



Q/What is the most effective treatment for acne rosacea?

EVIDENCE-BASED ANSWER

A/ **TOPICAL METRONIDAZOLE AND AZELAIC ACID** are equally effective for the papulopustular lesions of acne rosacea, although metronidazole is better tolerated. Oral doxycycline, tetracycline, and metronidazole are also effective, but not enough evidence exists to determine whether one is more effective than another or more effective than topical therapy (strength of recommendation [SOR]: **A**, systematic review and individual randomized controlled trials [RCTs]).

Some evidence supports a benefit for topical sodium sulfacetamide with sulfur, and benzoyl peroxide (SOR: **B**, small single RCTs).

Pulsed-light and laser therapy may improve the erythema and telangiectasias associated with acne rosacea (SOR: **C**, case series).

All patients with acne rosacea should use sunscreen and emollients, and avoid skin irritants (SOR: **C**, expert opinion).

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Topical metronidazole and azelaic acid are equally effective, but metronidazole is better tolerated.

Evidence summary

A Cochrane systematic review found that topical metronidazole and azelaic acid are both more effective than placebo for patients with papulopustular lesions of acne rosacea (TABLE). The authors noted that the studies were generally weak because of poor methodology and reporting, small sample sizes, and lack of quality-of-life measures (only 2 RCTs evaluated patient assessment of treatment effectiveness).¹

Another systematic review reported small case series suggesting possible effectiveness with topical tretinoin (43 cases), oral clindamycin (43 cases), oral erythromycin (13 cases), and topical tacrolimus (3 cases).²

Oral metronidazole and tetracycline also work

The Cochrane systematic review also found that oral metronidazole and tetracycline were more effective than placebo for papulopustular lesions.¹ A subsequent systematic review found that anti-inflammatory doses of oral doxycycline (20-40 mg daily) were effective.^{3,4}

Evidence for other oral drugs is limited or inconclusive

Limited supporting evidence exists for oral macrolides, isotretinoin, and spironolactone.^{1,2} Three small placebo-controlled RCTs found insignificant or inconclusive benefits for ampicillin, oral clarithromycin plus omeprazole, and oral rilmenidine (a centrally acting, sympatholytic antihypertensive).¹

Many studies, little difference in drug effects

A large number of studies have compared the effectiveness of one treatment against another, but only one comparison demonstrated a statistically significant benefit. Two RCTs enrolling 104 patients found that oral doxycycline (40 mg daily) in combination with topical metronidazole reduced the number of lesions more than topical metronidazole alone (4 and 7 fewer lesions; $P < .01$ for both studies). It is unclear whether the reduction is clinically significant.^{3,5}

Other comparisons that found no significant difference in effectiveness included:

- 3 RCTs (N=491) that compared topi-

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Pulsed-light and laser therapy may improve the erythema and telangiectasias of acne rosacea.

TABLE

Papulopustular acne rosacea: Doctors assess treatment efficacy in placebo-controlled trials^{1,2}

Primary intervention	Number of trials	Number of patients	Physician assessment of improvement vs placebo
Topical metronidazole	9	488	OR=7.01 (95% CI, 2.5-20)
Topical azelaic acid	4	778	OR=2.23 (95% CI, 1.66-3.00)
Topical benzoyl peroxide	1	58	OR=3.17 (95% CI, 1.08-9.31)
Topical sodium sulfacetamide with sulfur	1	94	90%-98% vs 58%-68% improved (<i>P</i> <.01)
Oral doxycycline	2	577	9.5 and 11.8 fewer lesions with doxycycline vs 4.3 and 5.9 fewer lesions with placebo (<i>P</i> <.001 for both RCTs)
Oral tetracycline	3	152	OR=6.06 (95% CI, 2.96-12.4)
Oral metronidazole	1	27	OR=13.75 (95% CI, 2.05-92.04)

CI, confidence interval; OR, odds ratio; RCTs, randomized controlled trials.

cal metronidazole with topical azelaic acid^{1,2}

- 1 RCT (N=72) that compared once-daily with twice-daily topical azelaic acid⁶
- 1 RCT (N=43) that compared topical metronidazole with topical permethrin¹
- 1 RCT (N=40) that compared oral metronidazole with oral tetracycline¹
- 1 RCT (N=91) that compared oral doxycycline 100 mg daily with 40 mg daily⁴
- 1 open trial (N=67) that compared oral doxycycline with oral azithromycin.⁷

Not all therapies were equally well-tolerated, however. Topical metronidazole produced fewer adverse events than topical azelaic acid (odds ratio=4.56; 95% confidence interval, 2.07-10.03).¹ Doxycycline dosed at 40 mg daily produced fewer gastrointestinal adverse effects than 100 mg daily (5% vs 26%; *P* value not given).⁴

Therapy for erythema and telangiectasia

A systematic review described multiple small case series that reported improvements in erythema and telangiectasias with pulsed-light therapy (188 cases) and laser therapy (82 cases).² Another case series with 17 patients

reported improvements with photodynamic therapy with red light.⁸

General skin care measures

A case series reported improved symptom scores among 20 patients using twice-daily metronidazole gel when they added moisturizing lotion to one side of their face.⁹ Expert opinion recommends using sunscreen and protective emollients and avoiding triggers that cause flushing, such as certain foods, beverages, and cosmetics.^{1,2}

Recommendations

The American Acne and Rosacea Society guidelines state that good evidence supports 3 topical treatments—metronidazole, azelaic acid, and sulfacetamide/sulfur—as well as anti-inflammatory doses of oral doxycycline.

The guidelines also list other topical and oral antibiotic treatments, but cite low-quality evidence for their efficacy and concerns about the emergence of antibiotic resistance. They advise appropriate skin care, including gentle cleansers, moisturizers, and sun protection.¹⁰

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