Interventions for rosacea
Cochrane review

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Rosacea

- Chronic skin condition in mainly fair-skinned people
- Starts 2nd-3rd decade in life
- 4 subtypes
  - Subtype 1: erythematotelangiectatic rosacea
  - Subtype 2: papulopustular rosacea
  - Subtype 3: phymatous rosacea
  - Subtype 4: ocular rosacea

  1 variant: granulomatous rosacea
- Pathogenesis?: multiple hypotheses
- Therapies?: numerous options….

Subtypes

Subtype 1

Subtype 2

Subtype 3

Subtype 4

The process..

- Course Evidence Based Medicine in Amsterdam
- Contact Skin Group van Cochrane Collaboration
- Title registration
- Finding coauthors
- Writing protocol
- Conducting the review
- First review published in 2004
- First update 2005
- Second update 2011

Methods

- RCTs
- Adults with rosacea
- Any type of intervention, either alone or in combination, versus placebo or active treatment
- Primary outcomes: QoL and participant-assessed changes in rosacea severity

- Secondary outcomes: Physician-assessed changes in rosacea severity (e.g. global evaluation, lesion count), drop-out rates and adverse events

Searches

2 authors independently, no language restrictions!

- MEDLINE
- EMBASE
- BIOSIS
- Science Citation Index
- Cochrane Skin Group Specialised Register
- Cochrane Central Register of Controlled Trials
- Ongoing trials
- Checking references of found studies
- Contact authors and pharmaceutical companies for unpublished studies

Selection of studies en data extraction

2 authors independently

- Checked all references for eligibility
- Risk of bias assessment
- Data extraction
- Data analyses

- Conclusions
- After peer reviewing etc, publication in Cochrane Library
- Keeping it up-to-date

Results

Number of identified records

- 2441 records identified for first review (2004)
- 640 additional records for first update (2005)
- 2198 additional records for last update (2011)

Total number of included studies : 58

Most studies were conducted in participants with papulopustular rosacea with a study duration of 2-3 months

Results for subtype 1

Several studies showed effect on erythema of:

- Topical metronidazole, azelaic acid and sulphacetamide/sulphur, however, limited data
- Doxycycline 40 and 100 mg, and zinc sulphate, however, more research is required

We could only include 2 RCTs with laser and/or light based therapies, those might be effective, but limited data were provided

PDL laser

Intense pulsed light

Before

6 months after last treatment (4 cycles)

Papageorgiou Br J Derm 2008

Results for subtype 2

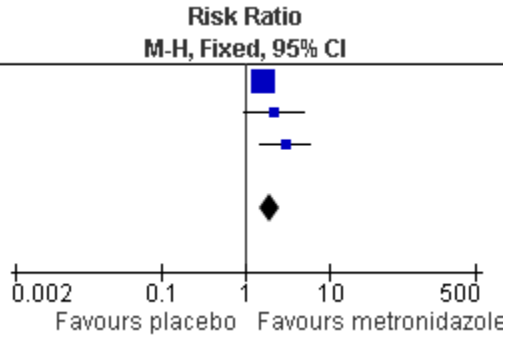
10 studies metronidazole vs placebo. Pooling was only possible for a few of those

Physician's global evaluation of improvement

	Topical metronidazole		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Bjerke 1989b	44	50	26	47	62.5%	1.59 [1.21, 2.10]
Breneman 1998	26	104	6	52	18.6%	2.17 [0.95, 4.93]
Nielsen 1983a	24	41	8	40	18.9%	2.93 [1.50, 5.73]
Total (95% CI)		**195**		**139**	**100.0%**	**1.95 [1.48, 2.56]**
Total events	94		40			

Heterogeneity: Chi² = 3.55, df = 2 (P = 0.17); I² = 44%

Test for overall effect: Z = 4.79 (P < 0.00001)



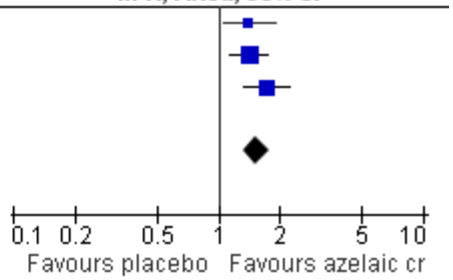
Metronidazole is effective for treatment of papulopustular rosacea

Results for subtype 2 (II)

4 studies with azelaic acid, 3 could be pooled

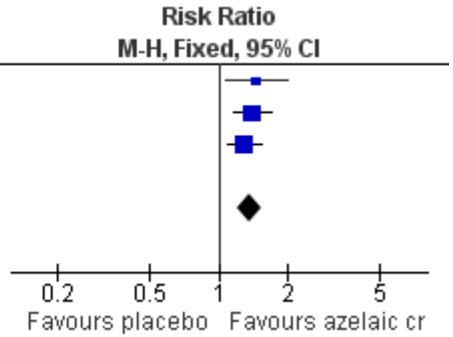
Study or Subgroup	Azelaic cream Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bjerke 1999	62	76	22	38	18.7%	1.41 [1.05, 1.89]
Thiboutot 2003a	100	164	71	165	45.2%	1.42 [1.14, 1.76]
Thiboutot 2003b	98	169	56	166	36.1%	1.72 [1.34, 2.20]
Total (95% CI)		**409**		**369**	**100.0%**	**1.52 [1.32, 1.76]**
Total events	260		149			

Heterogeneity: Chi² = 1.62, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 5.77 (P < 0.00001)



Study or Subgroup	Azelaic cream Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bjerke 1999	61	76	21	38	14.1%	1.45 [1.07, 1.97]
Thiboutot 2003a	110	164	79	165	39.7%	1.40 [1.16, 1.70]
Thiboutot 2003b	120	169	91	166	46.2%	1.30 [1.09, 1.53]
Total (95% CI)		**409**		**369**	**100.0%**	**1.36 [1.21, 1.53]**
Total events	291		191			

Heterogeneity: Chi² = 0.59, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 5.13 (P < 0.00001)



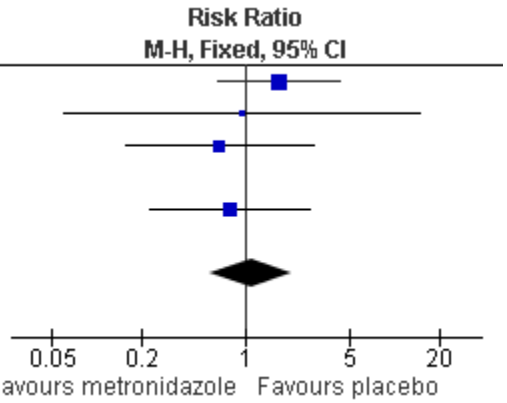
Azelaic acid is effective for treatment of papulopustular rosacea

Results for subtype 2 (III)

Adverse events metronidazole vs placebo

Study or Subgroup	Topical metronidazole Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bitar 1990	10	50	6	50	37.3%	1.67 [0.66, 4.24]
Bjerke 1989b	1	50	1	47	6.4%	0.94 [0.06, 14.60]
Breneman 1998	4	104	3	52	24.9%	0.67 [0.15, 2.87]
Koçak 2002	0	20	0	20		Not estimable
Nielsen 1983a	4	41	5	40	31.5%	0.78 [0.23, 2.70]
Total (95% CI)		**265**		**209**	**100.0%**	**1.09 [0.58, 2.06]**
Total events	19		15			

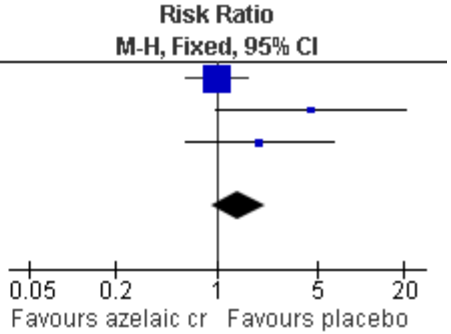
Heterogeneity: Chi² = 1.52, df = 3 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)



Adverse events azelaic acid vs placebo

Study or Subgroup	Azelaic cream Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bjerke 1999	30	76	15	38	76.8%	1.00 [0.62, 1.62]
Thiboutot 2003a	9	164	2	165	7.7%	4.53 [0.99, 20.64]
Thiboutot 2003b	8	169	4	166	15.5%	1.96 [0.60, 6.40]
Total (95% CI)		**409**		**369**	**100.0%**	**1.42 [0.92, 2.19]**
Total events	47		21			

Heterogeneity: Chi² = 4.57, df = 2 (P = 0.10); I² = 56%
Test for overall effect: Z = 1.59 (P = 0.11)



Results for subtype 2 (IV)

3 studies topical metronidazole versus azelaic acid

Rosacea improvement patient-assessed:

- in *Elewski 2003* and *Wolf 2006*: no statistical significant difference
- in *Maddin 1999* azelaic acid was more effective

Rosacea improvement physicians-assessed:

- in *Elewski* and *Maddin* azelaic acid more effective (in *Wolf* : no statistical difference)

More adverse events with azelaic acid in *Elewski*, but not in *Wolf* and *Maddin*

Results and conclusions topicals

- Topical metronidazole and azelaic acid are both effective and safe
- Azelaic acid might be more effective than metronidazole but more research is needed

Data not presented today, but

- Topical metronidazole has shown to be effective in maintaining remission
- Azelaic acid once a day is as effective as twice a day (one study)

Results and conclusions topicals (II)

No evidence that these treatments are effective:

- Benzoylperoxide (or combined with clindamycin)
- Sulphacetamide 10% + sulphur 5%
- Permethrin
- Pimecrolimus
- 4-ethoxybenzaldehyde (flavonoid cream)

No studies could be included regarding topical retinoids or special cosmetics

Results of oral treatments for subtype 2

2 studies with tetracyclines: old (1966, 1971), short (4-6 weeks) and of poor quality. Clinicians have no doubt about effectiveness, but evidence is lacking

- Physician-assessed: tetracycline was more effective than placebo
- Patient-assessed (1 study): no difference between the groups

Studies of *del Rosso 2007, Fowler 2007, Sanchez 2005*) showed effectiveness of doxycycline 40 mg over placebo

Results of oral treatments for subtype 2

No statistical significant difference in number of adverse events between both groups

There is evidence that 40 mg is at least as effective as 100 mg but with less adverse effects (*Del Rosso 2008*)

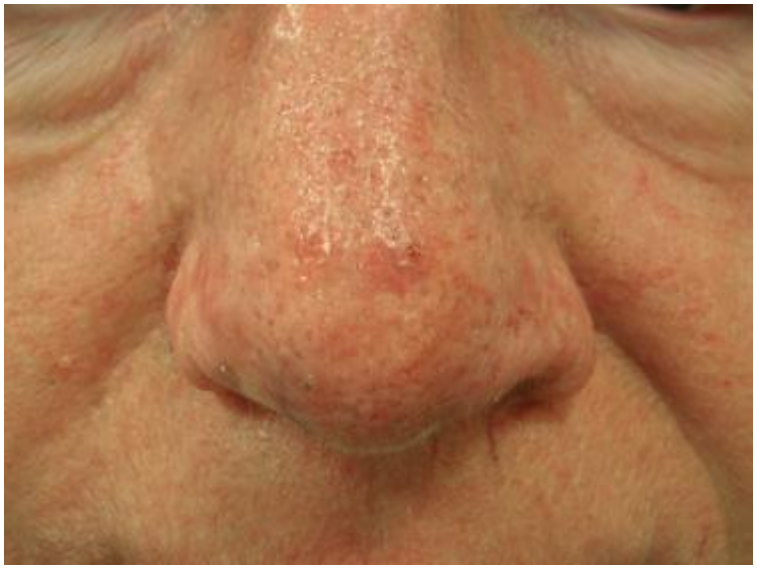
No studies could be included with azithromycin, minocycline or isotretinoin

Results for subtype 3

Subtype 3 (phymas):

- Evidence is lacking (no RCTs). Both surgical as well as laser therapy show good cosmetic results

Before



After Co2 laser

(Madan et al, Br J Dermatol 2009)

Results for subtype 4

- Some evidence that topical cyclosporine 0.05% ophthalmic emulsion is more effective than artificial tears
- Up to 60% have ocular rosacea
- RCTs investigating effect of different treatment modalities on ocular rosacea are warranted

Further conclusions

No studies could be included that addressed the effectiveness of:

- Dietary measures (avoiding triggers in food)
- Avoiding triggers in general
- Use of sunscreens
- Use of certain cosmetics (non-irritating, camouflaging redness etc)

Take Home messages

- Insufficient evidence for interventions subtype 1
- For subtype 2, topical metronidazole, azelaic acid, and doxycycline (40 mg) are effective and safe for short-term use
- 40 mg is at least as effective as 100 mg with evidence of less adverse effects
- Some evidence that tetracycline is effective
- No studies could be included for subtype 3
- For ocular rosacea (subtype 4) cyclosporine 0.05% ophthalmic emulsion more effective than artificial tears

Future research…

- High-quality studies of the more widely-used treatments for rosacea, i.e. tetracycline, minocycline, azithromycin, isotretinoin, topical retinoids, and light-based therapies

- RCTs addressing
  - interventions for ocular rosacea
  - interventions for phymas
  - dietary measures, sunscreens, special cosmetics etc. for reducing symptoms of rosacea

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