

Additional File 4. Shortened format: Initial 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

Background Rosacea is a common chronic skin and ocular condition.

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 general practitioner who prescribed prednicarbat cream for topical application on the affected regions. She observed a slight improvement of the skin condition during the first week, but suddenly developed a severe worsening with erythema, papules and many pustules later on.

She presented to a dermatologist and was diagnosed with "steroid rosacea". She went off the steroid, started 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.

SYSTEMATIC REVIEW SYNOPSIS

This systematic review 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. See **Table 1**.

Limitations The quality of the studies was generally poor.

Clinical Bottom Line

- There is evidence that topical metronidazole and azelaic acid are effective **①②③④○**
- There is some evidence that oral metronidazole and tetracycline are effective **①②③○○**

Strength of Evidence Rating

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

- STRONG RESEARCH SUPPORT** **①②③④⑤**
- MODERATE RESEARCH SUPPORT** **①②③④○**
- WEAK RESEARCH SUPPORT** **①②③○○**
- STRONG EXPERT OPINION** **①②○○○**
- WEAK EXPERT OPINION** **①○○○○**

Table 1. Rosacea Therapies

| Signs / Symptoms | Treatment | Issues (if any) | 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 and placebo OR: 5.96, 95% CI: 2.96, 12.06 Level of Evidence ① ② ③ ④ ○ |
| | Proposed therapies <ul style="list-style-type: none"> Tacrolimus Topical NADH | NADH, reduced form of β-nicotinamide adenine inucleotide | Topical azelaic acid and placebo OR: 2.45, 95% CI: 1.82, 3.28 Level of Evidence ① ② ③ ④ ○ |
| 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 and placebo OR: 2.59, 95% CI: 0.70, 9.64 Level of Evidence ① ② ③ ○ ○ |
| | Oral / topical therapy combination | <ul style="list-style-type: none"> Discontinue oral treatment once sufficient efficacy noted Maintenance therapy with topical medications | |
| Vascular symptoms | Pulse dye laser, intense pulsed light Level of Evidence ① ② ③ ○ ○ | | |
| Severe or persistent rosacea | Oral isotretinoin <ul style="list-style-type: none"> 13-cis-retinoic acid Level of Evidence ① ② ③ ○ ○ | 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 | |
| Control of flushing | Oral hypotensives <ul style="list-style-type: none"> Clonidine Rilmenidine Level of Evidence ① ② ③ ○ ○ | | |
| Rhinophyma | Oral Low-dose isotretinoin Laser therapy Surgical intervention Level of Evidence ① ② ③ ○ ○ | | |
| Ocular rosacea | Oral antibiotics: Tetracycline Topicals Metronidazole Fusidic acid gel Level of Evidence ① ② ③ ○ ○ | | |

Learning Points & Take Home Messages

- 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.

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Summary of Findings

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.)

Expert Clinician Interpretation:

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- 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 dapsone, 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.

Limitations of Study

The quality of the studies was generally poor.

| Treatment | Period | Self Assessed Improvement of Severity | Physician' s evaluation | Adverse Events |
|--|--------------|---|--|--|
| Symptom: Limited number of papules/pustules | | | | |
| Topical metronidazole ①②③④○ | 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 ①②③④○ | 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 15 ①②③○○ | | Poorly designed study favoured metronidazole plus sunscreen over placebo | | |
| Topical azelaic acid ①②③○○ | 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 Level of evidence: ①②③○○ | | Inferior to topical metronidazole | | |
| Sodium sulfacetamide 10%/sulfur 5% ①②③○○ | | 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, erythema, pruritus |
| Clarithromycin and omeprazole ①②③○○ | | Impossible to draw conclusions from data | | |

| Treatment | Period | Self Assessed Improvement of Severity | Physician' s evaluation | Adverse Events |
|---|-----------|--|---|---|
| Symptom: More extensive skin lesions | | | | |
| Oral Tetracycline ①②③○○ | 8 week | No significant difference with topical metronidazole | | |
| | 6 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 ①②③○○ | 4-6 weeks | Insufficient evidence according to patient assessment. | Physican assessment found tetracyclines more effective than placebo (OR 6.06; 95% CI 2.96 - 12.42) | |
| Oral metronidazole and topical hydrocortisone 1% cream ①②③○○ | | | Considered 10 of 14 participants improved versus 2 of 13 on placebo (OR 13.75; 95% CI 2.05 - 92.04) | |
| Ampicillin ①②③○○ | 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 |
| Oral oxytetracycline | 12 weeks | One study found no statistical difference with oral metronidazole | | None reported |
| Benzoyl peroxide ①②③○○ | 4 weeks | | Improvement on physician' s global evaluation compared with placebo (OR 3.17; 95% CI 1.08 - 9.31) | Adverse effects include irritation and burning. |
| Benzoyl peroxide 5%/clindamycin 1% gel ①②③○○ | 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. |
| Rilmnidine ①②③○○ | | No significant difference | | |
| Oral metronidazole ①②③○○ | 12 weeks | | | None reported |
| Symptom: Flushing | | | | |
| Rilmnidine ①②③○○ | | No significant difference | | |
| Symptom: Ocular Rosacea | | | | |
| Tetracycline ①②③○○ | 4-6 weeks | Insufficient evidence according to patient assessment. | Physican assessment found tetracyclines more effective than placebo (OR 6.06; 95% CI 2.96 - 12.42) | |
| Other | | | | |
| Benzoyl peroxide 5%/erthromycin 3% gel ①②③○○ | 4 weeks | no significant difference with metronidazole gel (OR 0.92; 95% CI 0.21 - 4.11) | | |