There was no statistically significant difference during maintenance phase between the azelaic acid group and vehicle-only group (RR 0·73, 95% CI 0·43–1·23).[35]

Studies comparing topical metronidazole and azelaic acid

Three studies provided data for this comparison, one of which had a within-patient study design; therefore pooling of data with the other two studies was not possible.[36–38] In two of the studies there was no statistically significant difference between the treatment groups in the patient-assessed outcomes.[36,38] However, in the Maddin[37] study the patients considered azelaic acid to be more effective. The investigators in both the Elewski *et al.*[36] and the Maddin[37] studies were more satisfied with the outcomes of treatment with azelaic acid compared with metronidazole.

Studies with other topical treatments

Most of the other comparisons consisted of single studies and investigated drug, e.g. permethrin, benzoyl peroxide, benzoyl peroxide combined with clindamycin, sodium sulphacetamide 10%/sulphur 5%, pimecrolimus, topical erythromycin, topical ciclosporin, ethoxybenzylaldehyde and adjunctive benefit of a polyhydroxy acid (PHA) regimen and flavonoid-rich cream.[15,16,28,39–49] The results are reported in Table 3, but are not discussed as most of these studies were judged to be at high risk of bias and had skewed or unusable data. However, two studies assessed our primary outcome 'quality of life'.[15,16] In Weissenbacher *et al.*[16] the efficacy of pimecrolimus vs. vehicle was investigated and 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. The study of Schechter *et al.*[15] demonstrated a moderate improvement in quality of life in the group with ocular rosacea which had been treated with ciclosporin 0·05% ophthalmic emulsion compared with artificial tears. The data based on physicians' assessments provide further supportive evidence for the effectiveness of topical ciclosporin 0·05% in the treatment of ocular rosacea.

Studies with oral antibiotics

Two studies which investigated the effect of tetracycline were included.[50,51] Based on the participant-assessed outcomes in

Table 2 Characteristics of included RCTs in the review

Study	Methods	Participants	Interventions	Outcomes
Akhyani *et al.* (2008)[55]	RCT open-label Teheran, Iran	67 (37 male/30 female) Mean age 47·93 yrs Papulopustular and erythematotelangiectatic rosacea	3 months A: Azithromycin – 1st month 500 mg 3 times/week, 2nd month 250 mg 3 times/week, 3rd month 250 mg twice/week B: Doxycycline – 100 mg once daily	Decrease in inflammatory lesions (mean %) Participants' own assessment of treatment at the end of the 3rd month Side-effects
Bamford *et al.* (1999)[54]	RCT double-blind Minnesota, U.S.A	44 (sex unspecified) Mean age 56·9 yrs (group A), 58·9 yrs (group B) Active rosacea tested positive for *Helicobacter pylori* (UBT RWBT tests)	2 weeks A: Clarithromycin – 500 mg TID and omeprazole 40 mg QD B: Placebo – QD	Extent and intensity of rosacea at follow-up as measured by the number of papules and pustules Extent and intensity of erythema and telangiectasia
Barnhorst *et al.* (1996)[14]	RCT within-patient comparison Cleveland, U.S.A.	13 (7 male/6 female) Age 72·8 yrs Ocular rosacea and previous diagnosis of facial rosacea	12 weeks A: Eyelid hygiene plus warm compresses plus metronidazole (0·75%) gel BID B: Eyelid hygiene and warm compresses BID	Eye and eyelid grading by physician Score: 1–5 (higher score is worse)
Beutner and Calvarese (2005)[19]	RCT investigator-blinded Multicentre, U.S.A.	1299 (340 male/959 female) Mean age 48·4 yrs (group A), 48·3 yrs (group B), 47·8 yrs (group C) Papulopustular rosacea	10 weeks A: Metronidazole gel 1% – QD B: Metronidazole cream 1% – QD C: Metronidazole gel vehicle – QD	% reduction lesion count % rated as success Noninferiority of metronidazole gel to metronidazole cream Safety and tolerability
Bitar *et al.* (1990)[20]	RCT double-blind Quebec, Canada only weeks 1–4	100 (41 male/59 female) Mean age 50·3 yrs (group A), 50·8 yrs (group B) Papulopustular rosacea	2 months A: Metronidazole cream 1% – BID B: Placebo cream – BID	Improvement in clinical evaluation by physician Improvement of global impression
Bjerke *et al.* (1989)[21]	RCT double-blind Trondheim, Norway	97 (44 male/53 female) Mean age 47 yrs Papulopustular and erythematotelangiectatic rosacea	2 months A: Metronidazole cream 1% – BID B: Placebo cream – BID	Self-assessed changes in rosacea severity, physician's global evaluation, lesion count reduction, reduction in erythema and telangiectasia, adverse events
Bjerke *et al.* (1999)[31]	RCT double-blind Oslo, Norway	116 (57 male/59 female) Age 48·4 yrs (group A), 50·3 yrs (group B) Papulopustular rosacea	3 months A: Azelaic acid cream 20% – BID B: Placebo (vehicle) – BID	Self-assessed changes in rosacea severity, decrease in N of lesions, physician's global impression of improvement, decrease in erythema and telangiectasia
Bleicher *et al.* (1987)[17]	RCT double-blind Boston, U.S.A.	40 (16 male/24 female) Mean age 48·7 yrs Moderate to severe rosacea	9 weeks A: Metronidazole 0·75% gel – BID B: Placebo (vehicle) – BID	Self-assessed changes in rosacea severity, physician's global evaluation, decrease in lesion counts, erythema and telangiectasia
Breneman *et al.* (1998)[22]	RCT double-blind Ohio, U.S.A.	156 (33% male/67% female) Mean age 48·5 yrs (group A), 46·9 yrs (group B) Papulopustular rosacea	10 weeks A: Metronidazole 1% cream – QD B: Placebo (vehicle) – QD	Change in lesion count, physician's global evaluation score of very good improvement (> 75%), decrease in erythema, telangiectasia

Table 2 Continued

Study	Methods	Participants	Interventions	Outcomes
Breneman *et al.* (2004)[39]	RCT double-blind 2 centres, U.S.A.	53 (18 male/35 female) Mean age 43·1 yrs (group A), 45·7 yrs (group B) Papulopustular rosacea	12 weeks A: Benzoyl peroxide 5% and clindamycin 1% gel – QD B: Placebo (vehicle) – QD	% change in N of papules and pustules, change in severity of erythema, telangiectasia, flushing, burning/stinging, overall rosacea severity assessment
Carmichael *et al.* (1993)[32]	RCT within-patient comparison Cardiff, U.K.	33 (15 male/18 female) Mean age 56·9 yrs (male), 52·8 yrs (female) Papulopustular rosacea	13 weeks A: Azelaic acid cream 20% – BID B: Placebo (vehicle) – BID	Subjective severity score, decrease in lesion count, erythema and telangiectasia, physician's overall rating of improvement
Dahl *et al.* (1998)[23]	RCT double-blind (second phase) Multicentre, U.S.A	88 (32 male/56 female) Mean age 48·6 yrs (group A), 43·7 yrs (group B) Moderate to severe rosacea	6 months A: Metronidazole 0·75% gel – BID B: Placebo (vehicle) – BID	Relapse (appearance of papules and pustules)
Dahl *et al.* (2001)[24]	RCT investigator-blinded Three centres, U.S.A.	72 (21 male/51 female) Mean age 45 yrs (group A), 47 yrs (group B) Papulopustular and erythematotelangiectatic rosacea	12 weeks A: Metronidazole 0·75% cream – QD B: Metronidazole 1% cream – QD	Median % change in lesion counts, % change in total erythema score, physician's assessment of global severity
Del Rosso *et al.* (2007) (study a)[18]	RCT double-blind Multicentre, U.S.A.	251 (91% female group A, 95% female group B) Mean age 46·8 yrs (group A), 47·6 yrs (group B) Papulopustular rosacea	16 weeks A: Doxycycline 40 mg capsule – QD B: Placebo capsule – QD	Mean change in total lesion count, mean change in Clinician's Erythema Assessment, mean change in IGA scale, adverse events
Del Rosso *et al.* (2007) (study b)[18]	RCT double-blind Multicentre, U.S.A.	286 (94% female treatment group, 95% female control group) Mean age 46·3 yrs (group A), 47·6 yrs (group B) Papulopustular rosacea	16 weeks A: Doxycycline 40 mg capsule – QD B: Placebo capsule – QD	Mean change in total lesion count, mean change in Clinician's Erythema Assessment, mean change in IGA scale, adverse events, 4-week post-treatment evaluation
Del Rosso *et al.* (2008)[53]	RCT double-blind Multicentre, U.S.A.	91 (27 males/64 females) Age 44·3 yrs (group A), 45·2 yrs (group B) Papulopustular and erythematotelangiectatic rosacea	16 weeks A: Doxycycline 40 mg QD + metronidazole gel 1% – QD B: Doxycycline 100 mg QD + metronidazole gel 1% – QD	Mean change in total lesion count, mean change in Clinician's Erythema Assessment, mean change in IGA scale, adverse events
Draelos and Fuller (2005)[40]	RCT double-blind Winston-Salem, U.S.A.	30 (male/female) Age 20–65 yrs Papulopustular and erythematotelangiectatic rosacea	4 weeks A: Lotion vehicle + 1% 4-ethoxybenzaldehyde – BID B: Lotion vehicle – BID	Ordinal assessment erythema, desquamation, dermatitis, uneven skin tone, overall disease severity, tolerability, adverse events
Draelos *et al.* (2006)[41]	RCT investigator-blinded Winston-Salem, U.S.A.	30 (male/female) Age 19–66 yrs Papulopustular and erythematotelangiectatic rosacea	12 weeks A: Azelaic acid 15% gel + self-selected skin cleanser and moisturizer – BID B: Azelaic acid 15% gel BID + standardized PHA containing cleanser and anti-ageing moisturizer	Number of lesions, IGA, participant's assessment of rosacea severity

Table 2 Continued

Study	Methods	Participants	Interventions	Outcomes
Dreno *et al.* (1998)[25]	RCT investigator-blinded Multicentre, France	100 (age and sex unspecified) Moderate to severe rosacea	12 weeks A: Metronidazole 0·75% cream – BID B: Metronidazole 0·75% gel – BID	Decrease in lesions and IGA, patient's preference, adverse events
Elewski *et al.* (2003)[36]	RCT double-blind Multicentre, U.S.A.	251 (56 male/195 female) Age 49 yrs (group A), 46 yrs (group B) Papulopustular rosacea	15 weeks A: Azelaic acid 15% gel – BID B: Metronidazole 0·75% gel – BID	Change in lesion count, % change in lesion count, change in severity for erythema and telangiectasia, IGA, participant's overall improvement ratings and cosmetic acceptability
Fowler (2007)[52]	RCT double-blind Multicentre, U.S.A.	72 (16 male/56 female) Age unclear Papulopustular and erythematotelangiectatic rosacea	16 weeks A: 40 mg doxycycline QD + metronidazole gel 1% BID B: Placebo capsules + metronidazole gel 1% – BID After 12 weeks metronidazole gel discontinued but oral medication or placebo continued until week 16	Mean change in lesion count, IGA, % change in lesion count, change in Clinician's Erythema Assessment score
Grosshans *et al.* (1997)[63]	RCT double-blind Strasbourg, France	34 (6 male/28 female) Mean age 44 yrs (group A), 49 yrs (group B) Papulopustular and erythematotelangiectatic rosacea	4 months A: Rilmenidine 1 mg – QD B: Placebo tablets	N of participants with a decrease of at least 50% in lesion count, decrease in lesion count and erythema, Physician's global investigation
Guillet *et al.* (1999)[26]	RCT investigator-blinded Multicentre, Europe	114 (sex unspecified) Age 22–82 yrs Papulopustular and erythematotelangiectatic rosacea	12 weeks A: Metronidazole 0·75% gel B: Metronidazole 0·75% lotion – application frequency unclear	Compare efficacy and safety of two formulations, reduction in lesion count, physician's global evaluation
Jorizzo *et al.* (1998)[27]	RCT double-blind Multicentre, U.S.A. (distribution of participants unclear)	277 (age and sex unclear) Papulopustular rosacea	10 weeks A: Metronidazole 1% – QD B: Metronidazole 1% – BID C: Placebo (vehicle) – QD D: Placebo – BID	Decrease in N of lesions and erythema, physician's global evaluation
Karsai *et al.* (2008)[68]	RCT double-blind within-patient comparison Karlsruhe, Germany	20 (14 male/6 female) Mean age 62 yrs Erythematotelangiectatic rosacea	One treatment A: 959-nm PDL + 1064-nm Nd:YAG laser (sequential application) B: 959-nm PDL C: 1064-nm Nd:YAG If no effect treatment was repeated up to three times in the same session	Improvement assessed by review of standardized photographs, side-effects
Koca *et al.* (2010)[42]	RCT open-label Zonguldak, Turkey Baseline imbalance	49 (29 male/20 female) Mean age 50·7 yrs (group A), 48·4 yrs (group B) Papulopustular rosacea	12 weeks A: Metronidazole cream 1% – BID B: Pimecrolimus cream 1% – BID	Change in N of lesions, severity of rating of erythema and telangiectasia

Table 2 Continued

Study	Methods	Participants	Interventions	Outcomes
Koch and Wilbrand (1999)[64]	RCT double-blind Kassel, Germany	40 (11 male/29 female) Age unclear Facial rosacea	6 weeks A: Dark sulphonated shale oil 200 mg 2 tab TID – after 2 weeks 2 tab BID B: Placebo	Reduction in lesions, reduction in erythema, reduction of scaling, IGA
Koçak *et al.* (2002)[28]	RCT double-blind Ankara, Turkey	63 (15 male/48 female) Mean age 51 yrs Papulopustular rosacea	2 months A: Permethrin 5% cream – BID B: Metronidazole 0·75% gel – BID C: Placebo – BID	Mean difference in erythema, telangiectasia, oedema and phyma, mean difference in N of lesions and *Demodex folliculorum*
Lebwohl *et al.* (1995)[43]	RCT investigator-blinded Multicentre, U.S.A.	63 (21 male/42 female) Age 25–80 yrs Papulopustular and erythematotelangiectatic rosacea	8 weeks A: Sodium sulphacetamide 10%/sulphur 5% – BID B: Metronidazole 0·75% gel – BID	PGA, overall severity of rosacea (papulopustules, erythema, telangiectasia), adverse events, patient evaluated global response, cosmetic acceptability
Maddin (1999)[37]	RCT double-blind within-patient comparison Vancouver, Canada	40 (11 male/29 female) Mean age 52·2 yrs (males), 49·6 yrs (females) Papulopustular rosacea	15 weeks A: Azelaic acid 20% cream – BID B: Metronidazole 0·75% cream – BID	Self-assessed changes in rosacea severity, decrease in redness, decrease in lesion count, physician's global evaluation
Marks and Ellis (1971)[50]	RCT double-blind London, U.K.	56 (27 male/29 female) Mean age 47·8 yrs Papulopustular and erythematotelangiectatic rosacea	6 weeks A: Tetracycline TID 250 mg for 1 week and then BID in weeks 2–6 B: Ampicillin dosage unspecified C: Placebo	Lesion count, N of participants with > 50% improvement, amount of erythema, participant's opinion, adverse events
Monk *et al.* (1991)[59]	RCT double-blind Multicentre, U.K.	33 (17 male/16 female) Mean age 46·9 yrs (group A), 50·7 yrs (group B) Papulopustular and erythematotelangiectatic rosacea	9 weeks A: Metronidazole gel 0·75% + placebo capsules – BID B: Placebo gel + oxytetracycline 250 mg – BID	Lesion count, assessment of erythema, physician's global evaluation, adverse events
Montes *et al.* (1983)[44]	RCT double-blind Buenos Aires, Argentina Only first 4 weeks included; bias after 4 weeks	64 (19 male/39 female/6 not known) Age unclear Papulopustular rosacea	4 weeks followed by 4 weeks for participants who showed improvement A: BZP acetone gel 5% QD first 4 weeks and 10% last 4 weeks B: Placebo (acetone gel vehicle)	Lesion count, overall response, erythema and telangiectasia
Mostafa *et al.* (2009)[45]	RCT double-blind, within-patient comparison Zagazig, Egypt	24 (1 male/23 female) Mean age 51·08 yrs Facial rosacea	15 weeks A: Azelaic acid 20% cream – BID B: Metronidazole 0·75% cream – BID C: Permethrin 5% cream – BID	Physician's assessment, photographic assessment, participant's assessment, side-effects
Neuhaus *et al.* (2009)[69]	RCT investigator-blinded within-patient comparison San Francisco, U.S.A.	30 (9 male/21 female) Mean age 45·8 yrs Erythematotelangiectatic rosacea	Three treatment sessions each month A: PDL B: IPL C: No treatment	Erythema (spectrophotometer), erythema grade and telangiectasia grade, quantitative telangiectasia counts, VAS for signs and symptoms

Table 2 Continued

Study	Methods	Participants	Interventions	Outcomes
Nielsen (1983) (study a)[29]	RCT double-blind Boden, Sweden	81 (32 male/49 female) Mean age 47 yrs Rosacea in different degrees	2 months A: Metronidazole cream 1% – QD B: Placebo (vehicle) – QD	Physician's global evaluation, lesion counts, reduction in erythema and telangiectasia, photographic evaluation, participant's opinion
Nielsen (1983) (study b)[60]	RCT double-blind Boden, Sweden	51 (17 male/34 female) Mean age 44 yrs Rosacea	2 months A: Placebo cream QD and oxytetracycline BID – 250 mg B: Metronidazole cream 1% QD and placebo tablets – BID	Reduction in erythema, lesions and telangiectasia, physician's global evaluation, photographic evaluation, participant's opinion
Pye and Burton (1976)[56]	RCT double-blind Bristol, U.K.	29 (sex unspecified) Age 24–86 yrs Variable degrees of rosacea	6 weeks A: Metronidazole 200 mg BID combined with hydrocortisone 1% cream B: Lactose BID combined with hydrocortisone 1% cream	Clinical severity assessed by physician
Rigopoulos *et al.* (2005)[46]	RCT double-blind Multicentre, Europe	246 (70 male/176 female) Mean age 48·9 yrs Facial rosacea	12 weeks A: Cream containing 1% extract of a flavonoid-rich plant, *Chrysanthellum indicum* – BID B: Placebo – BID	Severity of erythema, erythema surface, investigator's overall assessment, investigator's final efficacy assessment
Saihan and Burton (1980)[57]	RCT double-blind Bristol, U.K.	40 (age and sex unspecified) Papulopustular rosacea	12 weeks A: Oxytetracycline 250 mg – BID B: Metronidazole 200 mg – BID	Clinical improvement assessed by participant and two doctors
Sanchez *et al.* (2005)[58]	RCT double-blind Multicentre, U.S.A.	40 (8 male/32 female) Age 41·6 yrs (group A), 38·8 yrs (group B) Papulopustular and erythematotelangiectatic rosacea	12 weeks A: Metronidazole 0·75% lotion BID + doxycycline hyclate 20 mg BID (followed by 4 weeks monotherapy of doxycycline hyclate) B: Metronidazole 0·75% lotion BID + placebo tablets BID (followed by 4 weeks placebo tablets)	Change in lesion count at 12- and 16-week visits, changes in Clinician's Global Severity Score and Clinician's Global Erythema Assessment, adverse events
Sauder *et al.* (1997)[47]	RCT double-blind Multicentre, Canada and U.S.A.; distribution of participants unclear	103 (40 male/63 female) Mean age 50 yrs Papulopustular and erythematotelangiectatic rosacea	8 weeks A: Topical sodium sulphacetamide 10% and sulphur 5% lotion BID B: Placebo (vehicle)	Physician's global evaluation, lesion count reduction, participant's assessment of improvement, erythema and adverse events
Schachter *et al.* (1991)[61]	RCT double-blind Multicentre, Canada	125 (40 male/61 female/24 not known) Mean age 45·4 yrs Papulopustular rosacea	2 months A: Metronidazole 1% cream BID and placebo capsules – TID B: Placebo cream BID and tetracycline 250 mg – TID	Clinical evaluation, adverse events, global evaluations, participant assessed global improvement
Schechter *et al.* (2009)[15]	RCT double-blind Florida, U.S.A.	37 (24 male/13 female) Age 65·7 yrs (group A), 69·6 yrs (group B) Ocular rosacea	3 months A: Ciclosporin 0·05% ophthalmic emulsion – BID B: Artificial tears – BID	Ocular Surface Disease Index (OSDI) to determine the impact on quality of life, Schirmer test, measurement of corneal staining, tear breaking-up time, corneal staining, N of meibomian glands expressed, quality of the excreta

Table 2 Continued

Study	Methods	Participants	Interventions	Outcomes
Sharquie *et al.* (2006)[65]	RCT double-blind Baghdad, Iraq	25 (9 male/16 female) Mean age 48·2 yrs Rosacea in different degrees	3 months (thereafter cross-over) A: Zinc sulphate 100 mg capsules – TID B: Placebo – TID	Disease severity, number of lesions and telangiectasia, and the presence or absence of rhinophyma, photographic assessment, side-effects, ocular response
Sneddon (1966)[51]	RCT double-blind Rotherham, U.K.	85 (26 male/52 female/7 not known) Mean age 47 yrs Papulopustular and erythematotelangiectatic rosacea	4 weeks A: Tetracycline 250 mg – BID B: Placebo – BID	Assessable improvement after 1 month
Tan *et al.* (2002)[30]	RCT double-blind Multicentre, Canada	120 (31 male/89 female) Mean age 51 yrs (group A), 47·7 yrs (group B) Moderate to severe rosacea	12 weeks A: Metronidazole 1% + sunscreen SPF 15 – BID B: Placebo – BID	Physician's global improvement, reduction in lesion counts, reduction facial erythema, local tolerance, reduction facial telangiectasia, safety and tolerability, self-assessed global evaluation
Thiboutot *et al.* (2003) (study a)[33]	RCT double-blind Multicentre, U.S.A.	329 (84 male/245 female) Age 48 yrs (group A), 49 yrs (group B) Papulopustular rosacea	12 weeks A: Azelaic acid 15% gel – BID B: Vehicle – BID	IGA, change in N of lesions, facial erythema, telangiectasia, participant's assessment of rosacea severity, adverse events
Thiboutot *et al.* (2003) (study b)[33]	RCT double-blind Multicentre, U.S.A.	335 (93 male/242 female) Age 48 yrs (group A), 47 yrs (group B) Papulopustular rosacea	12 weeks A: Azelaic acid 15% gel – BID B: Vehicle – BID	IGA, change in N of lesions, facial erythema, telangiectasia, participant's assessment of rosacea severity, adverse events
Thiboutot *et al.* (2008)[34]	RCT double-blind Multicentre, U.S.A. Exclusions (20) in one centre due to protocol deviation	92 (28 male/64 female) Mean age 48·5 yrs (group A), 49·6 yrs (group B) Papulopustular and erythematotelangiectatic rosacea	12 weeks A: Azelaic acid 15% gel QD + placebo gel – QD B: Azelaic acid 15% – BID	IGA, treatment response, change in lesion count, erythema, telangiectasia, investigator's and participant's assessment of overall improvement, participant's opinion on cosmetic acceptability and tolerability
Thiboutot *et al.* (2009)[35]	RCT double-blind (only second phase) Multicentre, U.S.A.	136 (35 male/101 female) Mean age 46·4 yrs (group A), 47·5 yrs (group B) Papulopustular and erythematotelangiectatic rosacea	24 weeks A: Azelaic acid 15% gel – BID B: Vehicle – BID	Relapse rate, adverse events, inflammatory lesion count, IGA, investigator's rating of overall improvement, rating by subject of cosmetic acceptability
Torok *et al.* (2005)[48]	RCT investigator-blind Multicentre, U.S.A.	152 (43 male/109 female) Mean age 47 yrs Papulopustular and erythematotelangiectatic rosacea	12 weeks A: Sodium sulphacetamide 10% and sulphur 5% cream including sunscreen SPF 15 – BID B: Metronidazole 0·75% cream – BID	Total N of lesions, erythema grade, investigator global severity, participant's assessment of global improvement, adverse events, tolerance
Veien *et al.* (1986)[62]	RCT double-blind Multicentre, Denmark	76 (36 male/40 female) Mean age 42·4 yrs Papulopustular and erythematotelangiectatic rosacea	8 weeks A: Metronidazole 1% cream and placebo tablets – BID B: Tetracycline tablets 250 mg BID and placebo cream	Reduction in lesion count, intensity of erythema

Table 2 Continued

Study	Methods	Participants	Interventions	Outcomes
Verea Hernando *et al.* (1992)[49]	RCT double-blind La Coruña, Spain	40 (13 male/27 female) Mean age 57·8 yrs (group A), 62·2 yrs (group B)	3 months A: Erythromycin gel 2% – BID B: Metronidazole gel 0·75% – BID	Number of lesions, erythema and teleangiectasia, global assessment by physician, patient's assessment
Weissenbacher *et al.* (2007)[16]	RCT double-blind (first 4 weeks only) Munich, Germany	40 (25 male/15 female) Mean age 58 yrs Papulopustular rosacea	4 weeks A: Pimecrolimus 1% cream – BID B: Vehicle cream – BID	Rosacea severity score, subjective severity assessment, quality of life assessment, photographic assessment
Wilkin (1989)[66]	RCT double-blind (only first study period) Richmond, U.S.A.	15 (4 male/11 female) Age 41–60 yrs Erythematotelangiectatic rosacea	53 days A: Placebo for 18 days (period A), placebo for 17 days (period B), followed by nadolol 40 mg QD for 18 days (period C) B: Placebo for 18 days (period A), placebo for 17 days (period B), and then nadolol 40 mg BID for 18 days (period C) C: Nadolol 40 mg for 18 days (period A), placebo for 17 days (period B), and then placebo for 18 days (period C) D: Nadolol 40 mg BID for 18 days (period A), placebo for 17 days (period B), and then placebo for 18 days (period C)	Reduction of flushing intensity, number and duration of flushes and intensity as assessed by participant
Wilkin and de Witt (1993)[67]	RCT investigator-blinded U.S.A. (Data largely unclear)	43 (sex distribution unclear) Age 25–70 yrs Papulopustular and erythematotelangiectatic rosacea	12 weeks A: Clindamycin 1% lotion BID + placebo capsules – 4 times daily during first 3 weeks and thereafter BID B: Vehicle lotion BID + tetracycline 250 mg – 4 times daily first 3 weeks and thereafter BID	% change in mean lesion count, skin tolerance, physician's and participant's assessment of result
Wolf *et al.* (2006)[38]	RCT investigator-blind Multicentre, U.S.A.	160 (44 male/116 female) Mean age 51·1 yrs (group A), 51·1 yrs (group B) Papulopustular rosacea	5 weeks A: Metronidazole 1% gel – QD B: Azelaic acid 15% gel – BID	Lesion counts, investigator global severity score, erythema severity, tolerability, adverse events, participant's satisfaction

BID, twice daily; BZP, benzoyl peroxide; IGA, Investigator Global Assessment; IPL, intense pulsed light; N, number; PDL, pulsed dye laser; PGA, Physician's Global Assessment; PHA, polyhydroxy acid; QD, once daily; RCT, randomized controlled trial; TID, three times daily; VAS, visual analogue scale; yrs, years.

Table 3 Summary of results of included studies

Study	Interventions	Summary outcomes	Comments
Akhyani *et al.* (2008)[55]	A: Azithromycin B: Doxycycline	29/37 vs. 24/30 considered themselves improved (RR 0·98, 95% CI 0·77–1·25) N of lesions at baseline 19·24 ± 9·67 and after 3 months 1·90 ± 3·28 for group A, and 18·86 ± 8·95 at baseline and after 3 months 2·34 ± 3·47 for group B	Both treatments reduce the N of lesions from baseline, no evidence of differences between the two groups. However, some data were skewed
Bamford *et al.* (1999)[54]	A: Clarithromycin + omeprazole B: Placebo	N of pustules (SD) 6·2 (8·3) vs. 12·6 (19·3). Total score (SD) 6·3 (2·5) vs. 7·9 (4·9)	No evidence of a difference between the treatment and placebo groups. Data on pustules quite skewed. Data on total score very skewed
Barnhorst *et al.* (1996)[14]	A: Lid hygiene plus warm compresses + metronidazole gel B: Lid hygiene and warm compresses	Eye and eyelid grading pre-post mean (SD) 1·5 (1·7) vs. 1·0 (1·7) (higher score is worse)	Small group, limited data. Participants not blinded. Data skewed
Beutner and Calvarese (2005)[19]	A: Metronidazole gel B: Metronidazole cream C: Metronidazole gel–vehicle	Reduction in lesion count 66·7% vs. 58·3% vs. 46·2% Subjects rated as success according to physicians 38·4% vs. 35·4% vs. 27·5%	Large 'vehicle' effect
Bitar *et al.* (1990)[20]	A: Metronidazole cream B: Placebo cream	N papules (SD) 4·5 (4·24) vs. 6·5 (4·95). N pustules 1·5 (1·41) vs. 3·4 (4·94). Erythema and telangiectasia, no statistical difference Mean change in severity (SD) was 2·80 (1·41) vs. 3·30 (1·41) with MD of −0·50 (95% CI fixed −1·05 to 0·05)	Data on papules and pustules are skewed
Bjerke *et al.* (1989)[21]	A: Metronidazole cream B: Placebo cream	43/50 in metronidazole group considered themselves improved compared with 24/47 in placebo group (RR 1·68, 95% CI 1·25–2·28) Lesion count reduction 78% vs. 48%	No SDs reported for lesion counts
Bjerke *et al.* (1999)[31]	A: Azelaic acid cream B: Placebo (vehicle)	62/76 in azelaic acid group considered themselves improved compared with 22/38 in placebo group (RR 1·41, 95% CI 1·05–1·89). Physician's global evaluation of improvement: 61/76 vs. 21/38 (RR 1·45 95% CI 1·07–1·97). Decrease in lesions 73·4% vs. 50·6%, in erythema 47·9% vs. 37·9%, in telangiectasia 22·3% vs. 23·5%	No SDs reported for lesion counts
Bleicher *et al.* (1987)[17]	A: Metronidazole gel B: Placebo (vehicle)	Self-assessment of improvement, 28/37 vs. 4/37 Physician's global evaluation of improvement, 29/37 vs. 1/37. Decrease in lesion counts, 65·1% vs. 14·9%. Reduction in erythema, 0·8 vs. 0·3 (erythema rating 0–3, higher is worse)	No SDs reported. Within-patient comparison
Breneman *et al.* (1998)[22]	A: Metronidazole cream B: Placebo (vehicle)	Physician's global evaluation of improvement 26/104 vs. 6/52 (RR 2·17, 95% CI 0·95–4·93). Decrease in lesion count 8 vs. 3	No SDs reported for lesion counts
Breneman *et al.* (2004)[39]	A: Benzoyl peroxide and clindamycin gel B: Placebo (vehicle)	Patient's global assessment 1·54 (much better to slightly better) vs. 2·50 (slightly better). Physician's global assessment 1·85 (marked improvement) vs. 2·96 (minimal improvement). Scale, ranging from 0, meaning 'clear', to 5, meaning 'worse'. Reduction in lesion counts 71·3% (25·3) vs. 19·3% (89·6), no statistically significant difference in erythema score, telangiectasia, burning or stinging. Overall rosacea severity assessment improvement 29·3% vs. 10·6%	Some SDs were missing, and most data were skewed

Table 3 Continued

Study	Interventions	Summary outcomes	Comments
Carmichael *et al.* (1993)[32]	A: Azelaic acid cream B: Placebo (vehicle)	On VAS 16/33 participants were improved in the azelaic cream-treated side vs. only 1/33 in the placebo-treated side. Physician's overall rating of improvement 30/33 improved vs. 11/33. Papule count 2·5 (2·87) vs. 6·3 (4·6), pustule count 0·0 (0·17) vs. 0·4 (0·57)	Data were skewed. Within-patient comparison
Dahl *et al.* (1998)[23]	A: Metronidazole gel B: Placebo (vehicle)	Lesion count 3·3 vs. 5·5, relapse rate 23% vs. 42%, free of lesions 53% vs. 32%. Erythema (74% had no or mild erythema vs. 55%), telangiectasia (no significant difference or effect) and dryness were also assessed	No SDs were provided N of adverse events unclear
Dahl *et al.* (2001)[24]	A: Metronidazole 0·75% cream B: Metronidazole 1% cream	Median % change, inflammatory lesion counts from baseline to end point −62% for group A vs. −60% for group B. % change in total erythema severity score from baseline to end point −26% for group A vs. −30% for group B	
Del Rosso *et al.* (2007) (study a)[18]	A: Doxycycline 40 mg B: Placebo	58/127 in group A achieved a two-point or greater improvement in IGA score compared with 32/124 in group B (RR 1·77, 95% CI 1·24–2·52); 39 participants in group A achieved an IGA score of 0 (clear) or 1 (near clear) vs. 24 in group B (RR 1·59, 95% CI 1·02–2·47). Mean change in Clinician's Erythema Assessment scale (0 = none and 4 = severe redness) −2·7 vs. −1·8 (authors state P = 0·017) Dropouts: 26/127 vs. 21/124 (RR 1·21, 95% CI 0·72–2·03). Adverse events: 56 in group A vs. 48 in group B (RR 1·14, 95% CI 0·85–1·53)	SDs were missing, some were calculated by B.R.C.
Del Rosso *et al.* (2007) (study b)[18]	A: Doxycycline 40 mg B: Placebo	32/142 in group A had achieved a two-point or greater improvement in IGA score compared with 23/144 in group B (RR 1·41, 95% CI 0·87–2·29). More than twice as many participants achieved an IGA score of 0 (clear) or 1 (near clear) in group A; 21 participants in group A achieved an IGA score of 0 or 1 vs. 9 in group B (RR 2·37, 95% CI 1·12–4·99). Mean change in Clinician's Erythema Assessment scale: no statistically significant difference. Mean total lesion count at week 20 was 10·3 vs. 15·3 Dropouts: 27/142 vs. 26/144 (RR 1·05, 95% CI 0·65–1·71). Adverse events: 93 vs. 74 (RR 1·27, 95% CI 1·04–1·55)	SDs were missing, some were calculated by B.R.C.
Del Rosso *et al.* (2008)[53]	A: Doxycycline 40 mg + metronidazole gel B: Doxycycline 100 mg + metronidazole gel	IGA mean change from baseline, −0·01 (95% CI fixed −0·12 to 0·10). Change in total inflammatory lesion count, −0·30 (95% CI fixed −3·03 to 2·43). Change in Clinician's Erythema Assessment from baseline. Scores range from 0 to 4, 0 = no redness present, 4 = severe redness. −4·2 for 40 mg group vs. −4·0 for 100 mg group. Adverse events: 6/44 participants treated with 40 mg vs. 26/47 participants in 100 mg group (RR 0·25, 95% CI 0·11–0·54)	Unclear how many people were screened N of lesions at baseline unclear SDs were missing. Some were calculated by B.R.C.
Draelos and Fuller (2005)[40]	A: Lotion (vehicle) + 1% 4-ethoxybenzaldehyde B: Lotion (vehicle)	% improvement in erythema: 43·7% in the active treatment group vs. 16·7% in vehicle group (authors state difference between the two groups is not statistically significant). % improvement in overall severity; 49% vs. 15% (authors state P < 0·05)	Percentage improvement in dermatitis is not addressed Data of subject evaluation not provided

Table 3 Continued

Study	Interventions	Summary outcomes	Comments
Draelos et al. (2006)[41]	A: Azelaic acid gel + self-selected skin cleanser and moisturizer B: Azelaic acid gel + standardized PHA-containing cleanser, and anti-ageing moisturizer	No statistically significant treatment difference in change in median lesion count, no exact data are provided, only figure. Statistically significant treatment difference in erythema severity in favour of PHA group after 8 and 12 weeks, no exact data are provided, only figure	Unclear how many patients were randomized in each group and because very limited outcomes data were reported no reliable conclusions could be drawn
Dreno et al. (1998)[25]	A: Metronidazole 0·75% cream B: Metronidazole 0·75% gel	Physician's global evaluation was good to excellent in 77·5% of participants in cream group vs. in 73·2% in gel group. Reduction in lesion counts was 61·3% in cream group vs. 63·5% in gel group	Stated as ITT analysis but the only data that were reported was PP 'analysis' at 12 weeks. 67 out of 100 were analysed
Elewski et al. (2003)[36]	A: Azelaic acid gel B: Metronidazole gel	50/124 participants in the azelaic acid gel group considered themselves improved vs. 43/127 in the metronidazole gel group (RR 1·19, 95% CI 0·68–1·65). 86/124 participants were considered to be improved by the physicians vs. 70/127 in the placebo group (RR 1·26, 95% CI 1·03–1·53). Decrease in lesions is 12·9 vs. 10·7 (P = 0·003), decrease in % lesions 72·7% vs. 55·8% (P < 0·002). Erythema improvement 56% vs. 42% (P = 0·02)	Difference of two lesions is statistically significant, but not clinically relevant, authors themselves stated that a difference of five lesions was considered relevant. SDs are lacking. Metronidazole seemed to be better tolerated with fewer side-effects
Fowler (2007)[52]	A: 40 mg doxycycline + metronidazole gel B: Placebo capsules + metronidazole gel	Mean change in physician's global evaluation score −1·3 vs. −0·8 (authors state P = 0·01). Mean change in lesion count −13·86 vs. −8·47 (authors state P = 0·002). Mean % change in lesions count −66·4% vs. −48·2% (authors state P = 0·008). Mean change from baseline in erythema score −1·3 vs. −0·7 (authors state no statistically significant difference)	No SDs were provided
Grosshans et al. (1997)[63]	A: Rilmenidine B: Placebo tablets	6/15 vs. 6/19 considered their rosacea improved (RR 1·27, 95% CI 0·51–3·14). The physicians reported that 5/15 vs. 1/19 showed improvement (RR 6·33, 95% CI 0·83–48·59), and in line with the participants' assessments rilmenidine was not considered to be effective. 69·2% vs. 57·1% had at least 50% decrease in lesion count. Decrease in lesion count 1 vs. 2	No SDs were provided
Guillet et al. (1999)[26]	A: Metronidazole 0·75% gel B: Metronidazole 0·75% lotion	PGA: 55% was markedly improved or clear in the gel group vs. 61% in the lotion group. Quote: '... reducing inflammatory lesion counts by more than 70% on gel and lotion'	Frequency of application not reported. Poster, data incomplete
Jorizzo et al. (1998)[27]	A: Metronidazole 1% QD B: Metronidazole 1% BID C: Placebo (vehicle) QD D: Placebo BID	Rates of improvement assessed by physicians 79% vs. 72% vs. 39% vs. 45%. Decrease in lesion count 58% vs. 58% vs. 30% vs. 40%. Physician's global evaluation of improvement 79% vs. 72% vs. 39% vs. 45%	Unclear how many participants were initially recruited. Unclear how many participants started in each group, no SDs, dropout rate unclear. Data seem very skewed
Karsai et al. (2008)[68]	A: PDL + Nd:YAG laser B: 959-nm PDL C: 1064-nm Nd:YAG	After 4 weeks the N of participants and treated sites with dual wavelength, grade 1 = 1 (participant), grade 2 = 1, grade 3 = 10 and grade 4 = 8 In the PDL group, grade 1 = 5 (participants), grade 2 = 3, grade 3 = 2, and grade 4 = 0 In the Nd:YAG group, grade 1 = 2 (participants), grade 2 = 6, grade 3 = 2, and grade 4 = 0 Adverse events were transient purpura and immediate post-treatment erythema. Authors state no statistical significance between group differences	Only nose was treated, no numbers of adverse events are provided

Table 3 Continued

Study	Interventions	Summary outcomes	Comments
Koca *et al.* (2010)[42]	A: Metronidazole cream B: Pimecrolimus cream	25/25 showed a measure of improvement compared with 22/25 (RR 1·13, 95% CI 0·96–1·33). Change in N of lesion counts from 16·0 ± 4·6 to 0·6 ± 1·5 vs. from 26 ± 14·4 to 3·7 ± 6·8. No significant difference from baseline to endpoint in both groups for erythema or telangiectasia	N of lesion counts is massively skewed and the baseline data for number of lesions in the two groups are not comparable (26 vs. 16)
Koch and Wilbrand (1999)[64]	A: Dark sulphonated shale oil B: Placebo	Lesion counts 15·9 to 4·3 in treatment group and 16·1 to 14·1 in placebo ($P < 0·0001$). No side-effects were noted	Total N randomized 30, unclear how many in each group. Poster, incomplete data. SD not reported
Koçak *et al.* (2002)[28]	A: Permethrin 5% cream B: Metronidazole gel C: Placebo	MD in erythema score (SD) 1·30 (0·76) vs. 1·45 (0·69) vs. 0·05 (0·22). MD in papules 4·30 (5·51) vs. 5·10 (5·44) vs. 0·25 (1·29). MD in pustules 1·78 (3·74) vs. 3·50 (3·55) vs. 0·25 (0·72). No effects on rhinophyma and telangiectasia	Most data are skewed. Except for pustules, permethrin 5% cream showed same results as metronidazole
Lebwohl *et al.* (1995)[43]	A: Sodium sulphacetamide/ sulphur B: Metronidazole gel	No statistically significant difference in decrease of papule count (MD −1·10, 95% CI −3·19 to 0·99). However, there was a statistically significant difference in decrease in the pustule count in favour of group A (MD −1·90, 95% CI −3·01 to −0·79). No statistically significant treatment differences in any of the patient evaluations. Adverse events: 6 (concerning five patients) vs. 3. The five patients discontinued treatment in group A vs. one in group B due to adverse events that were rated as related to treatment	There are also data of physician's global evaluation; however, no baseline data are provided. No exact data are provided for patient evaluations
Maddin (1999)[37]	A: Azelaic acid cream B: Metronidazole cream	Mean score on the azelaic acid-treated side was according to the patients 1·87 (SD 0·76) compared with 2·33 (SD 0·95) on the metronidazole-treated side ($P = 0·02$, higher score is worse). Regarding the physicians: 2·7 (SD 1·0) compared with 3·1 (SD 1·0) on the metronidazole-treated side ($P = 0·05$). Decrease in lesion count 78·5% vs. 69·4%	Large SDs, data skewed
Marks and Ellis (1971)[50]	A: Tetracycline B: Ampicillin C: Placebo	14/20 vs. 14/17 vs. 9/19 considered themselves improved. Lesion count post-treatment 4·60 (6·20) vs. 9·53 (8·79) vs. 16·63 (12·81). N improved > 50% 17/20 vs. 9/17 vs. 4/19 were considered to be improved according to the physicians	Large SDs, data skewed. Dropouts unclear
Monk *et al.* (1991)[59]	A: Metronidazole gel + placebo capsules B: Placebo gel + oxytetracycline	8/16 vs. 12/17 considered themselves improved (RR 0·71, 95% CI 0·40–1·26). 9/16 vs. 12/17 were improved according to physicians (RR 0·80, 95% CI 0·47–1·35). Reduction in lesion count of more than 50% in both groups, with 100% clearing in 75% vs. 66%	The data were analysed using a χ^2test comparing proportion of patients with no lesions at week 9 vs. those with them. The Ns are small (27 in total) and the analysis was a completers' analysis. Analysis should have been a 'change from baseline' in line with all the other papers presented this time, rather than a χ^2 test. Some SD are missing
Montes *et al.* (1983)[44]	A: BZP acetone gel B: Placebo	19/31 vs. 9/27 were considered improved (RR 1·84, 95% CI 1·01–3·36). Overall response 2·69 vs. 3·71, papule score 0·89 vs. 1·91, pustule score 0·46 vs. 1·31 in favour of BZP (higher score is worse)	Unclear how many participants started, only first 4 weeks included

Table 3 Continued

Study	Interventions	Summary outcomes	Comments
Mostafa *et al.* (2009)[45]	A: Azelaic acid cream B: Metronidazole cream C: Permethrin cream	At end of treatment azelaic acid was statistically significantly more effective on inflammatory lesions than both metronidazole and permethrin creams, while there was no statistically significant difference between metronidazole and permethrin (authors state). There was a statistically significant difference in the mean score of erythema at end of treatment for the three groups ($P < 0{\cdot}05$). The effect of the three creams on erythema was not statistically significantly different from each other. (Side-effects included itching, burning sensation, oedema and scales. No significant differences in side-effects between the three groups)	The study analysis has been carried out on skewed data
Neuhaus *et al.* (2009)[69]	A: PDL B: IPL C: No treatment	Patient assessment – repeated-measures analysis using GEEs revealed statistically significantly better results after IPL or PDL in all of the following patient-rated signs and symptoms than in untreated controls: erythema, flushing, dryness, burning and pruritus (all $P < 0{\cdot}05$). Blinded investigator rating – statistically significant lower erythema and telangiectasia grades were seen in IPL- and PDL-treated groups (all $P < 0{\cdot}01$) than the nontreated group, but no statistically significant differences were seen between IPL and PDL ($P > 0{\cdot}6$)	No exact data were provided, making the data unusable
Nielsen (1983) (study a)[29]	A: Metronidazole cream B: Placebo (vehicle)	Physician's global evaluation of improvement 24/41 vs. 8/40 (RR 2·93, 95% CI 1·50–5·73). Papule count 8·6 vs. 16·6, and pustule count 0·3 vs. 0·8. Reduction on erythema from 3·8 to 2·5 for metronidazole group and from 3·7 to 3·1 in placebo group. Authors state $P < 0{\cdot}05$. No effects on telangiectasia	No SDs were provided
Nielsen (1983) (study b)[60]	A: Placebo cream and oxytetracycline B: Metronidazole cream and placebo tablets	24/22 vs. 24/26 patients considered themselves improved (RR 0·99, 95% CI 0·84–1·17). 24/25 vs. 25/26 were improved according to the physicians (RR 1·0, 95% CI 0·78–1·12). No adverse events in both groups	
Pye and Burton (1976)[56]	A: Metronidazole orally combined with hydrocortisone 1% cream B: Lactose combined with hydrocortisone 1% cream	The physicians considered that 10/15 vs. 2/14 improved (RR 4·64, 95% CI 1·23–17·68)	Only limited data were given in this study
Rigopoulos *et al.* (2005)[46]	A: Cream containing 1% extract of a flavonoid-rich plant, *Chrysanthellum indicum* B: Placebo	98/125 vs. 92/121 patients considered themselves improved (RR 1·03, 95% CI 0·90–1·18). 68/125 showed improvement vs. 54/121 according to physicians (RR 1·22, 95% CI 0·94–1·57). Mean change in rosacea severity score from base line: difference was −0·34 in favour of the flavonoid-rich cream (fixed 95% CI −0·50 to −0·18)	
Saihan and Burton (1980)[57]	A: Oxytetracycline orally B: Metronidazole orally	According to the combined rating of participants and physicians, no evidence of a difference between treatments was found at end of study. Scale 1–3, a higher rating indicating lesser severity. The mean scores were 2·30 (SD 1·00) vs. 2·60 (SD 0·70), difference −0·30 (95% CI −0·83 to 0·23)	Limited data were provided in this study
Sanchez *et al.* (2005)[58]	A: Metronidazole lotion + doxycycline hyclate 40 mg B: Metronidazole lotion + placebo tablets	Reduction in lesions 15 vs. 6. Authors state that reduction in doxycycline group was still statistically significant at week 16 ($P < 0{\cdot}01$) Clinician's global severity score (0–4, lower is better): decrease from baseline of 0·9 vs. 0·4	Data from graphs, SDs are missing

Table 3 Continued

Study	Interventions	Summary outcomes	Comments
Sauder *et al.* (1997)[47]	A: Topical sodium sulphacetamide and sulphur lotion B: Placebo (vehicle)	Self-assessed improvement in rosacea severity 90% vs. 58%. Physician's evaluation of improvement 98% vs. 68%, participants and physicians 7-point improvement score both showed $P < 0{\cdot}001$ using nonparametric test. Lesion count reduction (SEM) 78% (4·5) vs. 36% (8·9), $P < 0{\cdot}001$ using nonparametric test. Improvement in erythema 83% vs. 31% (authors state $P < 0{\cdot}001$)	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
Schachter *et al.* (1991)[61]	A: Metronidazole cream and placebo capsules B: Placebo cream and tetracycline orally	The trialists concluded that topical metronidazole and oral tetracycline both improve the papule and pustule counts and, that 'metronidazole applied topically as a 1% cream is well tolerated and is as effective as standard therapy with tetracycline 250 mg 3 times a day'	No exact data are provided. Data estimated from figures. 125 were randomized, unclear how many in each group, there were 24 withdrawals. The study is at high risk of bias due to the significant number of dropouts and based on the data reported we are unable to concur with the conclusions of equivalent effectiveness reached by the investigators
Schechter *et al.* (2009)[15]	A: Ciclosporin 0·05% ophthalmic emulsion B: Artificial tears	Assessment of changes in quality of life were carried out with the Ocular Surface Disease Index (scale 0–100, 100 = worst). Baseline scores were 19·1 (SD 13·9) vs. 16·9 (SD 15·8). Difference between the change scores at completion of the study was 8·6 in favour of topical ciclosporin ($P = 0{\cdot}022$, 95% CI 1·78–15·42). Data of physicians' assessments confirm efficacy of topical ciclosporin (Schirmer score, tear break-up time, corneal staining and number of unoccluded expressible meibomian glands)	
Sharquie (2006)[65]	A: Zinc sulphate orally B: Placebo	Lesions showed a statistically significant decrease 1 month after starting treatment with zinc sulphate and become 0 after 3 months of therapy in all participants on zinc sulphate, but not in placebo group. Erythema was also statistically significantly reduced after 3 months in zinc sulphate group but not in placebo group. There was no significant effect of zinc sulphate on telangiectasia. No important side-effects were reported apart from mild gastric upset in three patients who were on zinc sulphate	SDs at 3 months missing. Numbers of papules and pustules are not provided
Sneddon (1966)[51]	A: Tetracycline orally B: Placebo	28/36 improved vs. 19/42 in placebo (RR 1·72, 95% CI 1·18–2·50). Assessable improvement after 1 month 78% vs. 45%	Dropouts unclear, adverse events unclear
Tan *et al.* (2002)[30]	A: Metronidazole 1% + sunscreen SPF 15 B: Placebo – BID	Without any reference to data it was reported that patient's self-assessment showed significant improvement ($P = 0002$). Reduction in N of lesions 13·57 (15·2) in metronidazole group vs. 4·56 (12·3) in placebo group. Reduction in erythema 0·89 (0·52) vs. 0·58 (0·13). No statistically significant difference in local tolerance	Data are skewed. High dropout rate: 17/61 metronidazole compared with 14/59 in the placebo group, and these were excluded from the efficacy analysis

Table 3 Continued

Study	Interventions	Summary outcomes	Comments
Thiboutot *et al.* (2003) (study a)[33]	A: Azelaic acid gel B: Vehicle	100/164 patients in azelaic acid group considered themselves improved compared with 71/165 in placebo group (RR 1·42, 95% CI 1·14–1·76). Physician's global evaluation of improvement: 110/164 vs. 79/165 (RR 1·40 95% CI 1·16–1·70). Change in N of lesions from 17·5 to 6·8 vs. 17·6 to 10·5. Overall improvement in erythema: 44% vs. 29% (P = 0·0017). Overall improvement in telangiectasia: 77% vs. 80% (not statistically significant). Overall improvement according to investigator: 51% vs. 27% (P < 0·001)	SDs not provided but can be estimated from figures
Thiboutot *et al.* (2003) (study b)[33]	A: Azelaic acid gel B: Vehicle	98/169 patients in azelaic acid group considered themselves improved compared with 65/166 in placebo group (RR 1·72, 95% CI 1·34–2·20). Physician's global evaluation of improvement: 120/169 vs. 91/166 (RR 1·30 95% CI 1·09–1·53). Change in N of lesions from 17·8 to 8·9 vs. 18·5 to 12·1. Overall improvement in erythema: 46% vs. 28% (P = 0·0005). Overall improvement in telangiectasia: 73% vs. 78% (not statistically significant). Overall improvement according to investigator: 46% vs. 31% (P < 0·0048)	SDs not provided but can be estimated from figures
Thiboutot *et al.* (2008)[34]	A: Azelaic acid gel QD + placebo gel – QD B: Azelaic acid gel BID	No statistically significant difference was found in any efficacy end point in the comparison azelaic acid 15% gel QD vs. BID (authors state P > 0·05 for all comparisons)	Patients had to achieve a 75% reduction in lesion count to enter the maintenance phase. Data cannot be extrapolated to all patients with papulopustular rosacea. Difference of two lesions is not clinically relevant
Thiboutot *et al.* (2009)[35]	A: Azelaic acid gel B: Vehicle	Relapses: 13 in azelaic acid group and 20 in vehicle group. The increase in mean lesion count in maintenance phase was 5·5 in azelaic acid group and 7·5 (data from figure), authors state P = 0·03. No change in erythema was observed nor in telangiectasia in both groups	
Torok *et al.* (2005)[48]	A: Sodium sulphacetamide and sulphur cream including sunscreen SPF 15 B: Metronidazole cream group	59/75 were considered to be improved vs. 45/77 (RR 1·35, 95% CI 1·08–1·68). Reduction in lesion counts: 80% vs. 72%. Proportion of subjects with improvement of erythema score 69% vs. 45%. 48 subjects reported adverse events in group A vs. 41 in group B. Of these 38 in group A and 20 in group B were related to treatment and this difference was statistically significant (P = 0·003)	No exact data were provided for lesions counts or erythema
Veien *et al.* (1986)[62]	A: Metronidazole cream and placebo tablets B: Tetracycline tablets and placebo cream	Median number of lesions after 8 weeks 11·1 vs. 0. Percentage of no improvement of erythema after 8 weeks 11·1 vs. 12·5	Tetracyclines had a more rapid onset on lesions. Dropout rate 1, but unclear in which group
Verea Hernando *et al.* (1992)[49]	A: Erythromycin gel B: Metronidazole gel	16/22 vs. 17/18 patients considered themselves improved (RR 0·77, 95% CI 0·58–1·02). The physicians' assessments were largely in agreement with these data	Lesion counts: baseline imbalance with respect to N of lesions placed the study at a serious risk of bias, so are not listed here
Weissenbacher *et al.* (2007)[16]	A: Pimecrolimus cream B: Vehicle cream	Dermatology Life Quality Index (score 0–30, higher score = more impairment) showed a reduction of the mean absolute value from 5·50 to 3·10 vs. 6·70 to 3·70 (authors state P = 0·75). VAS (0–100 mm, higher = worse) from 53·45 to 48·95 vs. from 64·75 to 43·35 (authors' reported value P = 0·48). Total rosacea severity score reduced from 6·88 to 4·68 vs. 7·00 to 4·33 (authors state P = 0·59)	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

Table 3 Continued

Study	Interventions	Summary outcomes	Comments
Wilkin (1989)[66]	A: Placebo B: Placebo C: Nadolol 40 mg D: Nadolol 40 mg BID	There were no statistically significant differences between nadolol and placebo pretreatments for flushing reactions provoked in the laboratory, either globally or within challenge agent or dosage categories	We included only first period (A). Small groups, unclear what dropout rate was. Data unusable
Wilkin and de Witt (1993)[67]	A: Clindamycin lotion + placebo capsules B: Vehicle lotion + tetracycline capsules	81·8% considered themselves improved in the clindamycin group vs. 90·5% in the tetracycline group. Physicians' rating of success 94·7% vs. 94·4% improved	Unclear how many patients were randomized in each group, making these data unusable. Total number randomized 43
Wolf *et al.* (2006)[38]	A: Metronidazole gel B: Azelaic acid gel	57/78 vs. 65/82 considered themselves improved (RR 0·92, 95% CI 0·77–1·10). 44/78 were considered by the physicians to be cleared or nearly cleared vs. 44/82, with no statistically significant difference between the groups (RR 1·05, 95% CI 0·79–1·39). Reduction in lesion count: 80% vs. 77%	Unclear if the questionnaire that had been used to assess 'Patient satisfaction' had been validated, tested and piloted. Of questionable face/construct validity, and with a wide range of very subjective and overlapping variables to be measured

BID, twice daily; BZP, benzoyl peroxide; CI, confidence interval; GEE, generalized estimating equations; IGA, Investigator's Global Assessment; IPL, intense pulsed light; ITT, intention to treat; MD, mean difference; N, number; PDL, pulsed dye laser; PGA, Physician's Global Assessment; PHA, polyhydroxy acid; PP, per protocol; QD, once daily; RR, relative risk; VAS, visual analogue scale.

Marks and Ellis (1971) there was insufficient evidence to demonstrate that tetracycline was more effective than placebo.[50] In contrast with the participant-assessed changes, the physicians' assessments indicated that tetracycline appeared to be significantly more effective than placebo. Seventeen of 20 participants in the tetracycline group were considered to be improved vs. four of 19 in the placebo group in the study of Marks and Ellis[50] (RR 4·04, 95% CI 1·66–9·83). The results of the study by Sneddon (1966) showed that 28 of 36 participants in the tetracycline group were improved vs. 19 of 42 in the placebo group (RR 1·72, 95% CI 1·18–2·50).[51]

Two studies which compared doxycycline vs. placebo were included in this review.[18] The data from the Investigator's Global Assessment (IGA) in Del Rosso *et al.*[18] (2007, study a) 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 2-point or greater improvement in IGA score compared with 32 out of 124 in the placebo group (RR 1·77, 95% CI 1·24–2·52). Thirty-nine participants in the doxycycline group achieved an IGA score of 0 (clear) or 1 (near clear) vs. 24 in the placebo group (RR 1·59, 95% CI 1·02–2·47).

In Del Rosso *et al.*[18] (2007, study b) there was no statistically significant difference in IGA; 32 participants of the 142 in the doxycycline 40 mg group had achieved a 2-point or greater improvement in IGA score compared with 23 of 144 in the placebo group (RR 1·41, 95% CI 0·87–2·29). 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 vs. 9 in the placebo group (RR 2·37, 95% CI 1·12–4·99). The dropout rate was comparable between both groups in each of the studies but the number of participants reporting adverse events was higher in the doxycycline groups. The study of Fowler (2007)[52] supported the efficacy data of doxycycline.

Physician-based assessments provided no evidence of any difference in efficacy between the 40 and 100 mg in Del Rosso *et al.* (2008)[53] but only a quarter of the side-effects were reported for the lower as opposed to the higher dose.

The data reported for treatment with clarithromycin and omeprazole were to a large extent considered unusable.[54] One study compared doxycycline (100 mg) with azithromycin and although both treatments appeared equally effective the standard deviations were large and the data were skewed.[55] Two studies which included treatment with oral metronidazole provided limited data.[56,57] Doxycycline 40 mg was compared with topical metronidazole in one study and most data had to be estimated from graphs; however, they indicated that doxycycline might be more effective than topical metronidazole.[58]

Four studies compared topical metronidazole and oral (oxy)tetracycline, but pooling of data was not possible due to clinical heterogeneity between the studies.[59–62] Although the quality of reporting of these studies was poor they did nevertheless indicate that there was no statistically significant difference in effectiveness between metronidazole cream and (oxy)tetracycline.

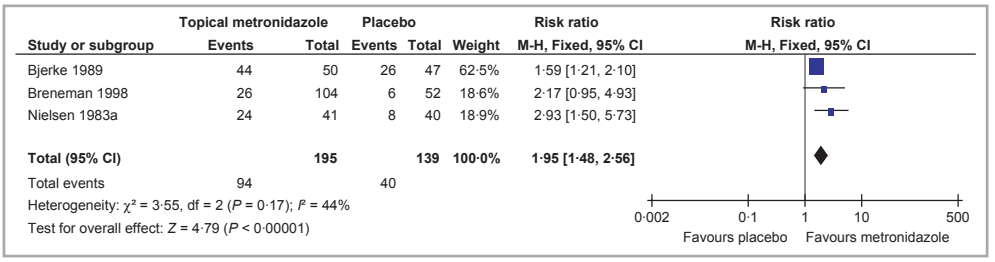

Fig 2. Physician's Global Evaluation of improvement of rosacea.

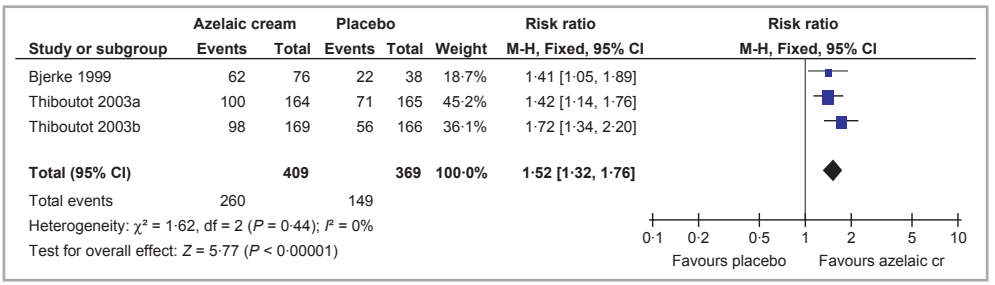

Fig 3. Participant-assessed improvement of rosacea.

We included studies which examined topical clindamycin vs. tetracycline, rilmenidine, dark sulphonated shale oil, zinc sulphate and nadolol but the data from these studies were considered largely unusable.[63–67]

Studies with laser- and/or light-based treatment

In one study the effectiveness of dual-wavelength 595-nm pulsed-dye laser (PDL) and 1064 nm Nd:YAG was investigated, but this was only on the nose.[68] In another study (PDL vs. intense pulsed light therapy vs. control) the data were limited and unusable.[69]

Discussion

Fifty-eight studies were included in this updated Cochrane review. It was somewhat disappointing to see that our principal outcome, 'quality of life', was assessed in only two of the studies[15,16] and that only half the studies addressed participants' assessments of improvement in rosacea severity. The majority of studies focused on numbers 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 participants of the effectiveness of interventions should not be underestimated.

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

Regarding treatments for erythematotelangiectatic rosacea (subtype 1), the use of different scoring systems to assess improvement of 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. Although topical treatments with metronidazole, azelaic acid and sodium sulphacetamide/sulphur as well as oral treatment with doxycycline appeared to be effective in reducing erythema (not telangiectasia), further research into their effects on erythema is needed to confirm these findings.[18,24,28,29,33,36,47,48,52,59] Lasers and light therapies appear to have a major role to play in the treatment of erythematotelangiectatic rosacea but these treatment modalities are still largely under-researched. There was some evidence that PDL and intense pulsed light therapy are capable of reducing erythema and telangiectasia on the face.[69] The effects of laser therapy for rosacea on the nose were investigated in only one study.[68]

For the treatment of papulopustular rosacea (subtype 2), pooled data for topical metronidazole and azelaic acid indicate that both are effective treatments for rosacea.[21,22,29,31,33] However, based on physicians' assessments in Elewski *et al.* (2003)[36] and both physician and participant assessments in Maddin (1999)[37] azelaic acid appears to be more effective than metronidazole albeit with more side-effects and, therefore, further evidence is required.

Topical metronidazole was also shown to be effective in maintaining remission.[23]

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.[34] RCTs investigating the effectiveness of azelaic acid and metronidazole used in maintenance therapy are still required.

The effectiveness of benzoyl peroxide (alone or combined with clindamycin) in the treatment of papulopustular rosacea is

unclear. Inadequate study design, and incomplete and skewed data did not enable definite conclusions to be drawn.[39,44]

Sodium sulphacetamide 10% in combination with sulphur 5% appeared to be more effective than metronidazole, but further research is warranted, as all the relevant included studies were assessed as being at 'high risk of bias'.[43,47,48]

The evidence for the effectiveness of permethrin was inconclusive and therefore further trials with a rigorous study design are required.[28,45]

There was no evidence to support the effectiveness of pimecrolimus; however, this was based on limited and largely unusable data presented in two studies.[16,42]

There was no evidence that 4-ethoxybenzaldehyde, flavonoid-rich plant cream or adjunctive PHA skin regimen were effective.[40,41,46] Although the use of skin products that contain no irritating ingredients are often recommended for the treatment of papulopustular rosacea, no studies on the use of these cosmetics could be included in this review. No eligible studies were identified for dapsone or topical tretinoin although these treatments are still fairly commonly used.[8,70,71]

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 methodologically sound clinical trials.[50,51]

While a number of studies included in this review 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.[18,52,58]

There is evidence that the 40-mg dose is at least as effective as the 100-mg dose, has a correspondingly lower risk of adverse effects, and that, albeit these events may be mild to moderate, more were reported with the 100-mg dose of doxycycline than the 40-mg dose.[53]

Only one study which examined the effects of azithromycin was included but the data were skewed, and consequently more methodologically robust research is required on the effects of this specific intervention.[55]

Several studies examined other interventions such as rilmenidine and ampicillin and although the latter showed some evidence of effectiveness, neither of these are currently considered as treatment options by clinicians.[50,63]

For treatment of phymatous rosacea (subtype 3), surgical therapies as well as ablative laser therapies have been used with reportedly good results, but no eligible randomized controlled trials were identified for this systematic review.

The symptoms of ocular rosacea (subtype 4) are often mild but can also be severe and debilitating, and although ocular involvement occurs in up to 58% of people with rosacea, only two trials included in this review examined the treatment of ocular rosacea.[14,15] Although there was insufficient evidence to support the efficacy of topical metronidazole for ocular rosacea, there was some evidence of a consistent improvement in all outcomes with ciclosporin 0·05% ophthalmic emulsion and that it was more effective than artificial tears in the treatment of ocular rosacea.[14,15]

For all treatments, the adverse events reported were mostly mild and transient and comprised 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 or completely.

In conclusion, evidence of treatment effect could be demonstrated for only a limited number of the interventions studied. These were for interventions with topical metronidazole, azelaic acid and doxycycline (40 mg) in the treatment of moderate to severe rosacea, and ciclosporin 0·05% ophthalmic emulsion for ocular rosacea.

There is insufficient evidence to support either the effectiveness or lack of effectiveness of interventions for the management of erythematotelangiectatic rosacea. Clearing of the 'redness of the face' in patients 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.

For papulopustular rosacea, topical metronidazole, azelaic acid and anti-inflammatory dose doxycycline (40 mg) appear to be effective and safe for short-term use, with similar rates of adverse events as in the placebo groups except for doxycycline 40 mg, which showed an increased risk of side-effects. There is evidence that 40 mg is at least as effective as 100 mg with evidence of fewer adverse effects and there is some evidence that tetracycline is effective. No clear evidence is available demonstrating 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. Well-designed RCTs addressing which is the most effective treatment for phymatous rosacea are therefore still required.

For ocular rosacea ciclosporin 0·05% ophthalmic emulsion showed some evidence of benefit over artificial tears. The impact of available treatment on ocular rosacea warrants further examination as up to 58% of patients with rosacea suffers from this subtype.

Finally, there is an urgent need for high-quality, well-designed and rigorously reported studies of the more widely used treatments for rosacea such as tetracycline, minocycline, azithromycin, isotretinoin, topical retinoids and light-based therapies. Less direct interventions, such as dietary adjustments, avoidance measures for trigger factors, the use of sunscreens, and patient education are further areas of much-needed research. Outcomes collected in future trials should be primarily based on a standardized 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. Standardized and uniform scales should be developed and used for physicians' assessments, and these should reliably reflect global evaluation, lesion counts and assessment of telangiectasia. 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.

It is hoped that clinicians treating patients with rosacea find this evidence-based review helpful and that it will alter their prescribing to improve patient outcomes. Clinical decision-making on the choice of intervention for rosacea should be based on high-level evidence if 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.

What's already known about this topic?

- Rosacea is an important dermatological condition with a significant impact on quality of life.
- There are various options available for treatment but it is unclear which are the most effective.

What does this study add?

- This study updates the existing Cochrane systematic review with additional trials and applies intention-to-treat principles to the meta-analyses.
- Topical metronidazole, azelaic acid and doxycycline (40 mg) appear to be effective and safe for papulopustular rosacea.
- There is evidence that doxycycline 40 mg is at least as effective as 100 mg with evidence of fewer adverse effects.
- Ciclosporin 0·05% ophthalmic emulsion is effective for ocular rosacea.

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