

Additional File 5. Shortened format: Revised versions of two prototypes

[Case Based]

Systematic review of rosacea treatments

van Zuuren EJ, Gupta AK, Gover MD, Graber M, Hollis S. Systematic review of rosacea treatments. J Am Acad Dermatol. 2007 Jan;56(1):107-15.

CASE STUDY

Case Presentation

- A 35-year-old woman had developed moderate swelling, erythema and papules of the central part of her face for 8 weeks.
- She had been applying various topical cosmetic products sold for acne with no change in her condition.
- One of her hobbies is hiking and she noticed sun exposure aggravated her skin condition, also resulting in burning and stinging sensations.

Treatment

- The patient consulted her family physician who prescribed topical treatment with metronidazole 1% and oral treatment with metronidazole 500 mg twice daily for 2 weeks.

Outcome & Follow-up

- After an initial worsening during the first 3 days the skin condition improved.
- The topical treatment was continued twice daily for 4 weeks and then reduced to once daily for an additional 4 weeks. As well, sun screen was applied whenever outdoors.
- She continued intermittent topical use of metronidazole 1% and remained free of symptoms except for sporadic slight centrofacial erythema.

Clinical Bottom Line

- Topical metronidazole and azelaic acid are effective **① ② ③ ④ ○**
- There is some evidence that oral metronidazole and tetracycline are effective **① ② ③ ○ ○**

SYSTEMATIC REVIEW SYNOPSIS

Purpose 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. The outcome measure was participant-assessed changes in rosacea severity

Results

- 29 studies met the 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.

Stats Tip Odds Ratio: A way of comparing whether the probability of an event is the same for 2 groups.

OR = 1: Event is equally likely in both groups

OR > 1: Event is more likely in the 1st group

See **Table 1** (next page) for more information on each therapy.

Limitations Quality of the studies was generally poor.

Strength of Evidence Rating Scale

The strength of evidence ratings for this guide are based on the overall quantity and quality of clinical evidence.

STRONG RESEARCH SUPPORT **① ② ③ ④ ⑤**

The results are consistent from high quality studies. The conclusions are unlikely to change with further research.

MODERATE RESEARCH SUPPORT **① ② ③ ④ ○**

Current research supports the findings. However, it is possible that conclusions could change with further research.

WEAK RESEARCH SUPPORT **① ② ③ ○ ○**

There are limited studies available for drawing conclusions, or the existing studies have significant limitations.

STRONG EXPERT OPINION **① ② ○ ○ ○ ○**

Consensus based on a panel of experts in the topic field.

WEAK EXPERT OPINION **① ○ ○ ○ ○ ○**

No research-based evidence.

Table 1. Rosacea Therapies

Symptom	Treatments	Adverse Events	Meta-analysis
Limited number of papules / pustules	Topical therapies <ul style="list-style-type: none"> Metronidazole (0.75%, 1%) Clindamycin lotion Permethrin 5% cream Tretinoin cream Sulfacetamide 10%/sulfur 5% Azelaic acid (15% gel, 20% cream) 		Topical metronidazole vs placebo OR: 5.96, 95% CI: 2.96, 12.06 Strength of Evidence ① ② ③ ④ ○ (2 trials) Topical azelaic acid vs placebo OR: 2.45, 95% CI: 1.82, 3.28 Strength of Evidence ① ② ③ ④ ○ (3 trials)
	Proposed therapies <ul style="list-style-type: none"> Tacrolimus Topical NADH 	NADH, reduced form of β -nicotinamide adenine inucleotide	
More extensive skin lesions	Oral antibiotics <ul style="list-style-type: none"> Tetracycline Ampicillin Metronidazole Erythromycin 	Possible side effects include: <ul style="list-style-type: none"> gastrointestinal symptoms photosensitivity candidal vaginitis reduction in oral contraceptive efficacy 	Oral tetracycline vs placebo OR: 2.59, 95% CI: 0.70, 9.64 Strength of Evidence ① ② ③ ○ ○ (2 trials)
	Oral / topical therapy combination	<ul style="list-style-type: none"> Discontinue oral treatment once sufficient efficacy noted Maintenance therapy with topical medications 	<i>No randomized controlled trials available for evaluation.</i>
Vascular symptoms	Pulse dye laser, intense pulsed light		<i>No randomized controlled trials available for evaluation.</i>
Severe or persistent rosacea	Oral isotretinoin <ul style="list-style-type: none"> 13-cis-retinoic acid 	Possible side effects include: <ul style="list-style-type: none"> dry sensitive skin dry mucosae dry eyes pruritis dermatitis myalgia elevated liver enzymes cholesterol and triglyceride elevation Routine monitoring of liver functions, cholesterol, triglycerides required Possible fetal abnormalities for women who become pregnant	<i>No randomized controlled trials available for evaluation.</i>
Control of flushing	Oral hypotensives <ul style="list-style-type: none"> Clonidine Rilmenidine Strength of Evidence ① ② ③ ○ ○ (1 trial: Rilmenidine)		
Rhinophyma	Oral: Low-dose isotretinoin Laser therapy Surgical intervention		<i>No randomized controlled trials available for evaluation.</i>
Ocular rosacea	Oral antibiotics: Tetracycline Topicals Metronidazole Fusidic acid gel Strength of Evidence ① ② ③ ○ ○ (2 trials: 1. Metronidazole ; 2. Oxytetracycline)		

Expert Interpretation:

- Topical metronidazole cream (0.75% and 1%) and azelaic acid cream (15 and 20%) are effective and safe for short term use (8 to 12 wks)
- Oral oxytetracycline (dose = (need from original study)) may be effective for ocular rosacea. Oral tetracycline is more effective than placebo for physician assessment but not for patient outcomes.
- There is no evidence for use of other agents including dapsons, erythromycin, topical tretinoin, benzoyl peroxide, diet or sun protection. The quality of reported studies is poor with lack of blinding, allocation concealment, and intention to treat analysis.

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. 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.)

Methodology: Reviewed 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 determined study quality based on a set of quality assessment criteria. 29 RCTS were included, 8 were classified as high quality and 21 as intermediate.

Limitations: The quality of the studies was generally poor.

Strength of Evidence Rating Scale

The strength of evidence ratings for this guide are based on the overall quantity and quality of clinical evidence.

Strong Research Support

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The results are consistent with high quality studies. The conclusions are unlikely to change with further research.

Moderate Research Support

●●●●●

Current research supports the findings. However, it is possible that conclusions could change with further research.

Weak Research Support

●●●●●

There are limited studies available for drawing conclusions, or the existing studies have significant limitations.

Strong Expert Opinion

●●●●●

Consensus based on a panel of experts in the topic field.

Weak Expert Opinion

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No research-based evidence.

Treatment	Follow Up	Outcomes		
		Self Assessed Improvement	Physician's Evaluation	Adverse Events
Symptom: Limited number of papules/pustules				
Topical metronidazole (9 trials) ●●●●●	8-9 weeks	Better than placebo: OR 7.0; 95% CI 2.5 - 20.0	Better than placebo: OR 7.01; 95% CI 3.56 - 13.81	Mild: pruritus, skin irritation, dry skin
Azelaic Acid (4 trials) ●●●●●	9-12 weeks	Improvement in azelaic acid group. Split-face, within-patient study confirmed results (marginal OR 30.1; P<.0003)		Side effects were considered mild and transient with burning, stinging, and irritation being reported most frequently. More side effects in azelaic group (11.5%) versus placebo group (5.7%) (OR 1.61; 95% CI 0.89 - 2.92)
Metronidazole plus sunscreen SPF 15 (1 trial) ●●●●●	n/a	Poorly designed study favoured metronidazole plus sunscreen over placebo		n/a
Topical azelaic acid (2 trials) ●●●●●	15 weeks	No significant difference with topical metronidazole	Rated azelaic acid more improved (OR 1.84; 95% CI 1.10 - 3.09)	Mild to moderate, mostly transient: burning, stinging, irritation
Topical Permethrin (1 trial) ●●●●●	n/a	Inferior to topical metronidazole	n/a	n/a
Sodium sulfacetamide 10%/sulfur 5% (1 trial) ●●●●●	n/a	90% of patients stated improvement from sodium sulfacetamide versus 58% in placebo group (P <.001).	Physicians found improvement from sodium sulfacetamide 10%/sulfur 5%	Dryness, erthema, pruritus
Clarithromycin and omeprazole (1 trial) ●●●●●	n/a	Impossible to draw conclusions from data		n/a

Treatment	Follow Up	Outcomes		
		Self Assessed Improvement	Physician's Evaluation	Adverse Events
Symptom: More extensive skin lesions				
Oral Tetracycline (2 trials) ●●●●●●	8 weeks	No significant different with topical metronidazole		n/a
	8 weeks	14/20 treated with tetracycline considered improved versus 14/17 treated with ampicillin (OR 0.50; 95% CI 0.10 - 2.41)	17/20 treated with tetracycline considered improved versus 9/17 treated with ampicillin (OR 5.04; 95% CI 1.07 - 23.82)	Mild and transient: 3/17 in ampicillin group reported adverse effects vs 1/20 in tetracycline group
Tetracycline (3 trials) ●●●●●●	4-6 weeks	Insufficient evidence according to patient assessment.	Physician assessment found tetracyclines more effective than placebo (OR 6.06; 95% CI 2.96 - 12.42)	n/a
Oral metronidazole and topical hydrocortisone 1% cream (1 trial) ●●●●●●	n/a	n/a	Considered 10 of 14 participants improved versus 2 of 13 on placebo (OR 13.75; 95% CI 2.05 - 92.04)	n/a
Ampicillin (1 trial) ●●●●●●	6 weeks	Favoured ampicillin over placebo (OR 5.19; 95% CI 1.11 - 24.14)	Favoured ampicillin over placebo, but not statistically significant. (OR 4.22; 95% CI 0.98 - 18.12)	Mild and transient
Benzoyl peroxide (1 trial) ●●●●●●	4 weeks	n/a	Improvement on physician's global evaluation compared with placebo (OR 3.17; 95% CI 1.08 - 9.31)	Adverse effects include irritation and burning.
Oral oxytetracycline (1 trial)	12 weeks	One study found no statistical difference with oral metronidazole		None reported
Benzoyl peroxide 5%/clindamycin 1% gel (1 trial) ●●●●●●	12 weeks	Patient's global assessment better in benzoyl peroxide and clindamycin group (1.54 - much to slightly better) versus placebo group (2.5 - slightly better to same)(P = .0002)	Physician's global assessment better in benzoyl peroxide and clindamycin group (1.85 - marked to definite improvement) versus placebo group (2.96 - minimal improvement) (P= .0026)	Adverse effects included site burning and itching.
Rilmenidine (1 trial) ●●●●●●	n/a	No significant difference		n/a
Oral metronidazole (1 trial) ●●●●●●	12 weeks			None reported
Symptom: Flushing				
Rilmenidine (1 trial) ●●●●●●	n/a	No significant difference		n/a
Symptom: Ocular Rosacea				
Tetracycline (3 trials) ●●●●●●	4-6 weeks	Insufficient evidence according to patient assessment.	Physician assessment found tetracyclines more effective than placebo (OR 6.06; 95% CI 2.96 - 12.42)	n/a
Symptom: Other				
Benzoyl peroxide 5%/erthromycin 3% gel (1 trial) ●●●●●●	4 weeks	no significant difference with metronidazole gel (OR 0.92; 95% CI 0.21 - 4.11)	n/a	n/a