Systematic review of rosacea treatments

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Background: Rosacea is a common chronic skin and ocular condition. It is unclear which treatments are most effective. We have conducted a Cochrane review of rosacea therapies.[1] This article is a distillation of that work.

Objective: We sought to assess the evidence for the efficacy and safety of rosacea therapies.

Methods: Multiple databases were systematically searched. Randomized controlled trials in people with moderate to severe rosacea were included. Study selection, assessment of methodologic quality, data extraction, and analysis were carried out by two independent researchers.

Results: In all, 29 studies met inclusion criteria. Topical metronidazole is more effective than placebo (odds ratio 5.96, 95% confidence interval 2.95-12.06). Azelaic acid is more effective than placebo (odds ratio 2.45, 95% confidence interval 1.82-3.28). Firm conclusions could not be drawn about other therapies.

Limitations: The quality of the studies was generally poor.

Conclusions: There is evidence that topical metronidazole and azelaic acid are effective. There is some evidence that oral metronidazole and tetracycline are effective. More well-designed, randomized controlled trials are required to provide better evidence of the efficacy and safety of other rosacea therapies. (J Am Acad Dermatol 2007;56:107-15.)

Rosacea is a chronic condition characterized by recurrent episodes of facial flushing, erythema, papules, pustules, and telangiectasia in a symmetrical, facial distribution.[1-4] Several well-defined types of rosacea are described including erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea, ocular rosacea, and the variant granulomatous rosacea.[3,4] Ocular rosacea can develop without involvement of other areas of the skin and may wax and wane.[2,5] Rosacea usually presents in the second or third decade of life and has a prevalence of up to 10%.[6] It is especially common in fair-skinned people of Celtic and northern European heritage, with women more often affected than men.[7-9] However, men will more often progress to the later stages.[9]

Abbreviations used:

CI: confidence interval
OR: odds ratio
RCT: randomized controlled trial

Traditionally, rosacea has been managed with a treatment tailored to the specific symptoms presented.[7] A brief overview of these therapies is presented in Table I.[7,9-24] Other treatments tried include facial massage (for edema), spironolactone, beta-blockers, dapsone, oral contraceptives, benzoyl peroxide, bifonazole cream, and treatment of *Helicobacter pylori*.[16,24] Unfortunately, many of these remain poorly studied. This review was performed to systematically evaluate rosacea treatments including the potential impact of nonpharmacologic

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Table I. Rosacea therapies[8-24]

Signs/symptoms	Treatments			
Limited no. of papules/pustules	Topical therapies	Metronidazole (0.75%, 1%) Clindamycin lotion Permethrin 5% cream Tretinoin cream Sulfacetamide 10%/sulfur 5% Azelaic acid (15% gel, 20% cream)		
	Proposed therapies	Tacrolimus Topical NADH		
More extensive skin lesions	Oral antibiotics	Tetracycline Ampicillin Metronidazole Erythromycin	Possible side effects including gastrointestinal symptoms, photosensitivity, candidal vaginitis, reduction in oral contraceptive efficacy	Metronidazole side effects may include neuropathy and mutagenicity
	Oral/topical therapy combination	Discontinue oral treatment once sufficient efficacy noted Maintenance therapy with topical medications		
Vascular symptoms	Pulse dye laser, intense pulsed light			
Severe or persistent rosacea	Oral isotretinoin	13-*cis*-retinoic acid	Possible side effects include: dry sensitive skin, dry mucosae, dry eyes, pruritis, dermatitis, myalgia, elevated liver enzymes, cholesterol and triglyceride elevation Possible fetal abnormalities for women who become pregnant	Routine monitoring of liver functions, cholesterol, triglycerides required
Control of flushing	Oral hypotensives	Clonidine Rilmenidine		
Rhinophyma	Oral Laser therapy Surgical intervention	Low-dose isotretinoin		
Ocular rosacea	Oral antibiotics Topicals	Tetracycline Metronidazole Fusidic acid gel		

NADH, reduced form of ß-nicotinamide adenine dinucleotide.

agents such as foods (eg, spicy food), certain cosmetics, and sunscreens.[10]

Unfortunately, there is no universally accepted clinical definition of rosacea, and there are no standard validated tools for assessing the severity of rosacea. As rosacea can cause shame, embarrassment, low self-esteem, anxiety, lack of confidence, and depression, our primary outcome was the patients' self-assessment of rosacea, and their perception of their quality of life.[8-10]

Table II. Criteria used to assess the methodologic quality of randomized controlled trials for rosacea therapies

Quality assessment criteria:
* Was the randomization procedure used appropriate?
* Was the allocation concealment adequate?
* Was an intention-to-treat analysis used?
* Were health workers and study personnel blind to treatment?
* Were participants blind to treatment?
Aside from the intervention, were groups treated equally?
* Was the study duration fixed/adequate (at least 4 weeks)?
Were number and timing of assessment points fixed?
* Was there an acceptable description or definition of rosacea?
* Was the site of evaluation recorded?
*,† Were concomitant medications permitted and recorded?
Was previous oral and topical rosacea therapy stopped a minimum of 4 weeks before the initial assessment?
Were the therapeutic interventions adequately described?
Were adequate details about how to use/take the medication given to all participants?
* Was the dropout rate less than 5%?

Modified[1] and used with permission.
*All these criteria must be "yes" to be high quality.
†Study must not allow concomitant medications that might change outcome.

METHODS

A systematic review of randomized controlled trials (RCTs) was performed according to a prespecified protocol.[1]

Search strategies

Two reviewers performed independent searches of the following 6 electronic databases: The Cochrane Skin Group Specialized Trials Register (February 2005), The Cochrane Central Register of Controlled Trials (February 2005), MEDLINE (1966-February 2005), EMBASE (1980-February 2005), Biosis (1970-March 2002), and Science Citation Index (1988-February 2005). In addition, the reference lists of all identified RCTs and key review articles were searched. Attempts were made to obtain details of unpublished and ongoing RCTs and grey literature through correspondence with authors and pharmaceutical companies.

Selection criteria

We considered all RCTs evaluating any type of intervention used to treat rosacea. Study participants had to be older than 19 years with moderate to severe rosacea as assessed by a physician. Two reviewers independently assessed these articles for eligibility. Any disagreement was resolved by discussion.

Study design quality assessment and data extraction

Study design was assessed by two reviewers as per the criteria in Table II. Studies meeting all the criteria were considered high quality, whereas studies meeting some, but not all, were generally classified as intermediate. Studies classified as low quality were excluded from analysis. Supporting methodology descriptions for each criterion had to be present in the published text to merit the grading. Details of eligible trials were extracted and summarized using structured data collection forms.

Outcome measures

The primary outcome measures included impact on quality of life and participant-assessed changes in rosacea severity. Secondary outcome measures were physician-assessed changes in rosacea severity, physician's global evaluation (improvement defined as $\geq 50\%$ change), lesion counts (treatment success defined as $>50\%$ reduction), time needed for improvement, and duration of remission. Other outcomes included dropout rates and incidence of adverse events.

Analysis

Quantitative pooling was performed using odds ratio (OR) for categorical measures or weighted mean differences for continuous measures. Where study results were heterogeneous, the reasons for this were explored (eg, treatment or participant factors) and a random effects model was used to reflect the increased uncertainty. Investigation of the robustness of the conclusions according to the methodologic quality of the contributing studies was not practical because there were only a few studies

contributing to each comparison; study quality was considered qualitatively when drawing conclusions.

Some studies used a split-face, within-patient design, where two interventions were allocated randomly to the left and right side of the face. Where possible, a conditional OR (based on the discordant cases only) was calculated; this can be interpreted in the same way as the ORs from parallel group studies.[25] However, the paired data necessary for this were sometimes unavailable, in which case marginal ORs (based on the overall rates for each treatment) were calculated and reported. These marginal ORs should be interpreted cautiously, because they differ from conditional ORs when there is correlation between the outcomes of the two treatments.

RESULTS

Description of studies and methodologic quality of included studies

Searches identified 71 possible RCTs. A total of 29 RCTs were included.[21-23,26-51] Breneman et al[34] and Leyden et al[51] described different outcome measures of the same study and Thiboutot et al[49] reported two RCTs in one publication. Most of the participants in the included studies had papulopustular rosacea and were between 40 and 50 years old; only two studies[27,28] addressed ocular rosacea. Of the 71 studies, 41 were excluded because allocation concealment was inadequate, the study was not blinded, the dropout rate was more than 10%, or other major methodologic flaws,[11,12,18,19,52-85] or because they were awaiting assessment.[13,86,87] Of the 29 included studies, 8 were classified as high quality.[23,26,28-30,32,34,36] The remaining 21 trials were of intermediate quality.[21,22,27,31,33,35,37-50] In only 14 of the 29 trials[23,26,28-30,32,34-36,40,42,47,49] was there adequate blinding of treatment allocation. Blinding of outcome assessment was demonstrated in all except two studies.[27,43] Intention-to-treat analysis was used in 17 of the 29 trials.[21-23,26,28-32,34-39,49] For 14 studies the variability (SD or SE) of continuous measurements were completely or partially lacking, making these data unusable in a meta-analysis.[21,30,32-34,36-38,41-43,46,48,50]

Analysis

The treatments could be categorized into 5 groups: topical metronidazole (15 trials),[21-23,27,29,30,32,33,36,38,39,42,43,48,50] oral antibiotics (8 trials),[23,26,28,40,44,45,47,50] topical azelaic acid (6 trials),[22,31,35,36,49] topical benzoyl peroxide combined with topical antibiotics (2 trials),[34,43] and other therapies (4 trials).[37,41,44,46] Five trials included comparisons in more than one category.[22,23,36,43,44] Even within these therapeutic categories, making comparisons and pooling of data was problematic because of heterogeneous study designs, skewed data, missing variability, and differences in comparators or dosing regimens. Only data on outcome measures from trials on topical metronidazole, topical azelaic acid, and oral tetracycline could be pooled. Most studies used numbers of papules or pustules as an outcome measure rather than a more clinically relevant measure, such as participant assessment of appearance. Below is a summary of the most important conclusions. For details and full reporting of the data, please refer to the complete Cochrane review as published in the Cochrane Library.[1]

METRONIDAZOLE

Topical metronidazole versus placebo

Nine trials assessed the efficacy of topical metronidazole versus placebo.[21,27,29,30,32,33,38,39,42] The treatment period ranged from 8 to 9 weeks in each trial, except for that of Dahl et al,[21] which was 6 months. Three studies addressed self-assessed improvement of rosacea severity.[30,32,42] Only data from two studies[30,42] could be pooled (Fig 1, *A*) and there was clear evidence that metronidazole was more effective than placebo. Bleicher et al[32] confirmed these data (OR 7.0; 95% confidence interval [CI] 2.5-20.0). Data on physician's global evaluation concerning improvement were similar to the patient-assessed measures in favor of metronidazole (OR 7.01; 95% CI 3.56-13.81).[30,33,42] The other studies showed comparable data.[21,27,29,32,38]

Most of the adverse events mentioned were mild, including pruritus, skin irritation, and dry skin. There were no significant differences in the number of adverse events between groups.

Topical azelaic acid versus topical metronidazole

There was no statistically significant difference in the patient self-assessment between topical azelaic acid and topical metronidazole.[22,36] However, physicians rated the azelaic acid group more improved (OR 1.84; 95% CI 1.10-3.09).[36] The number of adverse events was lower in the metronidazole group (OR 4.56; 95% CI 2.07-10.03).[36] However, the severity of adverse events in both groups was reported as mild to moderate and mostly transient.

Topical metronidazole versus oral tetracycline

In two 8-week studies[23,50] no statistically significant treatment difference was seen between metronidazole cream and (oxy)-tetracycline.

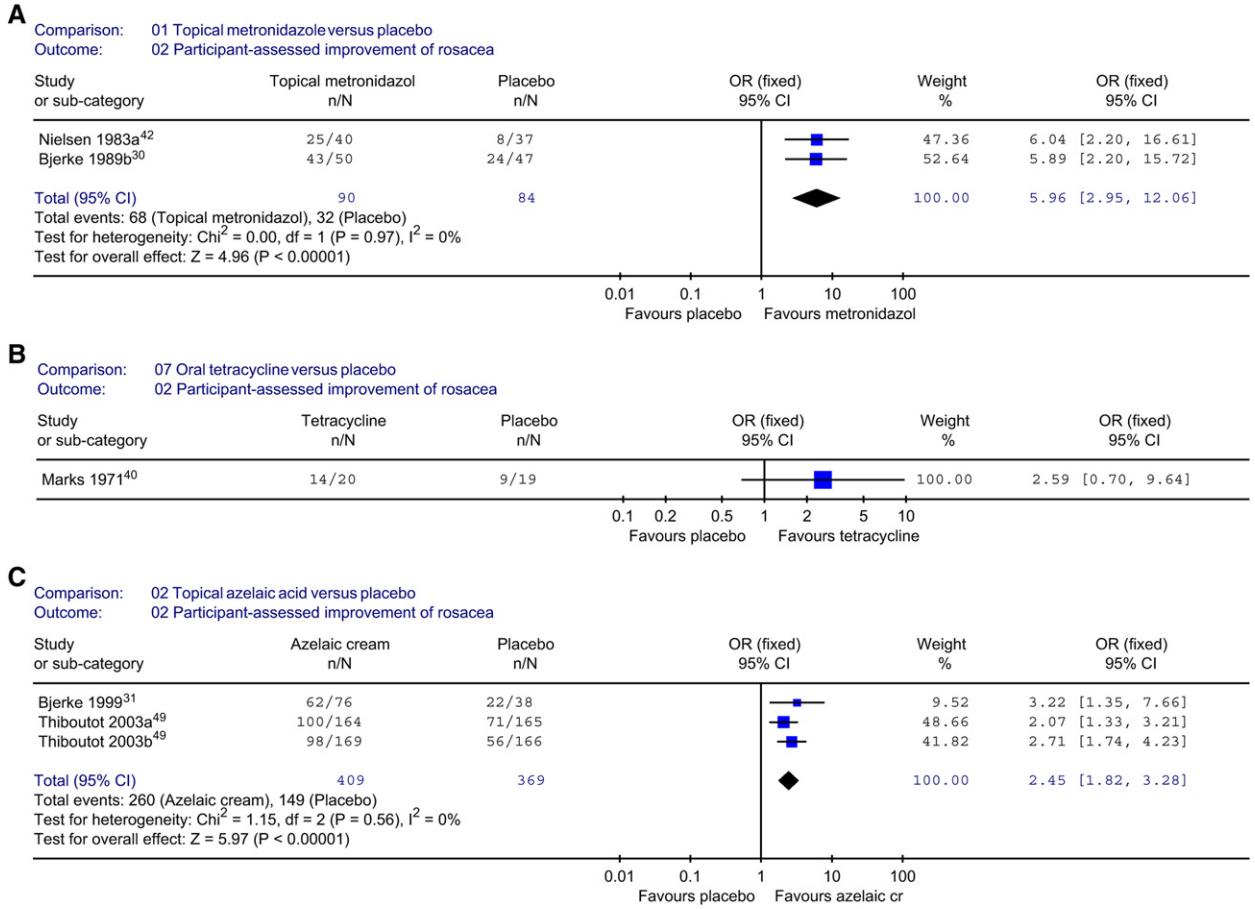

Fig 1. Meta-analytic comparisons of participant-assessed improvement between topical metronidazole and placebo (**A**), oral tetracycline and placebo (**B**), and topical azelaic acid and placebo (**C**). Modified[1] and used with permission. *CI*, Confidence interval; *OR*, odds ratio.

Metronidazole plus sunscreen (sun protection factor 15) versus placebo

A poorly designed study favored metronidazole plus sunscreen over placebo.[48]

Topical metronidazole versus topical permethrin versus placebo

Koçak et al[39] investigated the efficacy and safety of permethrin for the treatment of rosacea. Permethrin was inferior to topical metronidazole because it showed no effect on pustules.

Benzoyl peroxide 5%/erythromycin 3% gel versus metronidazole gel

No significant difference was shown between the two therapies in 4 weeks (OR 0.92; 95% CI 0.21-4.11).[43]

ORAL ANTIBIOTICS

Oral metronidazole versus oral oxytetracycline

In one study, oral metronidazole and oral oxytetracycline were not statistically different at 12 weeks by both physician and patient assessment.[45] No adverse events were reported in either group.

Tetracycline versus placebo

One trial[28] compared oral oxytetracycline with placebo, and in two trials[40,47] oral tetracycline was compared with placebo. These are both (older) tetracyclines with a similar molecular structure and the same pharmacokinetic and pharmacodynamic profile and so the results were pooled. Study duration ranged from 4 to 6 weeks. Bartholomew et al[28] addressed treatment efficacy in ocular rosacea.

There was insufficient evidence of any advantage of tetracycline over placebo according to patients'

Table III. Data to be included in future rosacea studies

Well-designed RCT with reporting the following[88]
Proper description of randomization procedure and allocation concealment
Data presented with appropriate summaries and analysis (including variability)
The number of participants who started in and dropped out from each group
Outcomes primarily based on: patient's opinion of treatment efficacy, quality of life, and patient-assessment
Physician's opinion, reflected by global evaluation, lesion counts, and assessment of telangiectasia
Use of intention-to-treat analysis

RCT, Randomized controlled trial.
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assessment (Fig 1, *B*).[40] However, the dropout rate was unclear and the data were skewed with large variability. By physician assessment, tetracyclines are far more effective than placebo in the treatment of rosacea (OR 6.06; 95% CI 2.96-12.42). Repeated courses of treatment with the same dose achieved lasting remission 3 to 6 months after stopping treatment.[28]

Clarithromycin and omeprazole versus placebo

These data were skewed with large variability and, thus, it is impossible to draw conclusions about this therapy.[26]

AZELAIC ACID

Azelaic acid versus placebo

Four trials compared azelaic acid with placebo.[31,35,49] The treatment period ranged from 9 to 12 weeks. Three studies[31,49] showed a clear improvement in the azelaic acid group as rated by both physicians and patients (Fig 1, *C*). A split-face, within-patient study[35] confirmed these results (marginal OR 30.1; $P < .0003$).

The data on lesion counts did not include variability and the data in the study by Carmichael et al[35] were skewed.

More side effects were reported in the azelaic group (11.5%) versus the placebo group (5.7%) (OR 1.61; 95% CI 0.89-2.92).[31,49] The same holds true for the study of Carmichael et al.[35] Side effects were considered mild and transient with burning, stinging, and irritation being reported most frequently.

BENZOYL PEROXIDE WITH ANTIBIOTICS

Benzoyl peroxide 5%/clindamycin 1% gel versus placebo

The mean scores at 12 weeks for patient's global assessment in the study of Breneman et al[34] were 1.54 (much to slightly better) in the benzoyl peroxide and clindamycin group versus 2.50 (slightly better to same) in the placebo group (authors state $P = .0002$). The mean scores at 12 weeks for physician's global assessment were 1.85 (marked to definite improvement) versus 2.96 for placebo (minimal improvement) (authors state $P = .0026$).

The data showed large variability and some data were missing. Most data were skewed. Treatment-related adverse events included site burning and itching, both well-known side effects of benzoyl peroxide.[34] The same study using photographic assessments as outcomes came to similar same conclusion.[51]

OTHER

Benzoyl peroxide acetone versus placebo

At 4 weeks, benzoyl peroxide showed an improvement on the physician's global evaluation score compared with placebo (OR 3.17; 95% CI 1.08-9.31).[41] The other measurements were also in favor of benzoyl peroxide ($P < .05$). Irritation and burning were frequently reported in both groups.

Oral metronidazole and topical hydrocortisone 1% cream versus oral placebo and topical hydrocortisone 1% cream

The physicians considered 10 of 14 participants treated with oral metronidazole improved versus only 2 of 13 participants on placebo (OR 13.75; 95% CI 2.05-92.04).[44] Only limited data were given in this study.[44]

Rilmenidine versus placebo

Both the patients and the physicians believed that there was no significant difference between rilmenidine and placebo; neither treatment was effective.[37]

Sodium sulfacetamide/sulfur versus placebo

The percentage of participants who considered themselves improved was 90% in the sodium sulfacetamide 10%/sulfur 5% group versus 58% in the placebo group (authors state $P < .001$).[46] The physicians shared this opinion. Adverse events were reported in 38% versus 29%, respectively. Application site reactions such as dryness, erythema, and

Table IV. Questions for which evidence is lacking in the literature

1. What is the efficacy and safety of commonly used treatments for rosacea (eg, tetracycline, minocycline, doxycycline, isotretinoin, and laser therapy)?
2. What is the efficacy and safety of treatments for ocular rosacea?
3. Is there any efficacy of dietary measures and/or sun-protective measures in the treatment of rosacea?
4. What is the efficacy and safety of benzoyl peroxide alone or in combination with topical antibiotics for rosacea?
5. Is permethrin effective and safe for rosacea treatment?

Studies to answer these questions should meet the criteria mentioned in Table III.

pruritus were the most commonly reported adverse events. It was unclear how many participants started in each group or how improvement was defined, and for continuous measurements the variability was large and the data skewed.[46]

DISCUSSION

There were significant limitations in the quality of evidence available for most treatments. Although the clinical design of the included studies was in theory adequate, closer examination revealed that the quality of reported data was often low. Tables III and IV summarize recommendations for future rosacea studies.[88] It should be noted that although split-face studies can be efficient, they are subject to potential biases. Contamination may occur if active cream is accidentally transferred onto the placebo side. Furthermore, a treatment may have systemic effects, beneficial or harmful, which will affect both sides.

Our principal outcome measure, quality of life, was not assessed in any of the studies and only a few studies assessed the participant's own opinion. It is interesting to note that the investigators were more satisfied at the end of the study than the participants.[35,36,40] For other diseases it is often the reverse. This may have implications for clinicians, as a patient's perception of a lack of sufficient efficacy can impact compliance and may lead to the use of alternative therapies. Topical metronidazole and azelaic acid appear to be effective and safe for short-term use, with the rate of adverse events in the placebo groups being similar to the active treatment groups. With regard to tetracycline, only 3 studies[28,40,47] could be included in this review, only one of which assessed the opinion of the participants; however, this study failed to detect any difference from placebo. It is possible that in this case the study duration of 6 weeks was too short.

There were no studies evaluating other treatment options, such as erythromycin, dapsone, and topical tretinoin,[7,16,89-92] that met the inclusion criteria. Three studies were included using benzoyl peroxide alone or in combination with topical antibiotics.[34,41,43] Unfortunately, the quality of these studies was suboptimal. The same holds true for the study with permethrin.[39] Both benzoyl peroxide and permethrin are well-known drugs and further investigation in the treatment of rosacea may be beneficial.

No studies could be included addressing dietary or sun-protective measures; however, two studies did combine treatment with a sun protection factor.[39,48] Although not really substantiated, most people with rosacea are given the advice to avoid trigger factors, (eg, spicy foods, alcohol, and sunlight).

Only two trials could be included on treatment of ocular rosacea,[27,28] even though almost 60% of people with rosacea have ocular involvement.[27,66,79,91] Although often mild, the ocular presentation can be both severe and debilitating. There was insufficient evidence for the efficacy of topical metronidazole.[27] Oral oxytetracycline seems to be effective for ocular rosacea,[28] although only the opinion of the physician was reported.

A very interesting treatment seems to be low-dose doxycycline (20 mg twice a day),[77,93] which is a subantimicrobial dose that reduces inflammation. Other potential advantages of this treatment include lessening the risks of *Propionibacterium* acne's resistance to tetracyclines and lowering the incidence of tetracycline-induced adverse events. Unfortunately, even though they are commonly used to treat rosacea, no RCTs evaluating doxycycline, minocycline, isotretinoin, or laser therapy could be included in this review (most often because of inadequate study design). There is an urgent need for better quality, adequately designed RCTs on the commonly used treatments for rosacea.

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