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[Intervention Review]

Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc and fruit acid (alpha-hydroxy acid) for acne

Haibo Liu[1], Haiyan Yu[2], Jun Xia[3], Ling Liu[4], Guan J Liu[5], Hong Sang[1], Frank Peinemann[6]

[1]Department of Dermatology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China. [2]Department of Dermatology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China. [3]Nottingham China Health Institute, The University of Nottingham Ningbo, Ningbo, China. [4]Department of Neurology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China. [5]Cochrane China, West China Hospital, Sichuan University, Chengdu, China. [6]Pediatric Oncology and Hematology, Children's Hospital, University of Cologne, Cologne, Germany

Contact: Hong Sang, shzwqzsl@163.com.

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ABSTRACT

Background

Acne is an inflammatory disorder with a high global burden. It is common in adolescents and primarily affects sebaceous gland-rich areas. The clinical benefit of the topical acne treatments azelaic acid, salicylic acid, nicotinamide, sulphur, zinc, and alpha-hydroxy acid is unclear.

Objectives

To assess the effects of topical treatments (azelaic acid, salicylic acid, nicotinamide, zinc, alpha-hydroxy acid, and sulphur) for acne.

Search methods

We searched the following databases up to May 2019: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, and LILACS. We also searched five trials registers.

Selection criteria

Clinical randomised controlled trials of the six topical treatments compared with other topical treatments, placebo, or no treatment in people with acne.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Key outcomes included participants' global self-assessment of acne improvement (PGA), withdrawal for any reason, minor adverse events (assessed as total number of participants who experienced at least one minor adverse event), and quality of life.

Main results

We included 49 trials (3880 reported participants) set in clinics, hospitals, research centres, and university settings in Europe, Asia, and the USA.

The vast majority of participants had mild to moderate acne, were aged between 12 to 30 years (range: 10 to 45 years), and were female. Treatment lasted over eight weeks in 59% of the studies. Study duration ranged from three months to three years.

We assessed 26 studies as being at high risk of bias in at least one domain, but most domains were at low or unclear risk of bias.

We grouped outcome assessment into short-term (less than or equal to 4 weeks), medium-term (from 5 to 8 weeks), and long-term treatment (more than 8 weeks). The following results were measured at the end of treatment, which was mainly long-term for the PGA outcome and mixed length (medium-term mainly) for minor adverse events.

Azelaic acid

In terms of treatment response (PGA), azelaic acid is probably less effective than benzoyl peroxide (risk ratio (RR) 0.82, 95% confidence interval (CI) 0.72 to 0.95; 1 study, 351 participants), but there is probably little or no difference when comparing azelaic acid to tretinoin (RR 0.94, 95% CI 0.78 to 1.14; 1 study, 289 participants) (both moderate-quality evidence). There may be little or no difference in PGA when comparing azelaic acid to clindamycin (RR 1.13, 95% CI 0.92 to 1.38; 1 study, 229 participants; low-quality evidence), but we are uncertain whether there is a difference between azelaic acid and adapalene (1 study, 55 participants; very low-quality evidence).

Low-quality evidence indicates there may be no differences in rates of withdrawal for any reason when comparing azelaic acid with benzoyl peroxide (RR 0.88, 95% CI 0.60 to 1.29; 1 study, 351 participants), clindamycin (RR 1.30, 95% CI 0.48 to 3.56; 2 studies, 329 participants), or tretinoin (RR 0.66, 95% CI 0.29 to 1.47; 2 studies, 309 participants), but we are uncertain whether there is a difference between azelaic acid and adapalene (1 study, 55 participants; very low-quality evidence).

In terms of total minor adverse events, we are uncertain if there is a difference between azelaic acid compared to adapalene (1 study; 55 participants) or benzoyl peroxide (1 study, 30 participants) (both very low-quality evidence). There may be no difference when comparing azelaic acid to clindamycin (RR 1.50, 95% CI 0.67 to 3.35; 1 study, 100 participants; low-quality evidence). Total minor adverse events were not reported in the comparison of azelaic acid versus tretinoin, but individual application site reactions were reported, such as scaling.

Salicylic acid

For PGA, there may be little or no difference between salicylic acid and tretinoin (RR 1.00, 95% CI 0.92 to 1.09; 1 study, 46 participants; low-quality evidence); we are not certain whether there is a difference between salicylic acid and pyruvic acid (1 study, 86 participants; very low-quality evidence); and PGA was not measured in the comparison of salicylic acid versus benzoyl peroxide.

There may be no difference between groups in withdrawals when comparing salicylic acid and pyruvic acid (RR 0.89, 95% CI 0.53 to 1.50; 1 study, 86 participants); when salicylic acid was compared to tretinoin, neither group had withdrawals (both based on low-quality evidence (2 studies, 74 participants)). We are uncertain whether there is a difference in withdrawals between salicylic acid and benzoyl peroxide (1 study, 41 participants; very low-quality evidence).

For total minor adverse events, we are uncertain if there is any difference between salicylic acid and benzoyl peroxide (1 study, 41 participants) or tretinoin (2 studies, 74 participants) (both very low-quality evidence). This outcome was not reported for salicylic acid versus pyruvic acid, but individual application site reactions were reported, such as scaling and redness.

Nicotinamide

Four studies evaluated nicotinamide against clindamycin or erythromycin, but none measured PGA. Low-quality evidence showed there may be no difference in withdrawals between nicotinamide and clindamycin (RR 1.12, 95% CI 0.49 to 2.60; 3 studies, 216 participants) or erythromycin (RR 1.40, 95% CI 0.46 to 4.22; 1 study, 158 participants), or in total minor adverse events between nicotinamide and clindamycin (RR 1.20, 95% CI 0.73 to 1.99; 3 studies, 216 participants; low-quality evidence). Total minor adverse events were not reported in the nicotinamide versus erythromycin comparison.

Alpha-hydroxy (fruit) acid

There may be no difference in PGA when comparing glycolic acid peel to salicylic-mandelic acid peel (RR 1.06, 95% CI 0.88 to 1.26; 1 study, 40 participants; low-quality evidence), and we are uncertain if there is a difference in total minor adverse events due to very low-quality evidence (1 study, 44 participants). Neither group had withdrawals (2 studies, 84 participants; low-quality evidence).

Authors' conclusions

Compared to benzoyl peroxide, azelaic acid probably leads to a worse treatment response, measured using PGA. When compared to tretinoin, azelaic acid probably makes little or no difference to treatment response. For other comparisons and outcomes the quality of evidence was low or very low.

Risk of bias and imprecision limit our confidence in the evidence. We encourage the comparison of more methodologically robust head-to-head trials against commonly used active drugs.

PLAIN LANGUAGE SUMMARY

Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc, and fruit acid (alpha-hydroxy acid) for acne

Background

Acne vulgaris ('acne') is a costly and common skin disorder in which hair follicles become blocked. Acne affects up to 85% of adolescents and young adults. Topical retinoids (treatment derived from vitamin A) and antimicrobials (treatment that kills micro-organisms such as bacteria) are common treatments. Other topical medications are also used, but there are concerns about their efficacy and safety.

Review question

This Cochrane Review aimed to assess the effects of six topical treatments (azelaic acid, salicylic acid, nicotinamide, sulphur, zinc, and alpha-hydroxy acid (organic acids found in food, sometimes known as fruit acid) on people with acne when compared with an inactive substance (placebo), no treatment, or other topical treatments. The evidence is current to May 2019.

Study characteristics

We included 49 trials (3880 reported participants). At least one study assessed each eligible treatment.

Most trial participants were female, aged between 12 and 30 years, with mild to moderate acne. Nearly 60% of the trials treated participants for longer than eight weeks. Study duration ranged from three months to three years.

Nine trials reported pharmaceutical support. The studies were mainly conducted in Europe, Asia, and the USA, in clinics, hospitals, research centres, and universities.

Key results

The following results were measured at the end of treatment, which was mainly long term (more than 8 weeks) for the outcome 'Participants' global self-assessment of acne improvement' (PGA) and mixed in length, but mainly medium term (from 5 to 8 weeks), for 'Total number of participants who experienced at least one minor side effect'.

Azelaic acid probably leads to worse PGA when compared to benzoyl peroxide, but when compared to tretinoin, there is probably little or no difference (both moderate-quality evidence). When comparing azelaic acid to clindamycin, there may be little or no difference in PGA (low-quality evidence), but we are uncertain whether azelaic acid reduces PGA compared to adapalene (very low-quality evidence).

In terms of participant withdrawal (for any reason), there may be no difference when azelaic acid is compared with benzoyl peroxide, clindamycin, and tretinoin (all low-quality evidence). We are uncertain whether azelaic acid reduces withdrawals when compared to adapalene (very low-quality evidence).

We are uncertain whether azelaic acid has fewer total minor adverse events when compared to adapalene or benzoyl peroxide (very-low quality evidence). When comparing azelaic acid to clindamycin, there may be no difference in total adverse events (low-quality evidence). The studies that compared azelaic acid with tretinoin only reported individual side effects (e.g. scaling).

We are uncertain if there is a difference between salicylic acid and pyruvic acid on PGA score (very low-quality evidence). There may be little or no difference between salicylic acid and tretinoin in PGA (low-quality evidence). No study comparing salicylic acid with benzoyl peroxide assessed PGA. There may be no difference in withdrawals when comparing salicylic acid and pyruvic acid; there were no withdrawals when salicylic acid was compared to tretinoin (both low-quality evidence). We are uncertain if there is a difference in withdrawals between salicylic acid and benzoyl peroxide (very low-quality evidence).

We are uncertain whether salicylic acid reduces total minor adverse events when compared to benzoyl peroxide or tretinoin (very low-quality evidence). For salicylic acid compared with pyruvic acid only individual application site reactions were reported (e.g. scaling and redness).

None of the four studies assessing nicotinamide (compared to clindamycin or erythromycin) assessed PGA. Nicotinamide may make no difference to withdrawals when compared to clindamycin or erythromycin, and may make no difference to total minor adverse events when compared to clindamycin (both low-quality evidence); however, no studies comparing nicotinamide with erythromycin looked at total minor adverse events.

Glycolic acid peels may make no difference to PGA when compared to salicylic-mandelic acid peels (low-quality evidence), we are uncertain of the effect on total minor adverse events (very low-quality evidence), and there were no withdrawals (low-quality evidence).

Quality of the evidence

Our evidence quality was mixed for the PGA outcome (very low to moderate), mainly low quality for withdrawals, and very low quality for total minor side effects. We had some concerns with the small size of the studies and how they were conducted.

SUMMARY OF FINDINGS

Summary of findings 1. Azelaic acid compared to adapalene

Azelaic acid compared to adapalene for acne

Patient or population: participants with acne
Settings: industry-sponsored, single-site study in Germany (1 study)
Intervention: topical azelaic acid
Comparison: topical adapalene

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical adapalene	Topical azelaic acid				
Participants' global self-assessment of acne improvement *Improved to very much improved* (long term: treatment duration > 8 weeks)	**842 per 1000**	**749 per 1000** (573 to 985)	**RR 0.89** (0.68 to 1.17)	55 (1 study)	⊕⊖⊖⊖ **Very low** [a]	-
Withdrawal for any reason (long term: treatment duration > 8 weeks)	**53 per 1000**	**139 per 1000** (17 to 1000)	**RR 2.64** (0.33 to 20.99)	55 (1 study)	⊕⊖⊖⊖ **Very low** [b]	-
Total number of participants who experienced at least one minor adverse event (medium term: treatment duration from 5 to 8 weeks)	**263 per 1000**	**305 per 1000** (124 to 750)	**RR 1.16** (0.47 to 2.85)	55 (1 study)	⊕⊖⊖⊖ **Very low** [c]	The authors reported no "significant difference" in the incidence of erythema, dryness, and itching between treatment groups.
Quality of life *Dermatology Life Quality Index* (long term: treatment duration > 8 weeks)	The authors reported that there was no "statistically significant" difference (P = 0.549) between azelaic acid and adapalene.			55 (1 study)	⊕⊖⊖⊖ **Very low** [d]	Skewed data reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included, and study had unclear allocation concealment and high risk of performance bias. Two levels for imprecision: wide CI and optimal sample size not met.
[b]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included, with unclear allocation concealment and high risk of performance bias. Two levels for imprecision: very wide CI and optimal sample size not met.
[c]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included, with high risk of performance bias and unclear allocation concealment and blinding of outcome assessment. Two levels for imprecision: wide CI and optimal sample size not met.
[d]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with unclear allocation concealment and high risk of performance bias. Two levels for imprecision: very small population size.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Summary of findings 2. Azelaic acid compared to benzoyl peroxide

Azelaic acid compared to benzoyl peroxide for acne

Patient or population: participants with acne
Settings: multicentres, recruitment in Germany, Netherlands, Norway, and Greece (1 study); not described (1 study)
Intervention: topical azelaic acid
Comparison: topical benzoyl peroxide

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical benzoyl peroxide	Topical azelaic acid				
Participants' global self-assessment of acne improvement *Good or very good improvement*	**771 per 1000**	**633 per 1000** (555 to 733)	**RR 0.82** (0.72 to 0.95)	351 (1 study)	⊕⊕⊕⊖ **Moderate** [a]	-

(long term: treatment duration > 8 weeks)						
Withdrawal for any reason (long term: treatment duration > 8 weeks)	**246 per 1000**	**216 per 1000** (147 to 317)	**RR 0.88** (0.60 to 1.29)	351 (1 studies)	⊕⊕⊝⊝ **Low** [b]	-
Total number of participants who experienced at least one minor adverse event (short term: treatment duration ≤ 4 weeks)	**133 per 1000**	**67 per 1000** (7 to 659)	**RR 0.50** (0.05 to 4.94)	30 (1 study)	⊕⊝⊝⊝ **Very low** [c]	The authors reported that people in the azelaic acid group experienced less dryness and desquamation, but more itching when compared to those in the benzoyl peroxide group.
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by one level to moderate quality evidence. One level for risk of bias: only one study included with unclear risk of selection, performance bias and other bias, and with high risk of attrition and reporting bias.
[b]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with unclear risk of selection, performance bias and other bias, and with high risk of attrition and reporting bias. One level for imprecision: wide CI.
[c]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with high risk of detection bias and unclear risk of selection, performance, attrition bias.Two levels for imprecision: wide CI and optimal sample size not met.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Summary of findings 3. Azelaic acid compared to clindamycin

Azelaic acid compared to clindamycin for acne

Patient or population: participants with acne
Settings: multicentres, recruitment in Germany, Netherlands, Norway, and Greece (1 study); three clinics in Tehran (1 study)
Intervention: topical azelaic acid

Comparison: topical clindamycin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical clindamycin	Topical azelaic acid				
Participants' global self-assessment of acne improvement *Good or very good improvement* (long term: treatment duration > 8 weeks)	**591 per 1000**	**668 per 1000** (544 to 816)	**RR 1.13** (0.92 to 1.38)	229 (1 study)	⊕⊕⊖⊖ **Low** [a]	-
Withdrawal for any reason (long term: treatment duration > 8 weeks)	**103 per 1000**	**134 per 1000** (49 to 367)	**RR 1.30** (0.48 to 3.56)	329 (2 studies)	⊕⊕⊖⊖ **Low** [b]	-
Total number of participants who experienced at least one minor adverse event (long term: treatment duration > 8 weeks)	**160 per 1000**	**240 per 1000**	**RR 1.5** (0.67 to 3.35)	100 (1 study)	⊕⊕⊖⊖ **Low** [c]	There was no difference in minor adverse events (such as scaling and dry skin) between azelaic acid 5% gel and clindamycin 2% gel.
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with unclear risk of selection, performance, and other bias, and with high risk of attrition and reporting bias. One level for imprecision: wide CI and optimal sample size not met.

[b]Downgraded by two levels to low quality evidence. One level for risk of bias: both studies had unclear risk of selection and performance bias, and one study had a high risk of attrition and reporting bias. One level for imprecision: wide CI and optimal sample size not met.
[c]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with unclear risk of selection, performance and detection bias. One level for imprecision: CI and optimal sample size not met.
*We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Summary of findings 4. Azelaic acid compared to tretinoin

Azelaic acid compared to tretinoin for acne

Patient or population: participants with acne
Settings: multicentres in one study; not described (1 study)
Intervention: topical azelaic acid
Comparison: topical tretinoin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical tretinoin	Topical azelaic acid				
Participants' global self-assessment of acne improvement *Good to excellent improvement* (long term: treatment duration > 8 weeks)	**623 per 1000**	**586 per 1000** (486 to 711)	**RR 0.94** (0.78 to 1.14)	289 (1 study)	⊕⊕⊕⊖ **Moderate** [a]	-
Withdrawal for any reason (long term: treatment duration > 8 weeks)	**90 per 1000**	**59 per 1000** (26 to 132)	**RR 0.66** (0.29 to 1.47)	309 (2 studies)	⊕⊕⊖⊖ **Low** [b]	-
Total number of participants who experienced at least one minor adverse event	See comment	See comment	See comment	See comment	See comment	Total number of participants who experienced at least one adverse event not reported. The rate of erythema and scaling was considerably higher in the tretinoin group

						than that in the azelaic acid group.
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by one level to moderate quality evidence. One level for risk of bias: only one study included with a high risk of attrition bias and unclear risk of selection and performance bias.
[b]Downgraded by two levels to low quality evidence. One level for risk of bias: both studies with unclear risk of selection and performance bias, one study with high risk of attrition bias and the other with high risk of reporting bias. One level for imprecision: wide CI and optimal sample size not met.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Summary of findings 5. Salicylic acid compared to benzoyl peroxide

Salicylic acid compared to benzoyl peroxide for acne

Patient or population: participants with acne
Settings: not described
Intervention: topical salicylic acid
Comparison: topical benzoyl peroxide

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Topical benzoyl peroxide	**Topical salicylic acid**				
Participants' global self-assessment of acne improvement	-	-	-	-	-	Not measured

Withdrawal for any reason (medium term: treatment duration from 5 to 8 weeks)	See comment	See comment	Not estimable	41 (1 study)	⊕⊖⊖⊖ **Very low** [a]	Neither treatment group had any withdrawals.
Total number of participants who experienced at least one minor adverse event (medium term: treatment duration from 5 to 8 weeks)	**95 per 1000**	**20 per 1000** (1 to 391)	**RR 0.21** (0.01 to 4.11)	41 (1 study)	⊕⊖⊖⊖ **Very low** [b]	The authors reported that zero out of 20 people in the 2% salicylic acid microgel group versus two out of 21 people in the benzoyl peroxide 10% cream group experienced minor adverse events.
Quality of life *ARQL* (medium term: treatment duration from 5 to 8 weeks)	The authors stated that subjects treated with salicylic acid microgel experienced better improvement when compared to 10% benzoyl peroxide.			41 (1 study)	⊕⊖⊖⊖ **Very low** [c]	No numerical data reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ARQL: acne-related quality of life; **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with unclear risk of selection, performance, detection, and reporting bias. Two levels for imprecision: very small total sample size.
[b]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with unclear selection, performance, and reporting bias. Two levels for imprecision: wide CI and optimal sample size not met.
[c]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with unclear risk of selection, performance, detection, and reporting bias. Two levels for imprecision: very small total sample size.
*We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Summary of findings 6. Salicylic acid compared to pyruvic acid

Salicylic acid compared to pyruvic acid for acne

Patient or population: participants with acne
Settings: Al-Zahra Hospital Dermatology Clinic and Isfahan Skin Research Centre
Intervention: topical salicylic acid
Comparison: topical pyruvic acid

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical pyruvic acid	Topical salicylic acid				
Participants' global self-assessment of acne improvement *Good to excellent improvement* (medium term: treatment duration from 5 to 8 weeks)	**395 per 1000**	**443 per 1000** (269 to 727)	**RR 1.12** (0.68 to 1.84)	86 (1 study)	⊕⊝⊝⊝ **Very low** [a]	-
Withdrawal for any reason (medium term: treatment duration from 5 to 8 weeks)	**419 per 1000**	**373 per 1000** (222 to 628)	**RR 0.89** (0.53 to 1.50)	86 (1 study)	⊕⊕⊝⊝ **Low** [b]	-
Total number of participants who experienced at least one minor adverse event	See comment	See comment	See comment	See comment	See comment	Total number of participants who experienced at least one adverse event not reported. Although the authors did report no "significant difference" in minor adverse events (scaling in the first to fourth sessions, redness, burning, and itching) between the two peeling (30% salicylic acid and 50% pyruvic acid).
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by three levels to very low quality evidence. Two levels for risk of bias: only one study included with high risk of attrition and other bias and unclear risk of selection and performance bias. One level for imprecision: wide CI and optimal sample size is not met.
[b]Downgraded by two levels to low quality evidence. One level for imprecision: wide CI and optimal sample size not met. One level for risk of bias: only one study included with high risk of attrition and other bias, and unclear risk of selection and performance bias.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Summary of findings 7. Salicylic acid compared to tretinoin

Salicylic acid compared to tretinoin for acne

Patient or population: participants with acne
Settings: Skin Disease and Leishmaniasis Research Center and Isfahan University of Medical Sciences clinics (1 study); not described (1 study)
Intervention: topical salicylic acid
Comparison: topical tretinoin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical tretinoin	Topical salicylic acid				
Participants' global self-assessment of acne improvement *Moderate to excellent improvement* (long term: treatment duration > 8 weeks)	**1000 per 1000**	**1000 per 1000** (920 to 1000)	**RR 1.00** (0.92 to 1.09)	46 (1 study)	⊕⊕⊝⊝ **Low** [a]	-
Withdrawal for any reason (long term: treatment duration > 8 weeks)	See comment	See comment	Not estimable	74 (2 studies)	⊕⊕⊝⊝ **Low** [b]	Neither study had any withdrawals.
Total number of participants who experienced at least one minor adverse event	**541 per 1000**	**741 per 1000** (357 to 1000)	**RR 1.37** (0.66 to 2.87)	74 (2 studies)	⊕⊝⊝⊝ **Very low** [c]	The authors in one study reported no "statistically significant" differences in the inci-

(long term: treatment duration > 8 weeks)				dence of dryness, peeling, erythema, burning and itching between treatment groups at any study week. All side effects reported in the two studies were of mild to moderate intensity and transient.
Quality of life *AQOL* (long term: treatment duration > 8 weeks)	The authors reported no "significant differences" in AQOL between salicylic acid group (end of study: 0.95 ± 1.9) and tretinoin group (end of study: 0.91 ± 1.64) at baseline and at the end of the study	46 (1 study)	⊕⊖⊖⊖ **Very low** [d]	Skewed data reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AQOL: acne quality of life; **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with unclear risk of random sequence generation, allocation concealment, and blinding of participants and personnel. One level for imprecision: optimal sample size not met.
[b]Downgraded by two levels to low quality evidence. One level for risk of bias: both studies with unclear risk of selection bias, one with unclear risk of performance bias and the other with high risk of performance and unclear risk of reporting bias. One level for imprecision: small total sample size.
[c]Downgraded by three levels to very low quality evidence. One level for risk of bias: two studies with unclear risk of selection bias and high risk of detection bias. Two levels for imprecision: wide CI and optimal sample size not met.
[d]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with unclear risk of random sequence generation, allocation concealment, and blinding of participants and personnel. Two levels for imprecision: very small population size and wide CI.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Summary of findings 8. Nicotinamide compared to clindamycin

Nicotinamide compared to clindamycin for acne

Patient or population: participants with acne
Settings: multicentres in USA (1 study); a teaching clinic of dermatology in Iran (1 study); St-Alzahra hospital, Isfahan University of Medical Sciences, Isfahan, Iran (1 study)
Intervention: topical nicotinamide

Comparison: topical clindamycin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical clindamycin	Topical nicotinamide				
Participants' global self-assessment of acne improvement	-	-	-	-	-	Not measured
Withdrawal for any reason (medium term: treatment duration from 5 to 8 weeks)	**74 per 1000**	**83 per 1000** (36 to 193)	**RR 1.12** (0.49 to 2.60)	216 (3 studies)	⊕⊕⊖⊖ **Low** [a]	Two trials had no withdrawals.
Total number of participants who experienced at least one minor adverse event (medium term: treatment duration from 5 to 8 weeks)	**185 per 1000**	**222 per 1000** (135 to 369)	**RR 1.20** (0.73 to 1.99)	216 (3 studies)	⊕⊕⊖⊖ **Low** [b]	Local application site reactions (e.g. itching, burning, crusting) were reported in two studies. In the third study, the authors reported no side effects during the treatment.
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: three studies included and all with unclear risk of bias, two with unclear risk of performance bias, one with high risk of attrition bias. One level for imprecision: wide CI and optimal sample size not met.
[b]Downgraded by two levels to low quality evidence. One level for risk of bias: all three studies with unclear risk of selection and detection bias, two out of three studies with unclear risk of performance bias. One level for imprecision: wide CI and optimal sample size not met.
*We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Summary of findings 9. Nicotinamide compared to erythromycin

Nicotinamide compared to erythromycin for acne

Patient or population: participants with acne
Settings: Laboratoire Dermscan (Villeurbanne)
Intervention: topical nicotinamide
Comparison: topical erythromycin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical erythromycin	Topical nicotinamide				
Participants' global self-assessment of acne improvement	-	-	-	-	-	Not measured
Withdrawal for any reason (medium term: treatment duration from 5 to 8 weeks)	**63 per 1000**	**89 per 1000** (29 to 267)	**RR 1.40** (0.46 to 4.22)	158 (1 study)	⊕⊕⊖⊖ **Low** [a]	-
Total number of participants who experienced at least one minor adverse event	See comment	See comment	See comment	See comment	See comment	Total number of participants who experienced at least one adverse event not reported. There was "no difference" in occurrence of pertinent clinical signs and functional or physical signs between treatment groups.
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with unclear risk of selection and performance bias. One level for imprecision: wide CI and optimal sample size not met.
*We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Summary of findings 10. Glycolic acid (alpha-hydroxy acid) compared to salicylic-mandelic acid

Glycolic acid (alpha-hydroxy acid) compared to salicylic-mandelic acid for acne

Patient or population: participants with acne
Settings: Dermatology and Andrology Department of Beha University hospital, Egyptian patients (only study); recruitment in India (1 study)
Intervention: topical glycolic acid (alpha-hydroxy acid)
Comparison: topical salicylic-mandelic acid

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical salicylic-mandelic acid	Topical glycolic acid				
Participants' global self-assessment of acne improvement *Fair to good improvement* (long term: treatment duration > 8 weeks)	**900 per 1000**	**954 per 1000** (792 to 1000)	**RR 1.06** (0.88 to 1.26)	40 (1 studies)	⊕⊕⊖⊖ **Low** [a]	-
Withdrawal for any reason (long term: treatment duration > 8 weeks)	See comment	See comment	Not estimable	84 (2 studies)	⊕⊕⊖⊖ **Low** [b]	Neither study had any withdrawals.
Total number of participants who experienced at least one minor adverse event	**227 per 1000**	**409 per 1000** (164 to 1000)	**RR 1.80** (0.72 to 4.52)	44 (1 study)	⊕⊖⊖⊖ **Very low** [c]	Four (20%) participants in salicylic-mandelic acid peel experienced a burning or stinging sensation against two (10%) in glycolic acid peel. Sixteen participants (80%)

(long term: treatment duration > 8 weeks)						in salicylic-mandelic acid peel developed visible desquamation against eight (40%) in glycolic acid peel (P = 0.025).
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. Two levels for imprecision: wide CI and optimal sample size not met.
[b]Downgraded by two levels to low quality evidence. One level for risk of bias: two studies included, one with unclear risk of selection, performance and reporting bias, the other with unclear risk of performance bias. One level for imprecision: small total sample size.
[c]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with high risk of detection bias and unclear risk of selection, performance bias. Two levels for imprecision: wide CI and optimal sample size not met.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

BACKGROUND

Please see the glossary in Table 1 for an explanation of medical terms used throughout the text.

Description of the condition

Acne is a common inflammatory disorder of pilosebaceous units (Landow 1997). It results in non-inflammatory lesions known as comedones (whiteheads or blackheads) and inflammatory lesions including papules, pustules, or nodules (Ramli 2012). Acne primarily affects sebaceous gland-rich areas, such as the face, shoulders, back, and upper chest (Katsambas 2008).

Acne comprises acne vulgaris, acne variants, and acneiform eruptions in clinical practice (Table 2). Acne vulgaris is the most common type of acne, which mainly affects adolescents and young adults. Prevalence in young people aged 12 to 24 years is as high as 85% (Bhate 2013). Acne severity in boys correlates with pubertal maturation. One study of healthy Danish boys showed that the mean age of onset of puberty has fallen from 11.92 between 1991 and 1993 to 11.66 between 2006 and 2008 (Sorensen 2010). Previous studies showed that 50% of boys aged 10 or 11 years had more than 10 comedones (Lucky 1991), and 78% of girls aged eight to 12 years had acne (Lucky 1997). Acne often begins in the early teens and it can persist through the third decade or even later, but the intensity and duration varies for each individual (Bhate 2013). Recently, several reports have suggested increased prevalence of an adult form of acne vulgaris (Khunger 2012; Rademaker 2014). Adult acne mainly affects women and the prevalence in adult women is estimated to be 14% (Williams 2006). In addition, although uncommon, physicians can come across people with childhood acne classified according to the age of onset (neonatal, infantile, mid-childhood, and prepubertal) (Antoniou 2009; Krakowski 2007).

To date, there are various grading systems for severity assessment, but with no consensus (Lehmann 2002; Ramli 2012). Moreover, there are no grading systems that fulfil all essential criteria required for an ideal acne grading scale (Tan 2012; Tan 2013). Acne experts suggest that scales served as investigator global assessment grading measures may be helpful to establish an ideal scale (Tan 2013). There are various grading systems used in clinical practice. According to the predominant types of lesions, study authors can classify acne vulgaris as comedonal, papulopustular, and nodular acne (Ramli 2012), or classify acne vulgaris as mild, moderate, severe, and cystic acne (Dayal 2017). However, when the predominant lesion type is difficult to determine, physicians may consider it as polymorphic acne (Kharfi 2001). Study authors may also classify acne vulgaris as mild, moderate, and severe based on the acne grading of the face, back and chest (O'Brien 1998). When conducting a clinical trial, study authors may classify acne based on different grading systems or scales such as the Allen-Smith Scale (Aksakal 1997), Cunliffe grading system (Bae 2013), investigator's static global assessment score (Schaller 2016), and Michaelson acne severity index (Kar 2013). However, all the current acne grading systems have shortcomings and a consistently applied standard for grading acne severity is urgently needed (Tan 2013).

The mechanism that causes the disease is unknown, but it is widely accepted that increased sebum excretion induced by androgens, follicular hyperkeratinisation, *Cutibacterium acnes* (*C acnes*, formerly *Propionibacterium acnes*) (Dreno 2018), and bacterial hypercolonisation, as well as inflammation, are the major pathogenetic factors for acne (Friedlander 2010). A keratinous plug forms at the follicular infundibulum resulting from hyperkeratosis in the follicle, initiating the formation of microcomedones (Cunliffe 2000). Within these microcomedones is an anaerobic lipid-rich environment suitable for the growth of *C acnes* (Brown 1998). The *C acnes* then hydrolyse triglycerides into glycerol and free fatty acids, which can initiate the inflammatory response (Dessinioti 2010; Thiboutot 2016). The cell surface toll-like receptors, which play critical roles in the immune response against micro-organisms, are involved in this bacteria-mediated inflammatory response by triggering the release of pro-inflammatory cytokines (Kim 2005).

Although acne vulgaris is not life-threatening and usually regresses in the third decade (Thiboutot 2016), it may cause serious psychological distress, as well as pain, and may considerably compromise the quality of life of the individual. Embarrassment, shame, and lack of confidence are important consequences resulting from acne vulgaris. Furthermore, scarring and embarrassment from acne begins at approximately the same age that adolescents are undergoing significant emotional and physical changes which, if combined, can be devastating. Indeed, there have been reports suggesting that severe acne can result in permanent physical scarring and even suicidal ideation (Dunn 2011; Misery 2011).

Description of the intervention

Treatment options for acne are often targeted at the factors implicated in acne development, such as sebaceous hypersecretion, abnormal keratinisation, *C acnes* bacteria colonisation, and the inflammation process (Titus 2012). The choice of treatments depends on the type and extent of acne (Gollnick 2003). Topical therapy is the preferred choice of treatment for mild acne and is also useful for moderate to severe acne (Akhavan 2003). The current mainstay of topical therapy for acne vulgaris includes retinoids (such as adapalene and tretinoin) and antimicrobials, such as benzoyl peroxide and antibiotics (Akhavan 2003; Titus 2012; Well 2013). However, other topical medications such as azelaic acid, salicylic acid, topical nicotinamide, sulphur, zinc, and alpha-hydroxy acid (such as glycolic acid and mandelic acid) are also effective for acne treatment (Akhavan 2003; ElRefaei 2015; Habbema 1989; Shahmoradi 2013; Sharad 2013).

How the intervention might work

Topical azelaic acid

As an ingredient found in many whole grain cereals and animal products, azelaic acid is a well-known aliphatic dicarboxylic acid, and it is useful in acne treatment due to its antimicrobial and anticomedonal properties (Akhavan 2003). Twice-daily application of 20% cream formation (Azelex) (Titus 2012), approved by the US Food and Drug Administration (FDA) for acne, can lead to an improvement of conditions within four weeks of initiation of therapy (Akhavan 2003; Cunliffe 1989). Compared to Azelex, the 15% gel (Finacea) has better bioavailability (Frampton 2004; Titus 2012). Azelaic acid 20% cream monotherapy or in combination therapy with glycolic acid (Graupe 1996; Spellman 1998), azelaic acid 20% (Iraji 2007) or 15% gel (Thiboutot 2008), azelaic acid 5% gel in combination with clindamycin 2% (Pazoki-Toroudi 2011), or erythromycin 2% (Pazoki-Toroudi 2010), are all effective treatments for acne. Azelaic acid 20% cream can reduce the number of both

non-inflammatory and inflammatory lesions and has an efficacy comparable to the other approved standard treatments, including benzoyl peroxide and erythromycin, as well as tretinoin, but it is better tolerated by people with fewer side effects (Simonart 2012; Spellman 1998).

Azelaic acid is able to competitively antagonise the activity of mitochondrial oxidoreductases and 5-alpha-reductase (Passi 1989; Stamatiadis 1988). The mechanism of action of azelaic acid in acne treatment may relate to its inhibitory effects on mitochondrial oxidoreductase and DNA synthesis (Fitton 1991). It has a predominant antibacterial activity on *C acnes* by inhibiting protein synthesis (Bojar 1991), and has a modest comedolytic effect by inhibiting the proliferation and differentiation of human keratinocytes, as well as an anti-inflammatory action by inhibiting the generation of pro-inflammatory oxygen derivatives in neutrophils (Akamatsu 1991; Sieber 2014). It can also reduce sebum production on the forehead, chin, and cheek through its inhibitory effect on the conversion from testosterone to 5-dehydrotestosterone (Passi 1989).

Adverse effects of azelaic acid are mild and transient. About 5% to 10% of people report a burning or stinging sensation, tightness of the skin, and erythema in the treated area, but this usually only lasts for a few weeks (Graupe 1996). Azelaic acid can cause hypopigmentation, so physicians should monitor its use in people with dark skin (Akhavan 2003). Azelaic acid is a US FDA pregnancy category B drug. It has minimal systemic absorption when used topically. Use in pregnancy and lactation should not be a cause for concern (Bozzo 2011), although the excretion of azelaic acid into milk has been demonstrated, and caution is advised in nursing mothers (Akhavan 2003).

Topical salicylic acid

Salicylic acid is often incorrectly recognised as a beta-hydroxy acid but it is actually an O-hydroxybenzoic acid (Kempiak 2008), and it is useful in the treatment of acne vulgaris due to its keratolytic and comedolytic effects (Akarsu 2012; Akhavan 2003). Salicylic acid is a component of most over-the-counter acne preparations (Simonart 2012). Its concentration varies from 0.5% to 3.0% (Babayeva 2011; Zander 1992), and it is available in washes (Choi 2010), creams (Zheng 2013), and lotions (Babayeva 2011). Chemical peel of salicylic acid at a concentration of 20% to 30% is also available and useful in acne treatment (Bae 2013). Salicylic acid monotherapy (Strauss 2007), or combination therapy with benzoyl peroxide (Akarsu 2012; Seidler 2010), or clindamycin phosphate (NilFroushzadeh 2009; Touitou 2008) can improve acne lesions. Salicylic acid 20% or 30% peels (Kempiak 2008), or salicylic 20%/mandelic acid 10% peels (Garg 2009) are also effective for the treatment of acne vulgaris. Previous studies have shown that topical salicylic acid has mild to moderate activity against both non-inflammatory lesions and inflammatory lesions in acne vulgaris (Akarsu 2012; Degitz 2008; Thiboutot 2009). It is approved for use in children with acne (Akhavan 2003).

Salicylic acid can break down the follicular keratotic plugs through dissolving the intercellular cement holding the stratum corneum cells and promoting the desquamation of follicular epithelium (Akarsu 2012; Akhavan 2003). It also has anti-inflammatory capabilities, affecting the arachidonic acid cascade (Lee 2003).

When used at concentrations of 2% or higher, salicylic acid can cause local skin peeling and discomfort to some degree (Akarsu 2012; Boutli 2003). Salicylic acid is a FDA pregnancy category C drug (Kempiak 2008). There are no studies conducted in lactating women on topical use of salicylic acid and little is known about the excretion of salicylic acid in breast milk. Therefore, physicians advise women during lactation to avoid the use of salicylate (Akhavan 2003; Bozzo 2011).

Topical nicotinamide

Nicotinamide serves as the active form of niacin, having anti-inflammatory effects in acne (Shalita 1995). Twice-daily application of 4% or 5% nicotinamide gel for eight weeks can lead to significant improvement of acne conditions (Khodaeiani 2013; Shalita 1995a). Researchers published the first study that assessed nicotinamide in 1995 and the data suggest that 4% nicotinamide gel has comparable efficacy to 1% clindamycin gel in the treatment of inflammatory acne vulgaris (Shalita 1995). Another study also supports the comparable efficacy of 4% nicotinamide gel to 1% clindamycin gel in moderate inflammatory acne vulgaris (Khodaeiani 2013). When used at a concentration of 5%, nicotinamide gel is as effective as clindamycin 2% gel for the treatment of mild to moderate acne vulgaris (Shahmoradi 2013). Nicotinamide 4% linoleic acid-rich phosphatidylcholine produced global clinical improvements in acne (Morganti 2011).

The mechanisms of action are mainly due to its potent anti-inflammatory effect (Shalita 1995a), and inhibition of sebum production (Draelos 2006a). Nicotinamide exerts its anti-inflammatory effects by inhibiting *C acnes*-induced chemokine IL-8 production in keratinocytes through interfering with NF-kappa B by inhibiting PARP-1 and mitogen-activated protein kinases (MAPK) pathways (Grange 2009).

Only mild stinging or burning at the application site is reported during topical use of nicotinamide (Shalita 1995a). It is safe for women in pregnancy, although the FDA pregnancy category rating of topical nicotinamide is not available (Rolfe 2014). Nicotinamide is excreted in breast milk, but no data regarding topical nicotinamide use in women who are pregnant or lactating are available (Rolfe 2014; Stockton 1990).

Topical sulphur

Sulphur is a yellow non-metallic chemical element with antifungal, antibacterial, and keratolytic properties (Gupta 2004). The topical sulphur-containing preparations at concentrations of 1% to 10% are helpful for acne treatment (Akhavan 2003), even though they may be both comedonal and comedolytic (Mills 1972). Sulphur is available in the form of lotions, foam, creams, ointments, and soaps. When used together with benzoyl peroxide or sodium sulphacetamide, sulphur shows a better therapeutic effect on acne vulgaris. For example, sodium sulphacetamide 10% with sulphur 5% emollient foam (Del Rosso 2009), sodium sulphacetamide with sulphur lotion (Breneman 1993), and benzoyl peroxide 10% plus sulphur in the range 2% to 5% cream (Danto 1966; Wilkinson 1966) are all effective acne treatments.

The mechanism of action may be due to sulphur's keratolytic action and consequent inhibitory effect on the proliferation of *C acnes* (Gupta 2004). It is thought that sulphur interacts with cysteine in keratinocytes resulting in the production of hydrogen sulphide,

which has a keratolytic effect by rupturing the disulphide bonds of cysteine molecules in keratin (Pace 1965).

Adverse events are rare during topical use of sulphur. Commonly reported adverse effects include dryness and itching of the skin (Breneman 1993; Gupta 2004; Tarimci 1997). Sulphur is a FDA pregnancy category C drug (Akhavan 2003). Little is known about the excretion of sulphur in breast milk. Therefore, caution should be used by breastfeeding mothers (Akhavan 2003).

Topical zinc

Zinc is known as an essential trace element (Sharquie 2008). It has antimicrobial as well as anti-inflammatory actions and it is useful for many dermatological problems (Habbema 1989; Sharquie 2007; Sharquie 2008). Physicians often use zinc plus antibiotic combination products for acne treatment (Cunliffe 2005; Habbema 1989). For example, researchers used the form of erythromycin (4%) plus zinc (1.2%) and clindamycin (1%) plus zinc (0.52%), which can be applied twice-daily for 12 weeks or more (Cunliffe 2005; Habbema 1989). Previous studies have documented that the combination of zinc with antibiotics is more advantageous to acne patients than antibiotics alone (Cunliffe 2005a; Habbema 1989). Some reports suggest that zinc acetate contributes most to the antimicrobial action of an erythromycin/zinc combination (Fluhr 1999). When used alone, topical zinc is also useful for acne patients. Recently, zinc sulphate solution has been showed to be effective in the treatment of acne vulgaris, though it may be less effective than tea lotion (Sharquie 2008).

The mechanism of action may be due to zinc's antimicrobial, anti-inflammatory, and other actions (Fluhr 1999; Sharquie 2008). Several reports have documented the anti-propionibacterial activity of zinc in vitro (Bojar 1994; Fluhr 1999). The efficacy on inflammatory lesions by zinc suggests the importance of its anti-inflammatory actions on acne treatment (Dreno 1989).

There are no important adverse effects reported during topical use of zinc (Cunliffe 2005; Sharquie 2008). The adverse effects include burning sensation and itching, but they are always mild and transient (Sharquie 2008). Although the FDA pregnancy category rating of topical zinc is not available, oral zinc sulphate is a pregnancy category C drug (Chien 2016).

Topical fruit acid (alpha-hydroxy acid)

Alpha-hydroxy acid (or fruit acid) refers to a special group of organic acids that can be found in natural foods (Hunt 1992). It is useful in a variety of dermatological conditions with abnormal keratinisation (Hunt 1992; Sharad 2013). Glycolic acid belongs to alpha-hydroxy acids, which can be used for chemical peeling at concentrations ranging from 20% to 70% (Sharad 2013). Glycolic acid peel is the most common fruit peel (Sharad 2013). In Asian acne patients, the use of 50% glycolic acid peels once in three weeks for 10 weeks can result in significant resolution of comedones, papules, and pustules (Wang 1997). Another study also suggests the efficacy of glycolic acid peels (20% to 70%) in the reduction of both non-inflamed and inflamed lesions when applied twice every four weeks for six months (Ilknur 2010). Moreover, they are also useful in nodule-cystic acne and acne scars (Atzori 1999; Wang 1997). Therefore, glycolic acid peel is a useful alternative treatment for acne (Sharad 2013). In addition to glycolic acid, gluconolactone (14%), another alpha-hydroxy acid, has showed a significant therapeutic effect in reducing acne lesions (Hunt 1992).

The mechanism of action may be due to the modification of keratinisation by alpha-hydroxy acids, and the anti-inflammatory activity of alpha-hydroxy acids may also play a role in acne improvement (Hunt 1992).

The adverse effects are always minimal during topical use of alpha-hydroxy acids (Hunt 1992; Ilknur 2010), and patient tolerance is reported to be good (Sharad 2013). Glycolic acid is a pregnancy category N drug (rating is not available) but there are no published reports demonstrating any adverse effects during pregnancy (Chien 2016).

Why it is important to do this review

The Global Burden of Disease (GBD) 2010 and 2013 projects measured disease burden using disability-adjusted life year (DALY) metrics (Hay 2014; Karimkhani 2017); of the 15 dermatologic conditions, acne vulgaris was the skin disease with the second highest percentage of total DALYs either in the GBD 2010 or GBD 2013 study (Hay 2014; Karimkhani 2017). Thus, the global burden of acne is very high (Hay 2014; Karimkhani 2017). A recent report, however, has demonstrated that the limited number of reviews and protocols published in the *Cochrane Database of Systematic Reviews* (CDSR) does not reflect disease disability estimates for acne and that this topic is underrepresented (Karimkhani 2014). Cochrane Reviews on oral treatments including minocycline (Garner 2012) and contraceptive pills (Arowojolu 2012) for acne have been conducted. Topical treatments including retinoids, benzoyl peroxide (Yang 2014), and antibiotics for acne are (or will be) dealt with in other Cochrane Reviews.

We know of several reviews on some of these topical treatments for acne (Gamble 2012; Haider 2004; Lehmann 2001; Purdy 2011; Seidler 2010). Three of these reviews demonstrated that use of topical azelaic acid shows benefits for mild and moderate acne and is comparable to topical retinoid or benzoyl peroxide (Gamble 2012; Haider 2004; Purdy 2011). However, there is only limited evidence to demonstrate that topical salicylic acid (Gamble 2012), nicotinamide (Purdy 2011), sulphur (Gamble 2012; Lehmann 2001), zinc (Gamble 2012), and alpha-hydroxy acid (Sharad 2013) may be beneficial for acne treatment. A review on salicylic acid did not include adequate intervention arms and did not assess side effects of the treatments (Seidler 2010). In summary, most of the up to date evidence on these medications is from summary reviews (Gamble 2012; Haider 2004; Purdy 2011; Sharad 2013), and the only two systematic reviews identified are either out of date (Lehmann 2001), or without clear assessment of the quality of evidence (Seidler 2010).

Given the various limitations of previous reviews and the new evidence from recent studies on the use of azelaic and salicylic acids, nicotinamide, sulphur, zinc, and alpha-hydroxy acid, we feel it is important to systematically assess their benefits and harms for the treatment of acne vulgaris using Cochrane methodology.

The plans for this review were published as a protocol with a slightly different title, 'Topical azelaic acid, salicylic acid, nicotinamide, and sulphur for acne' (Liu 2014).

OBJECTIVES

To assess the effects of topical treatments (azelaic acid, salicylic acid, nicotinamide, zinc, alpha-hydroxy acid, and sulphur) for acne.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Randomised trials with a cross-over design were eligible. We excluded cluster-RCTs and quasi-RCTs trials (e.g. trials that allocate by using date of birth, case record number, or alternation).

Types of participants

We included participants with acne vulgaris who have been diagnosed based on clinical definition, regardless of age, gender, acne severity, and previous treatments. Studies were also eligible where participants were diagnosed as having papulopustular, inflammatory, juvenile, or polymorphic acne.

We excluded trials in which participants had a diagnosis of other forms of acne variants or acneiform eruptions, as listed in Table 2.

Types of interventions

Topical azelaic acid, topical salicylic acid, topical nicotinamide, topical sulphur, topical zinc, and topical fruit acid (alpha-hydroxy acid) with any treatment regimen, duration, dose, and delivery mode, compared with:

- other topical treatments;
- placebo;
- no treatment.

The trials that compared the intervention treatments with each other were eligible for inclusion. The concomitant use of other topical or oral medications for acne vulgaris had to be the same in both intervention arms.

Types of outcome measures

Primary outcomes

- Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor)
- Withdrawal for any reason

Secondary outcomes

- Change in lesion counts (total, or inflamed and non-inflamed separately)
- Physicians' global evaluation of acne improvement
- Minor adverse events (assessed as the total number of participants who experienced at least 1 minor adverse event)
- Quality of life

Timing

We assessed treatment efficacy by grouping the outcomes into short-term treatment (less than or equal to 4 weeks), medium-term treatment (from 5 to 8 weeks) and long-term treatment (more than 8 weeks). Where there was more than one follow-up point within the same time period, we used the longest one.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist searched the following databases up to 1 May 2019.

- Cochrane Skin Group Specialised Register using the search strategy in Appendix 1
- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 5) in the Cochrane Library using the search strategy in Appendix 2.
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 3.
- Embase via OVID (from 1974) using the strategy in Appendix 4.
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 5.

Trials registers

We (HL and HY) searched the following trials registers up to 1 May 2019 using the search terms (azelaic acid, salicylic acid, o-hydroxybenzoic acid, nicotinamide, niacinamide, sulphur, sulfur, zinc, fruit acid, alpha-hydroxy acid, and glycolic acid) combined with health condition 'acne'.

- ISRCTN registry (www.isrctn.com).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch).
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

References from included studies

We checked the bibliographies of included studies for further references to relevant trials.

Adverse effects

We did not perform a separate search for adverse events of the target interventions. However, we examined data on adverse effects from the included studies we identified if present.

Data collection and analysis

Selection of studies

Two review authors (HL and HY) independently inspected the titles and abstracts of all studies identified for eligibility. For studies that appeared to be eligible, we retrieved the full text of reports for reassessment to see whether they met the inclusion criteria. We resolved discrepancies by discussion between review authors (HL and HY) and, if necessary, input by a third review author (JX or HS).

Data extraction and management

For data collection, we used a data extraction form adapted from a standard one and the form was piloted followed by minor revisions.

We extracted data on an intention-to-treat (ITT) basis and used Review Manager 5 for the analysis of data (Review Manager 2014).

Two review authors (HL and HY) independently extracted data from eligible studies using an ITT approach and one review author (FP) extracted data from studies published in German. We collected both qualitative and quantitative information according to Table 7.3.a, 'Checklist of items to consider in data collection or data extraction', in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we collected characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies'. Where further information was required, we contacted the authors for clarification. We resolved any disagreements by discussion and, if necessary, involved a third review author (JX or HS). In the case of data displayed only in graphs or figures, if we were unable to contact study authors, we extracted the data manually using a ruler but only included the data if two review authors independently collected the same results.

The review authors were not blinded to journals, authors, or their academic affiliations. HL, HS and HY entered the data into the Review Manager 5 software (Review Manager 2014).

Assessment of risk of bias in included studies

Two authors (HL and HS) independently assessed the methodological quality of eligible studies using the 'Risk of bias' tool, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion and, if necessary, involved a third review author (JX or GL). We assessed the following domains for bias.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias.

We categorised the risk of bias in each domain as either 'low', 'high', or 'unclear'. Where two or more out of seven domains within a trial were rated as 'high' risk of bias, we considered including the trial in a sensitivity analysis.

Measures of treatment effect

Interpretation

If possible, we compared the pooled estimates with the minimally important difference (MID) values for both primary and secondary outcomes to aid interpretation. We used the suggested MID from the literature, such as MID estimates for acne lesion counts (Gerlinger 2011), and Acne-Specific Quality of Life Questionnaire (Acne-QoL) outcomes (McLeod 2003).

Dichotomous data

For binary outcomes, we calculated the risk ratio (RR) and its 95% confidence interval (CI) to summarise estimates of treatment effect, because the RR was more intuitive than the odds ratio (OR) (Boissel 1999), which was often misinterpreted as RR by clinicians (Deeks 2002).

Continuous data

Summary statistic

For continuous outcomes, we calculated the mean difference (MD) and its 95% CI to summarise data, and used standardised mean difference (SMD) with 95% CI where different measurement scales had been used across studies.

Skewed data

Data from continuous outcomes were often not normally distributed and statistics to summarise average (medians) and spread of data (quartiles, minimum and maximum, and ranges) were used in this case. We summarised such variables using the summary statistics for skewed data in additional tables rather than in the main analysis, and we did not analyse the treatment effect sizes to avoid applying parametric tests to data with skewed distribution. We classified data as skewed when the mean was less than twice the standard deviation (SD), but only when the data were from a scale or outcome measure that had positive values with a minimum value of zero (Altman 1996). Sometimes trials used means to summarise skewed data from very large trials. In this situation, we entered the data into analysis but a sensitivity analysis was necessary.

Ordinal data

Results of participant and doctor evaluations may be presented as short ordinal data. In this situation, we converted this type of data into dichotomous data (e.g. 'improved' or 'not improved'), and we conducted a sensitivity analysis using different cut off points (e.g. 'greatly improved' or 'not greatly improved'). We treated long ordinal data as continuous data.

Unit of analysis issues

We considered the individual participant to be our unit of analysis. For trials with a cross-over design, we extracted data from a paired t-test and approximated a paired analysis using the generic inverse variance method. We pooled the randomised cross-over trials separately from parallel trials.

Where a trial had more than two intervention arms, we identified the interventions relevant to our review and combined arms to create a single pair-wise comparison. If the combination of groups was impossible, we directly included the correlated or eligible comparisons and addressed them in different meta-analyses as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

For 'split-face' design trials, in which different body parts were randomised to different interventions, we treated them as specific forms of cross-over trials, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In this case, we incorporated these trials to approximate a paired analysis using the generic inverse variance method and we conducted a sensitivity analysis. We conducted meta-analyses of these trials separately from parallel trials.

Finally, trials in which randomisation occurred at a per person level, but multiple body parts received the same intervention and a separate outcome measure was made for each body part, were similar to cluster-randomised trials except that each participant was a cluster. We excluded these trials, as previously stated.

Dealing with missing data

Overall loss of credibility

Data lose their credibility after a certain degree of loss to follow-up (Xia 2007; Xia 2009). Where more than 50% of participants withdrew before the end of the trial, we excluded these data from the analysis (with the exception of outcome of 'withdrawal for any reason' and 'minor adverse events').

Binary data

Where there was attrition between 0% and 50% for a binary outcome, we managed data based on the ITT principle. We made 'lost to follow-up' the worst outcome, that was to say, we imputed participants reported as 'lost to follow-up' as treatment failures for analysis. This assumption was also applicable to negative outcomes such as adverse events.

Continuous data

Where there was attrition between 0% and 50% for a continuous outcome, we reproduced the completer-only data and used them within the analysis. In many cases, we could not extract the measures of variance for continuous data directly from the report. We calculated the SD from available data (e.g. 95% CI, standard error, exact P value, and t statistic) according to the method described in Section 7.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We contacted the trial authors for further information. If these methods were unsuccessful, we used the mean SDs from other studies within the same analysis.

Assessment of heterogeneity

We assessed heterogeneity across studies using the Chi^2 test and the I^2 statistic. If the I^2 statistic was equal to or greater than 50%, significant heterogeneity was present, and we investigated the included studies for their clinical, methodological, and statistical similarities. When necessary, we also employed prespecified subgroup analyses to explore any unexplained heterogeneity. If the I^2 statistic was equal to or greater than 80%, we presented the data in a forest plot but did not calculate a pooled estimate.

Assessment of reporting biases

Funnel plots are useful to assess reporting biases but have limited power in the case of small-study effects (Higgins 2011). We had planned to assess reporting bias by using funnel plots. However, as none of the meta-analyses had 10 or more studies on primary outcomes for a test intervention, we were not able to produce funnel plots.

Data synthesis

We employed a random-effect model for all pooled analyses. Where results were estimated for individual studies with low numbers of events (fewer than 10 in total), or where the total sample size was fewer than 30 participants and a RR was used, we reported the proportion of outcomes in each treatment group together with a P value from Fisher's Exact test.

Subgroup analysis and investigation of heterogeneity

We set up subgroup analyses according to the different comparators used in the control group and the different time periods of treatment duration for the test interventions. However, we did not conduct a test for subgroup differences due to a lack of adequate numbers of studies per group. In future updates, we plan to conduct subgroup analyses if we find substantial heterogeneity in a meta-analysis with at least 10 trials on primary outcomes. We will consider the forms, concentrations, and dosing regimens of the interventions for subgroup analyses.

Sensitivity analysis

Where possible, we employed sensitivity analyses by excluding low methodological quality trials from the meta-analysis: those with 'high' risk of bias for two or more of the seven domains as defined in the 'Risk of bias' tables. Where inclusion or exclusion of these low methodological quality trials did not make significant changes to treatment efficacy, we retained these trials in the final meta-analysis.

If trials were reported with randomisation and balanced baseline demographic characteristics in each group, we included the trials and entered them into a sensitivity analysis.

'Summary of findings' tables and GRADE assessments

We created 'Summary of findings' tables in our review, in which we summarised the primary outcomes (participants' global self-assessment of acne improvement, and withdrawal for any reason), and secondary outcomes (minor adverse events and quality of life) for the most important comparisons. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for these four outcomes, and documented all the assessments of the body of evidence using the GRADEpro GDT software (Higgins 2011).

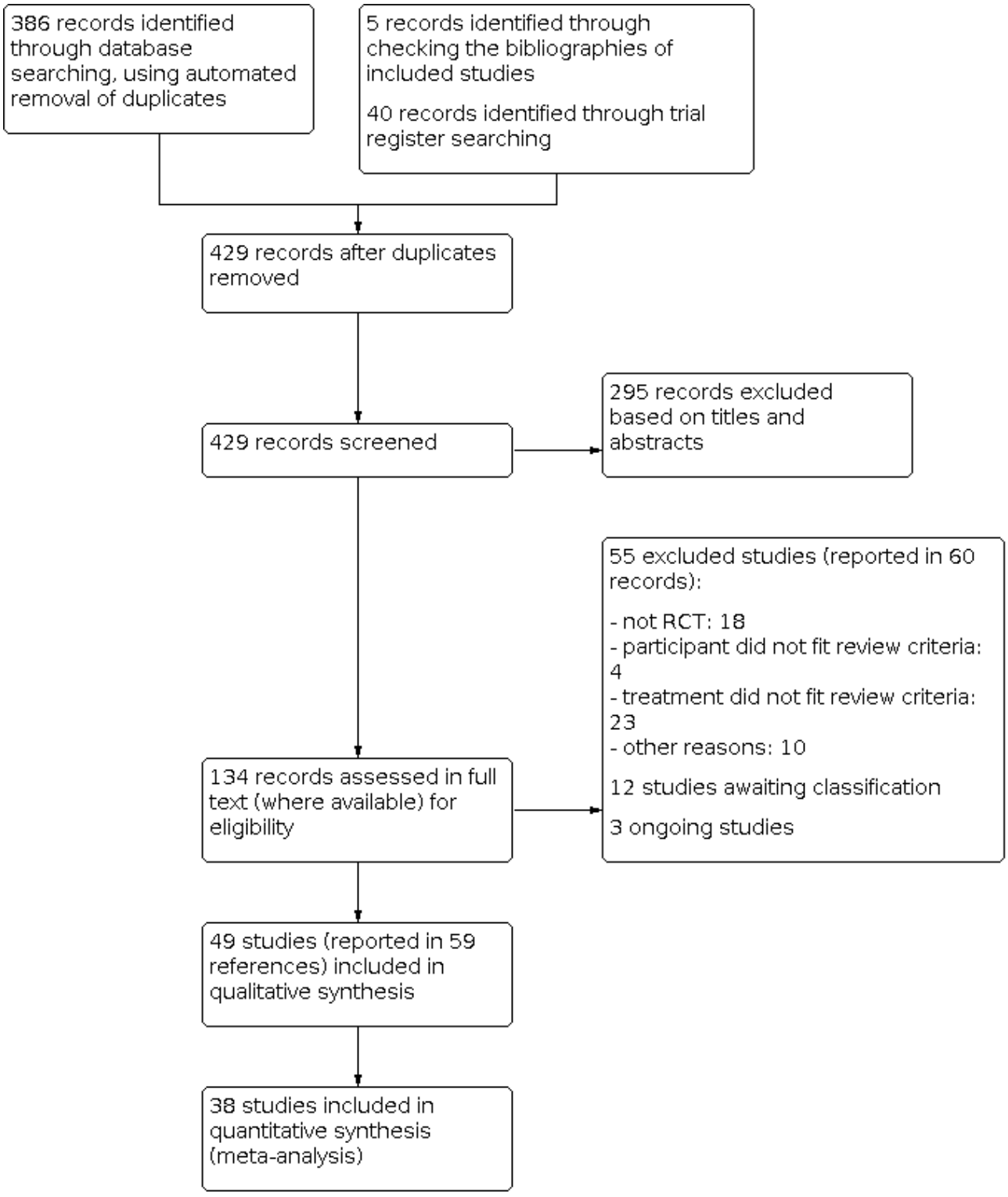
RESULTS

Description of studies

Results of the search

The Electronic searches identified 386 records. Our screening of the bibliographies of included studies identified five studies. Our search in the trial registers identified 40 studies. Therefore, we had a total of 431 records. After removing duplicates, we had 429 records. We excluded 295 records based on titles and abstracts. We attempted to obtain the full texts or abstracts of the remaining 134 records. We excluded 55 studies reported in 60 references that did not meet the inclusion criteria (see Characteristics of excluded studies). We added 12 records to Studies awaiting classification and classified three studies as Ongoing studies. We included 49 studies reported in the remaining 59 references (see Characteristics of included studies). Please see the study flow diagram for a further description of our screening process (Figure 1).

Figure 1. Study flow diagram



Included studies

We included a total number of 49 studies. Of these studies, 47 included 3880 participants, whereas the other two studies did not report the sample size (Chantalat 2007; Chen 2007). See 'Characteristics of included studies' tables for detailed descriptions of each included study. We attempted to contact eight authors in order to obtain additional data. Only two authors provided data, four authors did not respond to our enquiries, and the other two authors responded with insufficient information.

Trial size

The trial size ranged from n = 13 to n = 351. In 19 studies, all participants completed the trial (n = 871), while 23 studies had various numbers of participants leaving the study early (between 2% to 39.5%). Seven studies did not describe dropout information (Cavicchini 1989; Chantalat 2005; Chantalat 2007; Chen 2007; Dunlap 1997; Hayashi 2012; Techapichetvanich 2011).

Unit of allocation

For unit of allocation, 42 studies randomised individual participants into parallel groups. Six studies with 175 participants were split-face studies (Bae 2013; Hayashi 2012; Ilknur 2010; Kessler 2008; Kim 1999; Levesque 2011). One study (n = 30) was a cross-over randomised trial (Shalita 1989).

Gollnick 2004a and Gollnick 2004b were two studies described in one report. Likewise, Katsambas 1989a and Katsambas 1989b were two studies reported in the same paper.

Participants

Forty-seven trials included 3880 participants, and the other two trials did not report the sample size (Chantalat 2007; Chen 2007). The authors in Chantalat 2007 did not report the severity of acne and authors in Chen 2007 included participants with mild to moderate acne. Of the 3880 participants from 47 trials, 2939 participants (75.7%) from 33 trials included mild to moderate acne vulgaris graded by various acne severity grading systems or scales. The severity of the remaining participants were as follows.

- 140 participants from three studies had moderate to severe acne (Aksakal 1997; ElRefaei 2015; Kar 2013).
- 20 participants from one study had mild to moderately severe acne (Kessler 2008).
- 188 participants from three studies had unknown severity illness (Hayashi 2012; Picosse 2015; Vasarinsh 1969).
- 399 participants from five studies probably had mild to moderate acne (Barbareschi 1991; Cavicchini 1989; Ilknur 2010; Katsambas 1989b; Levesque 2011).
- 150 participants from one study probably had moderate to severe acne (Dunlap 1997).
- 44 participants from one study probably had moderate to severe/cystic acne (Garg 2009).

With respect to seven studies with no acne severity grading, we presented a possible grading by using a simple system (mild, moderate, severe, cystic) based on the predominant lesions present as reported in Dayal 2017. For a detailed description, please see Table 3.

Forty-one studies described the age of participants (ranging from 10 years to 45 years old). One study included participants ≥ 16 years old (range unclear) (Hayashi 2012), and one study reported the means and standard deviations (SDs) for age (range unclear) (Dayal 2017). Six studies did not report this information. Most people were aged between 12 and 30 years old. As for sex distribution, 38 studies with 3154 participants described this information, of which 1295 were males and 1842 were females (there was no gender information about 17 withdrawals from Bojar 1994, Ilknur 2010 and Schaller 2016). Eleven studies did not report the exact number of male and female participants.

Settings

Twenty-two studies did not provide information on setting. Seven studies were multiple-centre clinical trials (Cunliffe 2005: 8 centres in the UK, 1 in France, and 1 in Germany; Gollnick 2004a and Gollnick 2004b: centres in Germany, Netherlands, Norway, and Greece; Hayashi 2012: centres in Japan; Katsambas 1989b: no details; Schaller 2016: 11 centres in Germany; Shalita 1995: centres in the USA).

Twenty studies were set in: clinics in Iran (Khodaeiani 2013; Pazoki-Toroudi 2010; Pazoki-Toroudi 2011), hospitals in India (Garg 2009; Kar 2013) and Iraq (Sharquie 2008), research centres in Iran (Jaffary 2016), university settings (Bae 2013; Kim 1999 in Korea; Dayal 2017 in India; ElRefaei 2015 in Egypt; Kessler 2008 in USA; Ozkan 2000 in Turkey; Shahmoradi 2013 in Iran; Thielitz 2015 in Germany; Vasarinsh 1969 in USA), or other (Draelos 2016; Levesque 2011 in USA; NilFroushzadeh 2009 in Iran; Weltert 2004 in France).

Interventions

For the treatment group, 18 studies assessed salicylic acid in the form of lotion (concentrations of 2% or 3%, e.g. Babayeva 2011), chemical peel (concentrations of 20% or 30%, e.g. Bae 2013), gel (concentration of 2%, e.g. Draelos 2016), microgel (concentrations of 0.5% or 2%, e.g. Chantalat 2006), and solution (concentration of 0.5%, e.g. Shalita 1981), and 18 studies addressed azelaic acid in the form of cream (concentration of 20%, e.g. Schaller 2016) and gel (concentrations of 5%, 15%, or 20%, e.g. Gollnick 2004a); four studies investigated nicotinamide in the form of gel (concentration of 4% or 5%, Khodaeiani 2013; Shahmoradi 2013; Shalita 1995; Weltert 2004), while three studies addressed zinc in the form of gel (concentration of 1%, Cunliffe 2005), lotion (concentration of 1.2%, Bojar 1994), and solution (concentration of 5%; Sharquie 2008); one study assessed sulphur in the form of lotion (concentration of 2%, Vasarinsh 1969); five studies tested the efficacy and safety of glycolic acid (alpha-hydroxy acid) in the form of chemical peel (concentration ranging from 20% to 70%, ElRefaei 2015; Garg 2009; Ilknur 2010; Kessler 2008; Kim 1999) and one study investigated gluconolactone (alpha-hydroxy acid) in the form of lotion (concentration of 14%, Hunt 1992). In the Kessler 2008 study, the authors compared salicylic acid with alpha-hydroxy acid (glycolic acid).

Seven studies used topical clindamycin, erythromycin, or benzoyl peroxide as co-interventions (Babayeva 2011; Bojar 1994; Cunliffe 2005; NilFroushzadeh 2009; Pazoki-Toroudi 2010; Pazoki-Toroudi 2011; Vasarinsh 1969). Two studies included a co-intervention of topical clindamycin plus benzoyl peroxide (Akarsu 2012; Techapichetvanich 2011). One study used oral isotretinoin as co-intervention (Kar 2013). The remaining 39 studies did not include co-interventions.

The treatment period of the interventions ranged from five days to 12 months. We grouped three studies into short-term (less than or equal to 4 weeks) treatment duration (Bae 2013; Draelos 2016; Shalita 1989), 15 studies into medium-term (from 5 to 8 weeks) treatment duration, and 29 studies into long-term (more than 8 weeks) treatment duration. Two studies did not report treatment duration (Chantalat 2005; Chantalat 2007).

Three studies had a post-treatment follow-up period ranging from eight weeks to 12 weeks (ElRefaei 2015; Garg 2009; Kessler 2008). In Thielitz 2015, one treatment arm had a post-treatment follow-

up period of 24 weeks. Forty-three studies did not report the post-treatment follow-up period. Two studies did not mention the treatment period of the interventions and the post-treatment follow-up period (Chantalat 2005; Chantalat 2007).

None of the studies reported the precise duration of the trial (from recruitment to last follow-up). Nine studies reported the study time period ranging from three months to three years (ElRefaei 2015; Gollnick 2004a; Gollnick 2004b; Kar 2013; Shahmoradi 2013; Shalita 1981; Sharquie 2008; Thielitz 2015; Vasarinsh 1969). Cunliffe 2005 ran through autumn, winter and early spring. Seven studies reported recruitment time periods ranging from six months to one year (Jaffary 2016; Khodaeiani 2013; Levesque 2011; NilFroushzadeh 2009; Pazoki-Toroudi 2010; Pazoki-Toroudi 2011; Schaller 2016).

Comparators

For the control group, 31 studies used active treatments, such as clindamycin, erythromycin, tretinoin, Jessner's solution, benzoyl peroxide, and so on. Fourteen studies had placebo/vehicle control or no treatment; and four studies had multiple treatment groups with both active therapy and placebo control (Barbareschi 1991; Draelos 2016; Hunt 1992; Vasarinsh 1969). In five included studies (Cunliffe 1989; Hunt 1992; Iraji 2007; Katsambas 1989a; Shalita 1981), study authors considered the term 'vehicle' to be the same as 'placebo'. In one study (Iraji 2007), the excipients used in the vehicle did not contain antimicrobial agents which may have some therapeutic effects. In another two studies (Eady 1996; Vasarinsh 1969), the study authors used a lotion base as placebo. Thus, 'vehicle' was equal to 'placebo' in this review and we pooled the two groups together in the same comparison.

Outcomes

Nineteen studies reported global self-assessment of acne improvement (assessed by the participants). Of the 19 studies, 16 used Likert-type or Likert-like scales, one used a visual analogue scale (Cunliffe 2005), one used a questionnaire with known contents (Kessler 2008), and one used a preference test (Kim 1999). Thirty studies did not report this primary outcome. Forty-two studies reported the withdrawal information (19 studies reported no withdrawals), while seven studies did not report this outcome (Cavicchini 1989; Chantalat 2005; Chantalat 2007; Chen 2007; Dunlap 1997; Hayashi 2012; Techapichetvanich 2011).

For secondary outcomes, 44 studies reported the change in lesion counts (assessed by the investigators or physicians), while five studies did not report this outcome (Draelos 2016; Kim 1999; Ozkan 2000; Picosse 2015; Shahmoradi 2013). Seventeen studies described the physicians' global evaluation of acne improvement (assessed by the physicians) (15 studies used Likert-like scales, two studies used visual analogue scales (Cunliffe 2005; ElRefaei 2015); the remaining 32 did not report this outcome.

Forty-five studies reported minor adverse events (assessed as total number of participants who experienced at least 1 minor adverse event), but the number of participants who experienced adverse events was not always reported. Of the 45 studies, four reported no adverse events during the study (Chen 2007; Draelos 2016; Shahmoradi 2013; Shalita 1981), eight used four-point Likert scales or similar scales (Akarsu 2012; Babayeva 2011; Cunliffe 1989; Cunliffe 2005; Hunt 1992; Schaller 2016; Stinco 2007; Thielitz 2015), and one used a visual analogue scale to assess the severity of adverse events (Levesque 2011). Four trials did not report this outcome (Barbareschi 1991; Bojar 1994; Dunlap 1997; Shalita 1989).

Six studies reported quality of life assessed by the participants (Akarsu 2012; Babayeva 2011; Chantalat 2006; Kim 1999; Schaller 2016; Thielitz 2015). Of these, three studies used the Acne-Specific Quality of Life Questionnaire (Acne-QoL) (Akarsu 2012; Babayeva 2011; Chantalat 2006), two studies used the Dermatology Life Quality Index (DLQI) Questionnaire (Schaller 2016; Thielitz 2015), and one study used preference test questions (Kim 1999). The rest of the studies (43) did not report quality of life. Of the 49 included studies, 24 studies reported other outcomes like skin barrier functions and acne severity Index.

Funding

Thirty-one trials did not describe the study funding sources. Authors from three trials were employees of a pharmaceutical company (Gollnick 2004a; Gollnick 2004b; Thielitz 2015). Nine trials received support from a pharmaceutical company or corporation (Bojar 1994; Chen 2007; Cunliffe 2005; Draelos 2016; Hunt 1992; Kar 2013; Schaller 2016; Shalita 1989; Shalita 1995). The posters from two trials were funded by Johnson & Johnson Consumer and Personal Products Worldwide (Chantalat 2006; Chantalat 2007). One trial received support from two persons with unknown positions (Eady 1996). One trial received funding from a university (Pazoki-Toroudi 2011), and one trial received support from the National Institute of Health, US Public Health Service and The Detroit General Hospital Research Corporation (Vasarinsh 1969). Only one trial clearly stated that there was no funding or financial source in support of the work (Khodaeiani 2013).

Excluded studies

We excluded 55 studies: 18 studies were not RCTs; four studies focused on healthy people or participants with rosacea; 23 presented ineligible interventions or comparisons; and in 10 studies we could not contact authors for clarification of randomisation. See 'Characteristics of excluded studies' tables for detailed descriptions of each excluded study.

Studies awaiting assessment

We added 12 records to studies awaiting classification (see the 'Characteristics of studies awaiting classification' tables). Reasons include: unable to obtain the full text (Bartosova 1978; Cavicchini 1989a; Draelos 2015; Giannotti 1989; Pisani 1991; Ponzio 1994, Zheng 2019), the study was listed as completed on a trial registry but no results could be obtained (IRCT201010094269N3; NCT00031096; NCT02755545; TCTR20190118001), and only a conference abstract was identified and it was not clear if the study met the inclusion criteria of the review (Kern 2019).

Ongoing studies

We identified three studies as ongoing and added details to the 'Characteristics of ongoing studies' tables. Comparisons included salicylic acid peel versus glycolic acid peel (ChiCTR1800018343), 35% glycolic acid peels versus 20% salicylic acid peels (CTRI/2018/06/014615), and salicylic acid plus Epiduo 0.1% to 2.5% topical gel versus moisturiser plus Epiduo 0.1% to 2.5% topical gel (NCT03832647).

Risk of bias in included studies

Please refer to Figure 2 and Figure 3 for a graphical overview of the risk of bias of included studies. See the 'Characteristics of included studies' tables for detailed assessment of risk of bias of each included study.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

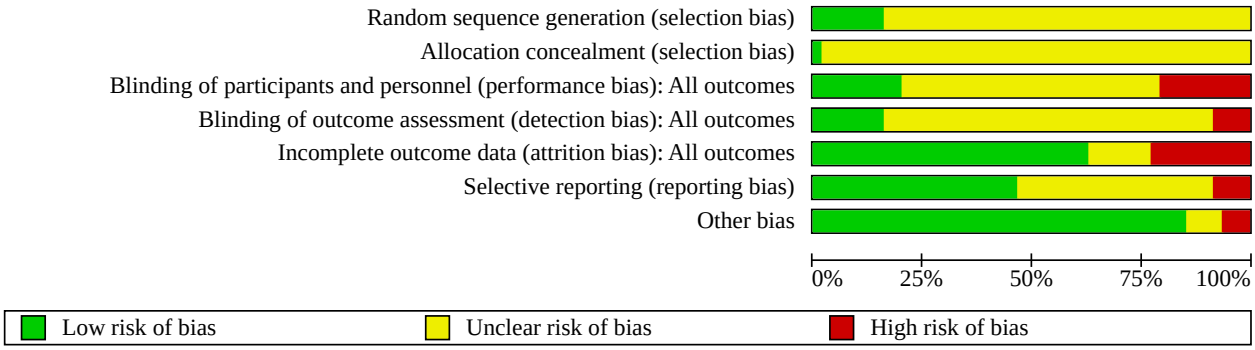


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

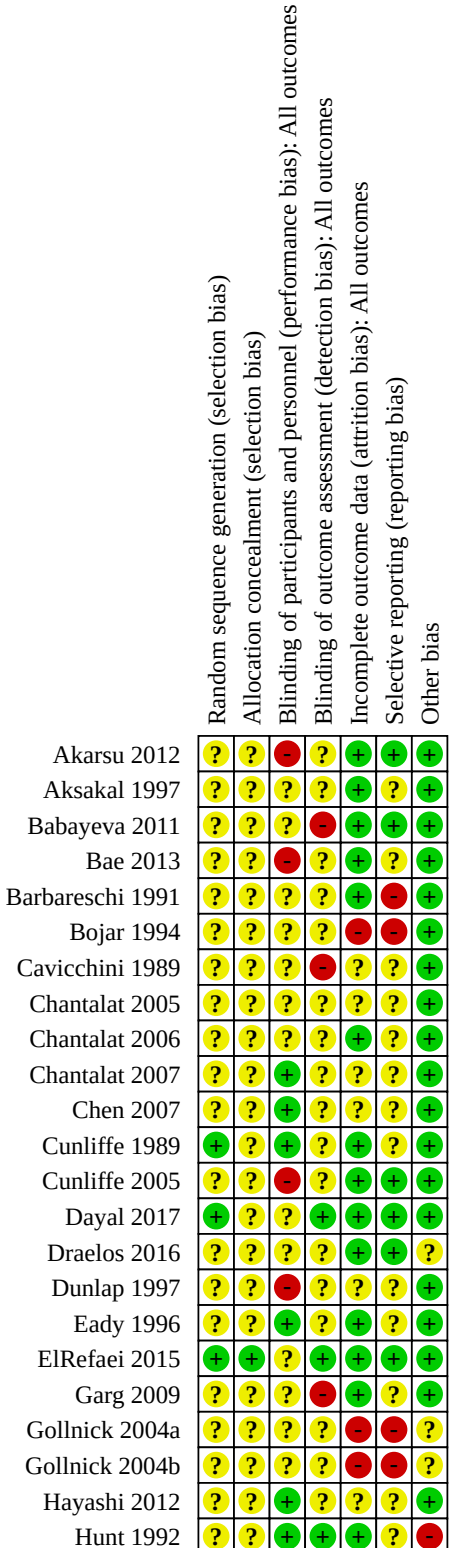
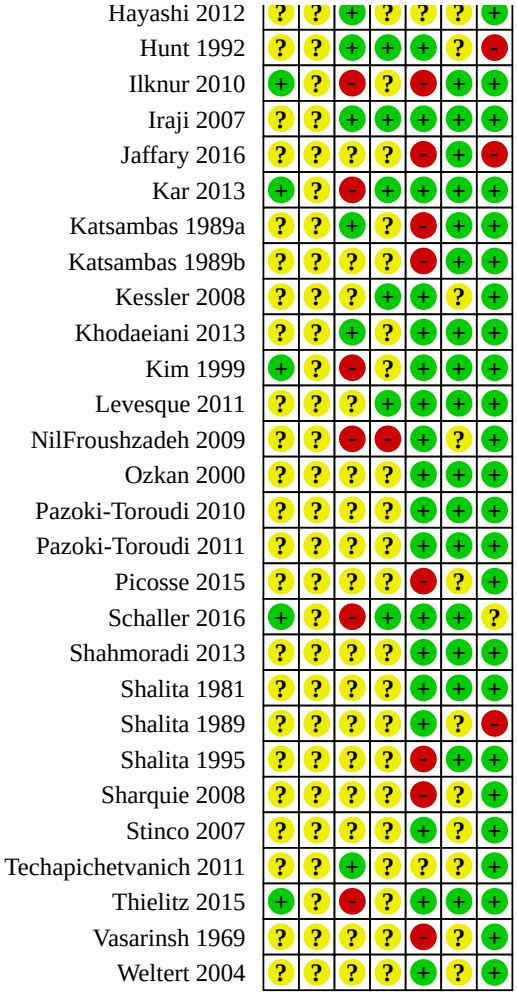


Figure 3. (Continued)



Allocation

Random sequence generation

Only eight studies (16.3%) mentioned appropriate randomisation methods and we judged them at low risk of bias. Of this group, the authors performed randomisation using the FORTRAN 77 RANDT program (Cunliffe 1989), computerized randomisation (Dayal 2017), sealed envelope (ElRefaei 2015), drawing (Ilknur 2010), random number table (Kar 2013), random permuted block (Kim 1999), computer-generated schedule (Schaller 2016), and minimisation method (Thielitz 2015). We judged the majority of included studies (41 studies) at unclear risk of bias for randomisation because these studies mentioned randomisation but provided inadequate description of randomisation methods.

Allocation concealment

Only one (2%) study reported the method used for allocation concealment and we rated it at low risk of bias (ElRefaei 2015; Figure 3). The remaining 48 studies did not address this issue or did not provide sufficient information to permit judgement.

Blinding

Of the 49 included studies, 21 had a double-blind design, 18 had a single-blind design, and the remaining 10 did not state this issue. Of the 21 studies (42.9%) with a double-blind design, only two clearly stated their method to ensure blinding of participants and assessors (Hunt 1992; Iraji 2007). We rated the two studies to be at low risk of bias for both domains. Eleven studies with a 'double-blind' design did not present sufficient information about method to ensure blinding of participants/personnel and assessors, we therefore judged them at unclear risk of bias for both domains in these studies (Bojar 1994; Chantalat 2005; Chantalat 2006; Draelos 2016; Gollnick 2004a; Gollnick 2004b; Pazoki-Toroudi 2010; Pazoki-Toroudi 2011; Shahmoradi 2013; Shalita 1995; Vasarinsh 1969). We judged the other seven of 21 double-blinded studies to be at low risk of performance bias and unclear risk of detection bias (Chantalat 2007; Chen 2007; Cunliffe 1989; Eady 1996; Katsambas 1989a; Khodaeiani 2013; Techapichetvanich 2011). In addition, we judged one of 21 double-blinded studies to be at unclear risk of performance bias and low risk of detection bias (Kessler 2008).

Of the 18 single-blind studies, eight followed an assessor or observer masked design. Of the eight studies, five did not provide sufficient information on method to ensure blinding of assessors

throughout the study, therefore we judged the risk of performance bias as high and detection bias as unclear (Akarsu 2012; Bae 2013; Ilknur 2010; Kim 1999; Cunliffe 2005). We judged two of the eight studies to be at unclear risk of performance bias and at low risk of detection bias (Dayal 2017; ElRefaei 2015), as the two studies clearly stated how blinding of assessors was ensured. Moreover, we judged one of the eight studies to be at high risk of performance bias and low risk of detection bias (Schaller 2016), as the participants and personnel were open to interventions.

Five of the 18 single-blind studies were investigator blinded. Of the five studies, three provided sufficient information on method to ensure blinding of investigators, we judged one to be at high risk of performance bias and at low risk of detection bias (Kar 2013), and one to be at unclear risk of performance bias and at low risk of detection bias (Levesque 2011), and one at high risk of performance bias and unclear risk of detection bias (Thielitz 2015). Two out of the five studies did not provide sufficient information on method to ensure blinding of investigators, we judged them to be at unclear risk of performance bias, and one to be at high risk (Dunlap 1997), and the other one to be at low risk of detection bias (Hayashi 2012).

Two of the 18 single-blind studies did not provide sufficient information on how blinding was ensured, and we judged them to be at unclear risk of bias for both domains (Jaffary 2016; Sharquie 2008). Another two of the 18 studies were participant-blinded, we judged them to be at high risk of detection bias, and one to be at unclear risk of performance bias due to the use of identical tubes (Cavicchini 1989), and the other one to be at high risk of performance bias due to probably insufficient blinding of personnel (NilFroushzadeh 2009). One of the 18 studies was open to assessor, and we judged it to be at unclear risk of performance bias and at high risk of detection bias (Babayeva 2011).

Ten studies did not mention blinding. For this reason, we judged nine of the 10 studies to be at unclear risk of bias for both domains (Aksakal 1997; Barbareschi 1991; Katsambas 1989b; Ozkan 2000; Picosse 2015; Shalita 1981; Shalita 1989; Stinco 2007; Weltert 2004). We judged one study to be at unclear risk of performance bias and at high risk of detection bias since the assessor was not blinded (Garg 2009).

Incomplete outcome data

We judged a total of 31 studies (63.3%) to be at low risk of attrition bias as they ensured the completeness of outcome data. Of this group, 19 studies had no dropouts, five studies provided data based on intention-to-treat (ITT) population, and in seven studies the dropout rate (< 10% per group) was not considered enough to introduce bias.

Of the 11 studies (22.4%) that did not provide complete outcome data, we judged at high risk of attrition bias. Of these, 10 studies had a dropout rate of more than 10% per group and one did not state which dropouts belonged to which treatment group (Bojar 1994).

It remained unclear if the outcome data were sufficiently addressed in seven trials (14.3%), we judged them to be at unclear risk of attrition bias.

Selective reporting

Twenty-three studies (46.9%) reported results for all prespecified outcomes mentioned in the study protocol or their methods section (if the protocol was not available), and we judged them to be at low risk of reporting bias. We judged four studies (8.2%) to be at high risk of reporting bias due to no results reported for prespecified outcomes or additionally reported outcomes that were not mentioned in the methods section. In the remaining 22 studies (44.9%), we rated them to be at unclear risk of reporting bias. Of this group, 14 studies did not provide data in a detailed manner and eight studies were published as abstract or poster only.

Other potential sources of bias

In 42 studies (85.7%), we identified no other potential sources of bias and we judged them to be at low risk of bias.

We judged three studies (6.1%) to be at high risk of other potential sources of bias. In one trial, there was baseline imbalance in total lesion counts across groups and the author used a Student's t-test with no post hoc analysis to compare the mean lesions of three treatment groups (Hunt 1992). In one study, there was a suspicion of fraudulent data reporting (Jaffary 2016). In a trial with a cross-over design, there was no washout period between the first and second phases of the study (Shalita 1989).

In four studies (8.2%) it was unclear whether the identified problems would introduce bias. One study reported in the statistical approach that they used non-inferiority borders of 15% (Gollnick 2004a); however, it was not fully clear whether they described an equivalence trial or an inferiority trial. In addition, the total number of participants in table one of the publication was incorrectly reported. In another study (Gollnick 2004b), the authors reported an advantage for azelaic acid, although the difference was not significant, moreover, the duration of therapy differed between treatment groups. The local adverse events were compared in an indirect fashion and the authors were employees of a pharmaceutical company that marketed azelaic acid in both studies (Gollnick 2004a and Gollnick 2004b). In another study (Draelos 2016), one author was an employee of GlaxoSmithKline Consumer Healthcare Ltd at the time the study was conducted and the sponsor reviewed the final manuscript before submission. Finally in one trial (Schaller 2016), three authors were employees of GlaxoSmithKline Consumer Healthcare Ltd and held stocks/shares in this company.

Effects of interventions

See: **Summary of findings 1** Azelaic acid compared to adapalene; **Summary of findings 2** Azelaic acid compared to benzoyl peroxide; **Summary of findings 3** Azelaic acid compared to clindamycin; **Summary of findings 4** Azelaic acid compared to tretinoin; **Summary of findings 5** Salicylic acid compared to benzoyl peroxide; **Summary of findings 6** Salicylic acid compared to pyruvic acid; **Summary of findings 7** Salicylic acid compared to tretinoin; **Summary of findings 8** Nicotinamide compared to clindamycin; **Summary of findings 9** Nicotinamide compared to erythromycin; **Summary of findings 10** Glycolic acid (alpha-hydroxy acid) compared to salicylic-mandelic acid

In this review, we assessed treatment efficacy of all six test interventions (topical azelaic acid, topical salicylic acid, topical nicotinamide, topical sulphur, topical zinc, and topical fruit acid (alpha-hydroxy acid) by grouping the outcomes into short-term treatment (less than or equal to 4 weeks), medium-term treatment (from 5 to 8 weeks) and long-term treatment (more than 8 weeks). Particularly, we specified the treatment duration for long-term

outcomes. The included studies measured their outcomes at the end of treatment unless otherwise specified. We presented outcome data collected in the post-treatment follow-up period in a narrative way.

With respect to the outcome, change in lesion counts, 'percentage reduction from baseline' referred to the difference between the mean lesion counts at the beginning and end of treatment divided by the mean lesion counts at the beginning of treatment, and 'number of lesions post-intervention' referred to the lesion counts after therapy.

Comparison 1: topical azelaic acid versus other topical treatments

Participants' global self-assessment of acne improvement

The single Thielitz 2015 trial compared azelaic acid 15% gel with adapalene 0.1% gel, and the authors assessed participants' global self-assessment of acne improvement using a one to seven grading system (7 grades between 'very much improved' (1) and 'very much worse' (7)). We found that there were no significant differences between the two groups in 'improved' to 'very much improved' in the medium term (risk ratio (RR) 0.74, 95% confidence interval (CI) 0.52 to 1.06; 1 study, 55 participants) and long term (3 months after start of treatment) (RR 0.89, 95% CI 0.68 to 1.17; 1 study, 55 participants; very low-quality evidence; Analysis 1.1; Summary of findings 1).

The single Gollnick 2004a trial compared azelaic acid 15% gel with benzoyl peroxide 5% gel, and the authors assessed the outcome using a four-point Likert-type rating scale (very good, good, moderate, poor). Results supported that benzoyl peroxide group had a statistically significant improvement (good or very good improvement) compared to azelaic acid in the long term (4 months after start of treatment) (RR 0.82, 95% CI 0.72 to 0.95; 1 study, 351 participants; moderate-quality evidence; Analysis 1.1; Summary of findings 2).

The single Pazoki-Toroudi 2011 trial compared azelaic acid 5% gel with clindamycin 2% gel, and the authors assessed this outcome using a five-point Likert-type scale (very satisfied, satisfied, moderately satisfied, unsatisfied, very unsatisfied). We found no significant difference in moderately to very satisfied improvement in the long term (3 months after start of treatment) (RR 0.95, 95% CI 0.81 to 1.12; 1 study, 100 participants; Analysis 1.1). Another single trial, Gollnick 2004b, compared azelaic acid 15% gel with clindamycin 1% gel, and the authors assessed the outcome using a four-point Likert-type rating scale (very good, good, moderate, poor). We found that there was no significant difference in good or very good improvement in the long term (4 months after start of treatment) (RR 1.13, 95% CI 0.92 to 1.38; 1 study, 229 participants; low-quality evidence; Analysis 1.1; Summary of findings 3).

The single Pazoki-Toroudi 2010 trial compared azelaic acid 20% gel with erythromycin 2% gel, and the authors assessed this outcome using a five-point Likert-type scale (very satisfied, satisfied, moderately satisfied, unsatisfied, very unsatisfied). We found no significant difference in moderately to very satisfied improvement in the long term (3 months after start of treatment) (RR 1.06, 95% CI 0.85 to 1.32; 1 study, 66 participants; Analysis 1.1).

The single Katsambas 1989b trial compared 20% azelaic acid cream with 0.05% tretinoin cream, and the authors reported the outcome using a four-point Likert-type rating scale (excellent, good, moderate, poor). Results showed that there was no significant difference in good to excellent improvement in the long term (6 months after start of treatment) (RR 0.94, 95% CI 0.78 to 1.14; 1 study, 289 participants; moderate-quality evidence; Analysis 1.1; Summary of findings 4).

The single Schaller 2016 trial compared azelaic acid 20% cream with benzoyl peroxide 3% + clindamycin 1% gel, and the authors reported this outcome using a 7-point scale (0 = very much improved, 1 = much improved, 2 = minimally improved, 3 = no change, 4 = minimally worse, 5 = much worse, 6 = very much worse) at all terms (4, 8, and 12 weeks after start of treatment). The study authors compared the proportion of participants with ratings of 'much improved/very much improved' and there was a clear difference between groups in favour of benzoyl peroxide 3% + clindamycin 1% gel in the medium and long term. Short term: RR 0.74 (95% CI 0.54 to 1.02; 1 study, 221 participants); medium term: RR 0.72 (95% CI 0.55 to 0.95; 1 study, 221 participants); and long term: RR 0.75 (95% CI 0.57 to 0.99; 1 study, 221 participants) (Analysis 1.1). The quality of evidence was low (Table 4).

We rated the findings measured in the long term as very low- to moderate-quality evidence due to risk of bias and/or imprecision (Summary of findings 1; Table 4; Summary of findings 2; Summary of findings 3; Summary of findings 4).

Withdrawal for any reason

For this outcome, two studies compared azelaic acid with adapalene (Stinco 2007; Thielitz 2015), and there was no clear difference in the short term (RR 0.80, 95% CI 0.05 to 12.01; 1 study, 45 participants) and long term (12 weeks after start of treatment) (RR 2.64, 95% CI 0.33 to 20.99; 1 study, 55 participants) (Analysis 1.2). The quality of evidence was very low (Summary of findings 1). When azelaic acid was compared with benzoyl peroxide (Gollnick 2004a; Stinco 2007), there was also no clear difference in the short term (RR 0.40, 95% CI 0.04 to 4.10; 1 study, 45 participants) and long term (16 weeks after start of treatment) (RR 0.88, 95% CI 0.60 to 1.29; 1 study, 351 participants) (Analysis 1.2). The quality of evidence was low (Summary of findings 2). When azelaic acid was compared with clindamycin, one study reported no withdrawals in the medium term (Ozkan 2000). Another two studies compared azelaic acid with clindamycin in the long term (treatment duration over 12 weeks) (Gollnick 2004b; Pazoki-Toroudi 2011), there was no clear difference (RR 1.30, 95% CI 0.48 to 3.56; 2 studies, 329 participants; low-quality evidence; Analysis 1.2; Summary of findings 3). When azelaic acid was compared with metronidazole, one study reported no withdrawals in the long term (12 weeks after start of treatment) (Analysis 1.2). When 20% azelaic acid cream was compared with 0.05% tretinoin cream (Barbareschi 1991; Katsambas 1989b), there was no statistically significant difference in the long term (treatment duration over 12 weeks) (RR 0.66, 95% CI 0.29 to 1.47; 2 studies, 309 participants; low-quality evidence; Analysis 1.2; Summary of findings 4). When azelaic acid 20% cream was compared with benzoyl peroxide 3% + clindamycin 1% gel (Schaller 2016), there was also no clear difference in the long term (12 weeks after start of treatment) (RR 1.15, 95% CI 0.43 to 3.07; 1 study, 221 participants; low-quality evidence; Analysis 1.2; Table 4).

We rated the findings measured in the long term as very low- to low-quality of evidence due to risk of bias and imprecision (Summary of

findings 1; Table 4; Summary of findings 2; Summary of findings 3; Summary of findings 4).

Change in lesion counts

Total (percentage reduction from baseline)

One study comparing azelaic acid 5% gel with clindamycin 2% gel contributed data for this outcome (Pazoki-Toroudi 2011). Clindamycin had an advantage over azelaic acid in reducing total lesion counts in the short term (mean difference (MD) -12.03, 95% CI -13.01 to -11.05; 1 study, 100 participants; Analysis 1.3), medium term (MD -14.41, 95% CI -15.47 to -13.35; 1 study, 96 participants; Analysis 1.3), and long term (12 weeks after start of treatment) (MD -11.95, 95% CI -13.28 to -10.62; 1 study, 88 participants; Analysis 1.3). The differences were statistically significant.

Another trial compared azelaic acid 20% cream with benzoyl peroxide 3% + clindamycin 1% gel (Schaller 2016). There was a clear difference for all treatment terms (4, 8 and 12 weeks after start of treatment) in favour of benzoyl peroxide 3% + clindamycin 1% gel. Short term: MD -13.00 (95% CI -19.23 to -6.77; 1 study, 212 participants); medium term: MD -15.10 (95% CI -23.01 to -7.19; 1 study, 206 participants); and long term: MD -18.50 (95% CI -26.46 to -10.54; 1 study, 211 participants) (Analysis 1.3).

Total

Only Thielitz 2015 compared azelaic acid 15% gel with adapalene 0.1% gel reported the data in the long term (3 months after start of treatment); however, the data were skewed and we could therefore not present the data in a forest plot and instead presented it in a table (see table in Analysis 1.4). There was no statistically significant difference between the azelaic acid and adapalene group in percentage reduction from baseline (P = 0.396).

In one study with no usable outcome data (Ozkan 2000), the authors stated that azelaic acid (form and concentration unknown) was more effective in reducing acne grade, assessed using the Leeds' technique, when compared to clindamycin phosphate (concentration unknown).

Inflamed (percentage reduction from baseline)

The single Schaller 2016 trial compared azelaic acid 20% cream with benzoyl peroxide 3% + clindamycin 1% gel. There was a clear difference between groups at all treatment terms (4, 8 and 12 weeks after start of treatment) in favour of benzoyl peroxide 3% + clindamycin 1% gel. Short term: MD -14.10 (95% CI -22.02 to -6.16; 1 study, 212 participants); medium term: MD -15.90 (95% CI -23.74 to -8.06; 1 study, 2016 participants); and long term: MD -17.30 (95% CI -24.73 to -9.87; 1 study, 211 participants) (Analysis 1.5).

Inflamed (number of lesions post-intervention)

The single Stinco 2007 trial compared azelaic acid (form and concentration unknown) with adapalene and benzoyl peroxide. There was no clear difference between azelaic acid and adapalene (MD 0.00, 95% CI -2.47 to 2.47; 1 study, 43 participants; Analysis 1.6) or benzoyl peroxide (MD -0.10, 95% CI -2.54 to 2.34; 1 study, 42 participants; Analysis 1.6).

Inflamed

Five studies reported data for this outcome; however, the data were not available for meta-analysis, so we presented the data in Analysis 1.7. Aksakal 1997 only reported the P value; the authors reported that azelaic acid 20% cream was more effective in reducing inflamed lesions when compared to metronidazole 1% cream (P < 0.001). Results from Dunlap 1997 demonstrated the significant advantage of 3% erythromycin/5% benzoyl peroxide over 20% azelaic acid in reducing inflammatory lesions. The authors from Gollnick 2004a reported that the median percentage reduction of inflamed lesions was 70% in the azelaic acid 15% gel group and 77% in the benzoyl peroxide 5% gel group (P > 0.05). Authors from Gollnick 2004b reported that the median percentage reduction of inflamed lesions was 71% in the azelaic acid 15% gel group and 63% in the clindamycin 1% gel group (P > 0.05). Data from Thielitz 2015 were skewed and the authors compared azelaic acid 15% gel with adapalene 0.1% gel; there was no significant difference between groups in percentage change of inflamed lesions in the long term (3 months after start of treatment) (P = 0.816).

Papules (percentage reduction from baseline)

Only one study that compared azelaic acid 5% gel with clindamycin 2% gel contributed data for this outcome (Pazoki-Toroudi 2011). Clindamycin 2% gel had an advantage over azelaic acid 5% gel in reducing the papular lesion count in the short term (MD -23.74, 95% CI -24.54 to -22.94; 1 study, 100 participants; Analysis 1.8), medium term (MD -34.25, 95% CI -35.51 to -32.99; 1 study, 96 participants; Analysis 1.8) and long term (12 weeks after start of treatment) (MD -25.03, 95% CI -26.38 to -23.68; 1 study, 88 participants; Analysis 1.8). The differences were statistically significant.

Papules (number of lesions post-intervention)

Only one study that compared azelaic acid 20% gel with erythromycin 2% gel contributed data for this outcome (Pazoki-Toroudi 2010). Participants in the erythromycin 2% gel group had less papules post-intervention than those in the azelaic acid 20% gel group in the short term (MD 3.40, 95% CI 2.99 to 3.81; 1 study, 66 participants; Analysis 1.9), and medium term (MD 2.05, 95% CI 1.60 to 2.50; 1 study, 66 participants; Analysis 1.9). The difference was statistically significant. There was no clear difference between topical azelaic acid 20% gel and erythromycin 2% gel in the long term (12 weeks after start of treatment) (MD -0.17, 95% CI -0.36 to 0.02; 1 study, 66 participants; Analysis 1.9).

Pustules (percentage reduction from baseline)

Only one study that compared azelaic acid 5% gel with clindamycin 2% gel contributed data for this outcome (Pazoki-Toroudi 2011). Clindamycin 2% gel was better than azelaic acid 5% gel in reducing the pustular lesion count in the short term (MD -6.53, 95% CI -7.45 to -5.61; 1 study, 100 participants; Analysis 1.10), medium term (MD -9.07, 95% CI -10.42 to -7.72; 1 study, 96 participants; Analysis 1.10), and long term (12 weeks after start of treatment) (MD -9.71, 95% CI -11.33 to -8.09; 1 study, 88 participants; Analysis 1.10).

Pustules (number of lesions post-intervention)

Only one study that compared azelaic acid 20% gel with erythromycin 2% gel contributed data for this outcome (Pazoki-Toroudi 2010). There was a difference between topical azelaic acid 20% gel and erythromycin 2% gel in the short term (MD -2.31, 95% CI -2.64 to -1.98; 1 study, 66 participants; Analysis 1.11), medium term (MD -2.95, 95% CI -3.24 to -2.66; 1 study, 66 participants; Analysis 1.11), and long term (12 weeks after start of treatment) (MD -1.80, 95% CI -1.97 to -1.63; 1 study, 66 participants; Analysis 1.11), which were all in favour of azelaic acid 20% gel.

Non-inflamed

We found five relevant trials that collected data for this outcome; however, the data were not available for meta-analysis, so we presented the data in a table (see table in Analysis 1.12). Aksakal 1997 only reported the P value; the authors reported that azelaic acid 20% cream was more effective in reducing non-inflamed lesions when compared to metronidazole 1% cream (P < 0.001). Barbareschi 1991 compared 20% azelaic acid cream with 0.05% retinoic acid cream; the authors did not report the P value and MDs. Results from Dunlap 1997 demonstrated significant advantage of 3% erythromycin/5% benzoyl peroxide over 20% azelaic acid in reducing comedones. The authors from Gollnick 2004a reported that the median percentage reduction of non-inflamed lesions was 60% in the azelaic acid 15% gel group and 71% in the benzoyl peroxide 5% gel group (P > 0.05). Authors from Gollnick 2004b reported that the median percentage reduction of non-inflamed lesions was 57% in the azelaic acid 15% gel group and 45% in the clindamycin 1% gel group (P < 0.05). Data from Thielitz 2015 were skewed and results also showed that there was no significant difference in percentage reduction of non-inflamed lesions (P = 0.063) or microcomedones (P = 0.25) in the long term (3 months after start of treatment) between azelaic acid 15% gel and adapalene 0.1% gel.

Non-inflamed (percentage reduction from baseline)

One study that compared azelaic acid 5% gel with clindamycin 2% gel contributed data for this outcome (Pazoki-Toroudi 2011). Clindamycin 2% gel was better than azelaic acid 5% gel in reducing the non-inflamed lesion (comedones) count in the short term (MD -5.81, 95% CI -6.80 to -4.82; 1 study, 100 participants; Analysis 1.13); however, this clear advantage was not observed in the medium term (MD 0.11, 95% CI -1.24 to 1.46; 1 study, 96 participants; Analysis 1.13) and long term (12 weeks after start of treatment) (MD -1.11, 95% CI -2.91 to 0.69; 1 study, 88 participants; Analysis 1.13).

Schaller 2016 compared azelaic acid 20% cream with benzoyl peroxide 3% + clindamycin 1% gel. There was a clear difference between groups for all treatment terms (4, 8 and 12 weeks after start of treatment) in favour of benzoyl peroxide 3% + clindamycin 1% gel. Short term: MD -11.10 (95% CI -18.64 to -3.56; 1 study, 212 participants); medium term: MD -13.00 (95% CI -22.76 to -3.24; 1 study, 206 participants); and long term: MD -18.50 (95% CI -28.33 to -8.67; 1 study, 211 participants) (Analysis 1.13).

Non-inflamed (number of lesions post-intervention)

One study compared azelaic acid 20% gel with erythromycin 2% gel (Pazoki-Toroudi 2010). There was a difference between topical azelaic acid 20% gel and erythromycin 2% gel in the short term (MD -2.68, 95% CI -2.89 to -2.47; 1 study, 66 participants; Analysis 1.14), medium term (MD -1.80, 95% CI -2.10 to -1.50; 1 study, 66 participants; Analysis 1.14) and long term (12 weeks after start of treatment) (MD -2.07, 95% CI -2.25 to -1.89; 1 study, 66 participants; Analysis 1.14), which were all in favour of azelaic acid 20% gel.

Another study compared azelaic acid (form and concentration unknown) with benzoyl peroxide and adapalene (Stinco 2007). There was no clear difference between azelaic acid and adapalene in the medium term (MD -3.00, 95% CI -8.07 to 2.07; 1 study, 43 participants; Analysis 1.14). In addition, there was also no clear difference between azelaic acid and benzoyl peroxide in the medium term (MD -4.40, 95% CI -10.77 to 1.97; 1 study, 42 participants; Analysis 1.14).

Physicians' global evaluation of acne improvement

For this outcome, no data reported in the short and medium term. Gollnick 2004a assessed the outcome using a four-point Likert-type rating scale (very good, good, moderate, poor). Study authors compared azelaic acid 15% gel with benzoyl peroxide 5% gel, and the benzoyl peroxide group demonstrated a statistically significant good or very good improvement in the long term (4 months after start of treatment) (RR 0.84, 95% CI 0.74 to 0.96; 1 study, 351 participants; Analysis 1.15).

Gollnick 2004b assessed the outcome using a four-point Likert-type rating scale (very good, good, moderate, poor). Study authors compared azelaic acid 15% gel with clindamycin 1% gel in good or very good improvement in the long term (4 months after start of treatment), and there was no significant difference (RR 0.92, 95% CI 0.78 to 1.10; 1 study, 229 participants; Analysis 1.15). Only Katsambas 1989b compared azelaic acid 20% cream with tretinoin 0.05% cream in good to excellent improvement in the long term (6 months after start of treatment), and there was no significant difference (RR 0.94, 95% CI 0.80 to 1.11; 1 study, 289 participants; Analysis 1.15).

Schaller 2016 compared azelaic acid 20% cream with benzoyl peroxide 3% + clindamycin 1% gel and the authors reported this outcome using a six-point scale (6 points from clear (0) to very clear (5)) for all treatment terms (4, 8 and 12 weeks after start of treatment). There was a clear significant difference in the medium term (RR 0.54, 95% CI 0.31 to 0.95; 1 study, 221 participants) and long term (RR 0.53, 95% CI 0.33 to 0.87; 1 study, 221 participants), which was in favour of benzoyl peroxide 3% + clindamycin 1% gel group. But there was no clear difference in the short term (RR 0.58, 95% CI 0.29 to 1.17; 1 study, 221 participants) (Analysis 1.15).

Dunlap 1997 had no usable outcome data and the authors stated that azelaic acid 20% cream was less effective in physician global evaluation when compared to 3% erythromycin/5% benzoyl peroxide gel. The authors also stated that azelaic acid 20% cream was inferior to 3% erythromycin/5% benzoyl peroxide gel in overall acne condition improvement and reduction of inflammatory lesions and comedones.

Minor adverse events

Total events - azelaic acid versus adapalene

Thielitz 2015 reported no "significant difference" between topical azelaic acid 15% gel and adapalene 1% gel (RR 1.16, 95% CI 0.47 to 2.85; 1 study, 55 participants; Analysis 1.16). We rated this finding as very low-quality evidence due to risk of bias and imprecision (Summary of findings 1).

Total events - azelaic acid versus benzoyl peroxide

Cavicchini 1989 reported that one out of 15 people in the azelaic acid 20% cream group versus two out of 15 people in the benzoyl peroxide 5% gel group experienced minor adverse events (P = 1.00, Fisher's Exact test). There was no clear difference between topical azelaic acid 20% cream and benzoyl peroxide 5% gel (RR 0.50, 95% CI 0.05 to 4.94; 1 study, 30 participants; Analysis 1.16). We rated this finding as very low-quality evidence due to risk of bias and imprecision (Summary of findings 2).

Total events - azelaic acid versus benzoyl + clindamycin

Schaller 2016 compared azelaic acid 20% cream with benzoyl peroxide 3% + clindamycin 1% gel. The participants who received benzoyl peroxide 3% + clindamycin 1% gel experienced fewer total number of events, though there was no clear significant difference (RR 1.24, 95% CI 1.01 to 1.52; 1 study, 221 participants; Analysis 1.16). We rated this finding as low-quality evidence due to risk of bias and imprecision (Table 4).

Total events - azelaic acid versus clindamycin

Pazoki-Toroudi 2011 compared azelaic acid 5% gel with clindamycin 2% gel. There was no clear difference between treatment groups (RR 1.50, 95% CI 0.67 to 3.35; 1 study, 100 participants; Analysis 1.16). We rated this finding as low-quality evidence due to risk of bias and imprecision (Summary of findings 3).

Total events - azelaic acid versus erythromycin

Pazoki-Toroudi 2010 reported that 16 out of 35 people in the azelaic acid 20% gel group versus 17 out of 31 people in the erythromycin 2% gel group experienced total events. There was no significant difference between topical azelaic acid 20% gel and erythromycin 2% gel (RR 0.83, 95% CI 0.51 to 1.35; 1 study, 66 participants; Analysis 1.16).

Application site pain - azelaic acid versus benzoyl + clindamycin

Schaller 2016 compared azelaic acid 20% cream with benzoyl peroxide 3% + clindamycin 1% gel. There was a significant difference between groups showing azelaic acid caused more application site pain (RR 3.17, 95% CI 1.41 to 7.12; 1 study, 221 participants; Analysis 1.16).

Burning - azelaic acid versus benzoyl peroxide

Gollnick 2004a showed there was no significant difference between topical azelaic acid 15% gel and benzoyl peroxide 5% gel (RR 1.10, 95% CI 0.61 to 1.97; 1 study, 351 participants; Analysis 1.16).

Burning - azelaic acid versus clindamycin

Gollnick 2004b reported burning in 12/114 participants in the azelaic acid 15% gel treatment group compared to 0/115 participants in the clindamycin 1% gel group. There was a significant difference between groups, showing azelaic acid caused more burning (RR 25.22, 95% CI 1.51 to 420.92; 1 study, 229 participants; Analysis 1.16), but the confidence interval was very wide.

Burning - azelaic acid versus tretinoin

Katsambas 1989b reported no significant difference between topical azelaic acid 20% cream and tretinoin 0.05% cream (RR 0.80, 95% CI 0.38 to 1.71; 1 study, 289 participants; Analysis 1.16).

Scaling - azelaic acid versus clindamycin

Pazoki-Toroudi 2011 reported that four out of 50 people in the azelaic acid 5% gel group versus six out of 50 people in the clindamycin 2% gel group experienced scaling (P = 0.741, Fisher's Exact test). There was no significant difference between topical azelaic acid 5% gel and clindamycin 2% gel (RR 0.67, 95% CI 0.20 to 2.22; 1 study, 100 participants; Analysis 1.16).

Scaling - azelaic acid versus erythromycin

Pazoki-Toroudi 2010 reported that four out of 35 people in the azelaic acid 20% gel group versus two out of 31 people in the erythromycin 2% gel group experienced scaling (P = 0.68, Fisher's Exact test). There was no significant difference between topical azelaic acid 20% gel and erythromycin 2% gel (RR 1.77, 95% CI 0.35 to 9.01; 1 study, 66 participants; Analysis 1.16).

Scaling - azelaic acid versus tretinoin

Katsambas 1989b reported that topical azelaic acid 20% cream had lower risk of scaling than tretinoin 0.05% cream (RR 0.58, 95% CI 0.37 to 0.91; 1 study, 289 participants; Analysis 1.16). This difference was statistically different.

Erythema - azelaic acid versus adapalene

Stinco 2007 reported no significant difference between topical azelaic acid (form and concentration unknown) and adapalene (RR 0.80, 95% CI 0.30 to 2.10; 1 study, 45 participants; Analysis 1.16).

Erythema - azelaic acid versus benzoyl peroxide

Stinco 2007 reported no significant difference between topical azelaic acid (form and concentration unknown) and benzoyl peroxide (RR 0.48, 95% CI 0.21 to 1.09; 1 study, 45 participants; Analysis 1.16).

Erythema - azelaic acid versus benzoyl peroxide/clindamycin

Schaller 2016 reported no significant difference between topical azelaic acid 20% cream and benzoyl peroxide 3% + clindamycin 1% gel (RR 1.68, 95% CI 0.41 to 6.87; 1 study, 221 participants; Analysis 1.16).

Erythema - azelaic acid versus clindamycin

Pazoki-Toroudi 2011 reported that three out of 50 people in the azelaic acid 5% gel group versus four out of 50 people in the clindamycin 2% gel group experienced erythema (P = 1.00, Fisher's Exact test). There was no significant difference between topical azelaic acid 5% gel and clindamycin 2% gel (RR 0.75, 95% CI 0.18 to 3.18; 1 study, 100 participants; Analysis 1.16).

Erythema - azelaic acid versus erythromycin

Pazoki-Toroudi 2010 reported that three out of 35 people in the azelaic acid 20% gel group versus four out of 31 people in the erythromycin 2% gel group experienced erythema (P = 0.70, Fisher's Exact test). There was no significant difference between topical azelaic acid 20% gel and erythromycin 2% gel (RR 0.66, 95% CI 0.16 to 2.74; 1 study, 66 participants; Analysis 1.16).

Erythema - azelaic acid versus tretinoin

Katsambas 1989b reported that topical azelaic acid 20% cream had lower risk of erythema than tretinoin 0.05% cream (RR 0.64, 95% CI 0.41 to 0.99; 1 study, 289 participants; Analysis 1.16), and this difference was statistically significant.

Dryness - azelaic acid versus adapalene

Stinco 2007 reported no significant difference between topical azelaic acid (form and concentration unknown) and adapalene (RR 0.80, 95% CI 0.51 to 1.26; 1 study, 45 participants; Analysis 1.16).

Dryness - azelaic acid versus benzoyl peroxide

Gollnick 2004a and Stinco 2007 reported no significant difference between topical azelaic acid and benzoyl peroxide (RR 0.56, 95% CI 0.27 to 1.16; 2 studies, 396 participants; Analysis 1.16).

Dryness - azelaic acid versus benzoyl peroxide/clindamycin

Schaller 2016 reported no significant difference between topical azelaic acid 20% cream and benzoyl peroxide 3% + clindamycin 1% gel (RR 1.51, 95% CI 0.26 to 8.88; 1 study, 221 participants; Analysis 1.16).

Dryness - azelaic acid versus clindamycin

Gollnick 2004b and Pazoki-Toroudi 2011 reported no significant difference between topical azelaic acid and clindamycin (RR 2.44, 95% CI 0.96 to 6.19; 2 studies, 329 participants; Analysis 1.16).

Dryness - azelaic acid versus erythromycin

Pazoki-Toroudi 2010 reported that two out of 35 people in the azelaic acid 20% gel group versus four out of 31 people in the erythromycin 2% gel group experienced dryness (P = 0.41, Fisher's Exact test). There was no significant difference between topical azelaic acid 20% gel and erythromycin 2% gel (RR 0.44, 95% CI 0.09 to 2.25; 1 study, 66 participants; Analysis 1.16).

Oiliness - azelaic acid versus clindamycin

Pazoki-Toroudi 2011 reported that five out of 50 people in the azelaic acid 5% gel group versus four out of 50 people in the clindamycin 2% gel group experienced oiliness (P = 1.00, Fisher's Exact test). There was no significant difference between topical azelaic acid 5% gel and clindamycin 2% gel (RR 1.25, 95% CI 0.36 to 4.38; 1 study, 100 participants; Analysis 1.16).

Oiliness - azelaic acid versus erythromycin

Pazoki-Toroudi 2010 reported that three out of 35 people in the azelaic acid 20% gel group versus three out of 31 people in the erythromycin 2% gel group experienced oiliness (P = 1.00, Fisher's Exact test). There was no significant difference between topical azelaic acid 20% gel and erythromycin 2% gel (RR 0.89, 95% CI 0.19 to 4.07; 1 study, 66 participants; Analysis 1.16).

Itching - azelaic acid versus adapalene

Stinco 2007 reported no significant difference between topical azelaic acid (form and concentration unknown) and adapalene (RR 1.23, 95% CI 0.84 to 1.79; 1 study, 45 participants; Analysis 1.16).

Itching - azelaic acid versus benzoyl peroxide

Gollnick 2004a and Stinco 2007 reported itching was higher in the azelaic acid group compared with the benzoyl peroxide group, but the RR was uncertain due to the wide CI spanning 1 (RR 3.29, 95% CI 0.24 to 45.29; 2 studies, 396 participants; Analysis 1.16).

Itching - azelaic acid versus benzoyl peroxide/clindamycin

Schaller 2016 reported a significant difference between groups, showing azelaic acid 20% cream caused more itching compared with benzoyl peroxide 3% + clindamycin 1% gel (RR 3.15, 95% CI 1.49 to 6.68; 1 study, 221 participants; Analysis 1.16).

Itching - azelaic acid versus clindamycin

Gollnick 2004b and Pazoki-Toroudi 2011 reported more itching in the azelaic acid group compared with the clindamycin group, but the RR was uncertain due to the wide CI spanning 1 (RR 2.56, 95% CI 0.68 to 9.57; 2 studies, 329 participants; Analysis 1.16).

Itching - azelaic acid versus erythromycin

Some studies, for example Pazoki-Toroudi 2010, reported this outcome as 'pruritus'. We contacted authors to confirm whether 'pruritus' was equal to 'itching'; authors from Schaller 2016 replied they were the same thing. Therefore, we considered 'pruritus' and 'itching' to be the same thing and we used 'itching' throughout the text.

Pazoki-Toroudi 2010 reported that four out of 35 people in the azelaic acid 20% gel group versus three out of 31 people in the erythromycin 2% gel group experienced itching (P = 1.00, Fisher's Exact test). There was no significant difference between topical azelaic acid 20% gel and erythromycin 2% gel (RR 1.18, 95% CI 0.29 to 4.87; 1 study, 66 participants; Analysis 1.16).

Red skin - azelaic acid versus benzoyl peroxide

Gollnick 2004a reported no significant difference between topical azelaic acid 15% gel and benzoyl peroxide 5% gel (RR 0.68, 95% CI 0.36 to 1.26; 1 study, 351 participants; Analysis 1.16).

Red skin - azelaic acid versus clindamycin

Gollnick 2004b reported that topical azelaic acid 15% gel had a higher risk of red skin than clindamycin 1% gel (RR 6.05, 95% CI 1.39 to 26.44; 1 study, 229 participants; Analysis 1.16), and the difference was statistically significant.

Desquamation - azelaic acid versus benzoyl peroxide

Gollnick 2004a reported a statistically significant difference between topical azelaic acid 15% gel and benzoyl peroxide 5% gel (RR 0.25, 95% CI 0.08 to 0.73; 1 study, 351 participants; Analysis 1.16), which indicated a lower risk of desquamation after using azelaic acid.

Eczema - azelaic acid versus clindamycin

Gollnick 2004b reported that zero out of 114 people in the azelaic acid 15% gel group versus four out of 115 people in the clindamycin 1% gel group experienced eczema (P = 0.12, Fisher's Exact test). There was no clear difference between topical azelaic acid 15% gel and clindamycin 1% gel (RR 0.11, 95% CI 0.01 to 2.06; 1 study, 229 participants; Analysis 1.16).

Quality of life

Schaller 2016 compared azelaic acid 20% cream with benzoyl peroxide 3% + clindamycin 1% gel (12 weeks after start of treatment) using the 10-question Children's Dermatology Life Quality Index (CDLQI; 0 = not at all, 1 = a little, 2 = a lot, 3 = very much, low = well) to assess how much the skin disease affected participants' lives. The percentage change from baseline (skewed data) was in favour of benzoyl peroxide 3% + clindamycin 1% gel (-36.8% ± 74.8 in azelaic acid group versus -60.5% ± 70.6 in benzoyl peroxide + clindamycin group). The quality of evidence was low (Table 4).

Thielitz 2015 compared azelaic acid 15% gel with adapalene 0.1% gel; we were unable to present the skewed data from this study in a forest plot, so we presented the data in a table (see table in Analysis 1.17). There was no "statistically significant" difference (P = 0.549) in absolute change of Dermatology Life Quality Index in the long term (3 months after start of treatment) between azelaic acid and adapalene (-1.88 ± 3.35 and -2.74 ± 2.90 in azelaic acid group versus -2.58 ± 4.68 in adapalene group). The quality of evidence was very low (Summary of findings 1).

Comparison 2: topical azelaic acid versus placebo

Participants' global self-assessment of acne improvement

No study collected data for this outcome.

Withdrawal for any reason

One trial compared azelaic acid 20% gel with placebo (Iraji 2007), neither treatment group experienced withdrawals in the medium term (Analysis 2.1). Three relevant trials reported data in the long term (Barbareschi 1991; Cunliffe 1989; Katsambas 1989a). There was no clear difference between topical azelaic acid 20% cream and placebo cream in the long term (treatment duration more than 8 weeks) (RR 1.60, 95% CI 0.55 to 4.66; 3 studies, 152 participants; low-quality evidence; Analysis 2.1; Table 5), and two of the three studies reporting zero events.

Change in lesion counts

> 50% inflamed reduction

For this outcome, we only found one relevant trial that reported data in the long term (3 months after start of treatment) (Cunliffe 1989). The study stated that 10 participants using azelaic acid 20% cream demonstrated a reduction of at least 50% in inflamed lesions, compared to only one participant using placebo cream by the end of study (RR 10.00, 95% CI 1.41 to 70.99; 1 study, 40 participants; Analysis 2.2). However, the result had serious imprecision due to a very small sample size.

Inflamed (percentage reduction from baseline)

Three studies reported data for this outcome in the short, medium and long term (Cunliffe 1989; Hayashi 2012; Katsambas 1989a). Cunliffe 1989 and Katsambas 1989a were parallel trials and Hayashi 2012 was a split-face trial. As there were no means ± standard deviations (SDs) or SDs presented, we described the data in a table (see table in Analysis 2.3). All three studies concluded that compared to placebo, azelaic acid showed a greater percentage reduction in inflamed lesions in the short, medium, and long term (3 months after start of treatment).

> 50% non-inflamed reduction

We only found one relevant trial and it reported data in the long term (3 months after start of treatment) (Cunliffe 1989). By the end of study, a higher rate of > 50% non-inflamed reduction was observed in the azelaic acid group 20% cream (11/20) than in the placebo cream group (4/20) (RR 2.75, 95% CI 1.05 to 7.20; 1 study, 40 participants; Analysis 2.4). However, the result had serious imprecision due to a very small sample size.

Non-inflamed (percentage reduction from baseline)

Cunliffe 1989 reported data over the medium and long term (3 months after start of treatment); however, the authors only reported the P value with no means and SDs, so we presented the data in a table (see table in Analysis 2.5). When compared to placebo cream, the azelaic acid 20% cream showed a greater percentage reduction in non-inflamed lesions in the medium (P < 0.027) and long term (P < 0.027). The other split-face study only reported the percentage reduction with no SDs and P value (Hayashi 2012; Analysis 2.5).

Various types of acne (percentage reduction from baseline)

Three studies reported data for medium and long term outcomes (Hayashi 2012; Iraji 2007; Katsambas 1989a); however, as the SDs were missing, we presented the data in a table (see table in Analysis 2.6). Apart from pustule number (the percentage reduction was greater in the azelaic acid group, P = 0.08), azelaic acid 20% gel showed a better effect in percentage reduction of total lesion numbers (P = 0.002), comedone numbers (P = 0.001), papule numbers (P = 0.003), and acne severity index (P = 0.001), when compared to placebo in the medium term (Iraji 2007). There was also a significant difference between azelaic acid 20% cream and placebo cream in comedone percentage reduction in the long term (3 months after start of treatment) (55.6% for azelaic acid, 0% for placebo) in favour of azelaic acid 20% cream (no exact P value reported) (Katsambas 1989a). Another split-face study (Hayashi 2012), also suggested the advantage of topical azelaic acid 20% cream over placebo in total lesion reduction in the long term (12 weeks after start of treatment) (P < 0.001).

Various types of acne (number of lesions post-intervention)

Pazoki-Toroudi 2010 reported short-term data. However, the number of participants in the azelaic acid group was missing, so we presented the data in a table (see table in Analysis 2.7). The azelaic acid 20% gel group showed lower papule numbers (P < 0.001), pustule numbers (P < 0.001), and comedone numbers (P < 0.001) when compared with placebo after treatment.

Comedones (reduction in number of lesions post-intervention)

Only Barbareschi 1991 reported data for this outcome and SDs were missing. The azelaic acid 20% cream reduced more lesion counts than placebo treatment in the long term (4 months after start of treatment); however, the authors did not test whether the difference was significant (Analysis 2.8). In addition, azelaic acid 20% cream showed better effect in reducing comedones (measured by scanning electron microscopy) than placebo in the long term (4 months after start of treatment) (Analysis 2.8).

Physicians' global evaluation of acne improvement

Katsambas 1989a reported data in the long term (3 months after start of treatment). The authors assessed this outcome using a four-point system (75% to 100% reduction of the initial total lesion count: excellent; 50% to 75% reduction: good; 25% to 50% reduction: moderate; less than 25%: poor response). There was a statistically significant difference between topical azelaic acid 20% cream and placebo cream in good to excellent improvement (RR 1.64, 95% CI 1.00 to 2.67; 1 study, 92 participants; Analysis 2.9), which was in favour of azelaic acid 20% cream. However, the estimated result was fairly imprecise due to the small sample size.

Minor adverse events

Burning

Katsambas 1989a reported that four out of 43 people in the azelaic acid 20% cream group versus one out of 49 people in the placebo cream group experienced burning (P = 0.18, Fisher's Exact test). Burning was reported more in the topical azelaic acid 20% cream group compared with the placebo cream but the RR was imprecise due to the uncertainty from the wide CI (RR 4.56, 95% CI 0.53 to 39.24; 1 study, 92 participants; Analysis 2.10).

Scaling

Katsambas 1989a and Pazoki-Toroudi 2010 reported that five out of 78 people in the azelaic acid group versus two out of 69 people in the placebo group experienced scaling (P = 0.448, Fisher's Exact test). There was no clear difference between topical azelaic acid and placebo due to the wide CIs surrounding the effect size (RR 1.49, 95% CI 0.16 to 13.48; 2 studies, 147 participants; Analysis 2.10).

Erythema

Katsambas 1989a and Pazoki-Toroudi 2010 reported that five out of 78 people in the azelaic acid group versus two out of 69 people in the placebo group experienced erythema (P = 0.448, Fisher's Exact test). There was no clear difference between topical azelaic acid and placebo (RR 1.96, 95% CI 0.39 to 9.78; 2 studies, 147 participants; Analysis 2.10).

Dryness

Pazoki-Toroudi 2010 reported that two out of 35 people in the azelaic acid 20% gel group versus zero out of 20 people in the placebo group experienced dryness (P = 0.529, Fisher's Exact test). There was no significant difference between treatment groups (RR 2.92, 95% CI 0.15 to 57.90; 1 study, 55 participants; Analysis 2.10)

Oiliness

Pazoki-Toroudi 2010 reported that three out of 35 people in the azelaic acid 20% gel group versus zero out of 20 people in the placebo group experienced oiliness (P = 0.293, Fisher's Exact test). There was no difference between treatment groups (RR 4.08, 95% CI 0.22 to 75.25; 1 study, 55 participants; Analysis 2.10)

Itching

Katsambas 1989a and Pazoki-Toroudi 2010 reported that six out of 78 people in the azelaic acid group versus zero out of 69 people in the placebo group experienced itching (P = 0.03, Fisher's Exact test). There was no clear difference between treatment groups (RR 5.45, 95% CI 0.68 to 43.53; 2 studies, 147 participants; Analysis 2.10).

Total events

Iraji 2007 reported that nine out of 30 people in the azelaic acid 20% gel group versus zero out of 30 people in the placebo group experienced minor adverse events (P = 0.002, Fisher's Exact test). Result of meta-analysis showed that topical azelaic acid 20% gel had a higher rate of adverse events than placebo (RR 19.00, 95% CI 1.16 to 312.42; 1 study, 60 participants; Analysis 2.10). However, the result was imprecise as the estimated CI was very wide. We assessed the evidence as very low quality due to risk of bias and imprecision (Table 5).

Quality of life

No study collected data for this outcome.

Comparison 3: topical azelaic acid versus no treatment (including studies with a co-intervention in both arms)

Participants' global self-assessment of acne improvement

Pazoki-Toroudi 2010 and Pazoki-Toroudi 2011 assessed this outcome using a five-point Likert-type scale (very satisfied, satisfied, moderately satisfied, unsatisfied, very unsatisfied). We found no significant difference in moderately to very satisfied improvement between treatment groups in the long term (3 months after start of treatment) (RR 1.08, 95% CI 0.94 to 1.24; 2 studies, 171 participants; Analysis 3.1).

Withdrawal for any reason

Pazoki-Toroudi 2011 and Picosse 2015 found no statistically significant difference between topical azelaic acid and no treatment in the long term (treatment duration over 8 weeks) (RR 0.67, 95% CI 0.37 to 1.22; 2 studies, 150 participants; Analysis 3.2).

Change in lesion counts

Total (percentage reduction from baseline)

Pazoki-Toroudi 2011 compared azelaic acid 5% and clindamycin 2% combination gel with clindamycin 2% gel alone. Results showed that the combination gel was superior to clindamycin 2% gel alone in percentage reduction of total lesions. There was a clear difference between treatment groups in the short term (MD 7.62, 95% CI 6.24 to 9.00; 1 study, 100 participants; Analysis 3.3), medium term (MD 12.48, 95% CI 11.12 to 13.84; 1 study, 97 participants; Analysis 3.3), and long term (3 months after start of treatment) (MD 16.08, 95% CI 14.56 to 17.60; 1 study, 87 participants; Analysis 3.3).

Non-inflamed (percentage reduction from baseline)

Pazoki-Toroudi 2011 compared azelaic acid 5% and clindamycin 2% combination gel with clindamycin 2% gel alone. Results showed that the combination gel was superior to clindamycin 2% gel alone in percentage reduction of non-inflamed lesions. There was a clear difference between treatment groups in the short term (MD 4.30, 95% CI 3.05 to 5.55; 1 study, 100 participants; Analysis 3.4), medium term (MD 14.63, 95% CI 12.89 to 16.37; 1 study, 97 participants; Analysis 3.4), and long term (3 months after start of treatment) (MD 13.67, 95% CI 11.59 to 15.75; 1 study, 87 participants; Analysis 3.4).

Papules (percentage reduction from baseline)

Pazoki-Toroudi 2011 compared azelaic acid 5% and clindamycin 2% combination gel with clindamycin 2% gel alone. Results showed that the combination gel was superior to clindamycin 2% gel alone in percentage reduction of papules. There was a clear difference between treatment groups in the short term (MD 6.59, 95% CI 5.40 to 7.78; 1 study, 100 participants; Analysis 3.5), medium term (MD 8.08, 95% CI 6.71 to 9.45; 1 study, 97 participants; Analysis 3.5), and long term (3 months after start of treatment) (MD 14.51, 95% CI 12.95 to 16.07; 1 study, 87 participants; Analysis 3.5).

Pustules (percentage reduction from baseline)

Pazoki-Toroudi 2011 compared azelaic acid 5% and clindamycin 2% combination gel with clindamycin 2% gel alone. Results showed that the combination gel was superior to clindamycin 2% gel alone in percentage reduction of pustules. There was a clear difference

between treatment groups in the short term (MD 9.89, 95% CI 8.66 to 11.12; 1 study, 100 participants; Analysis 3.6), medium term (MD 14.73, 95% CI 13.03 to 16.43; 1 study, 97 participants; Analysis 3.6), and long term (3 months after start of treatment) (MD 20.05, 95% CI 17.96 to 22.14; 1 study, 87 participants; Analysis 3.6).

Inflamed (number of lesions post-intervention)

Pazoki-Toroudi 2010 reported data for this outcome, but the number of participants was missing. When compared to erythromycin 2% gel alone, the azelaic acid 5% and erythromycin 2% combination gel group showed lower papule numbers and pustule numbers after treatment in the short, medium, and long term (3 months after start of treatment) ($P < 0.01$) (Analysis 3.7).

Comedones (number of lesions post-intervention)

Pazoki-Toroudi 2010 reported data for this outcome, but the number of participants was missing. When compared to erythromycin 2% gel alone, the azelaic acid 5% and erythromycin 2% combination gel group showed lower comedone numbers after treatment in the short, medium, and long term (3 months after start of treatment) ($P < 0.01$) (Analysis 3.8).

Physicians' global evaluation of acne improvement

No study collected data for this outcome.

Minor adverse events

Scaling

Pazoki-Toroudi 2010 and Pazoki-Toroudi 2011 reported that four out of 90 people in the azelaic acid group versus eight out of 81 people in the no treatment group experienced scaling. There was no clear difference between topical azelaic acid and no treatment (RR 0.47, 95% CI 0.15 to 1.50; 2 studies, 171 participants; Analysis 3.9).

Erythema

Pazoki-Toroudi 2010 and Pazoki-Toroudi 2011 reported that four out of 90 people in the azelaic acid group versus nine out of 81 people in the no treatment group experienced erythema. There was no clear difference between topical azelaic acid and no treatment (RR 0.39, 95% CI 0.12 to 1.21; 2 studies, 171 participants; Analysis 3.9).

Dryness

Pazoki-Toroudi 2010 and Pazoki-Toroudi 2011 reported that five out of 90 people in the azelaic acid group versus seven out of 81 people in the no treatment group experienced dryness. There was no clear difference between topical azelaic acid and no treatment (RR 0.61, 95% CI 0.20 to 1.85; 2 studies, 171 participants; Analysis 3.9).

Oiliness

Pazoki-Toroudi 2010 and Pazoki-Toroudi 2011 reported that six out of 90 people in the azelaic acid group versus seven out of 81 people in the no treatment group experienced oiliness. There was no clear difference between topical azelaic acid and no treatment (RR 0.78, 95% CI 0.27 to 2.24; 2 studies, 171 participants; Analysis 3.9).

Itching

Pazoki-Toroudi 2010 and Pazoki-Toroudi 2011 reported that five out of 90 people in the azelaic acid group versus six out of 81 people in the no treatment group experienced itching (RR 0.73, 95% CI 0.23 to 2.29; 2 studies, 171 participants; Analysis 3.9).

Total events

Pazoki-Toroudi 2010 and Pazoki-Toroudi 2011 reported that 18 out of 90 people in the azelaic acid group versus 25 out of 81 people in the no treatment group experienced total events (RR 0.59, 95% CI 0.36 to 0.97; 2 studies, 171 participants; Analysis 3.9).

Quality of life

No study collected data for this outcome.

Comparison 4: topical salicylic acid versus other topical treatments

Participants' global self-assessment of acne improvement

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion (n = 46) and the authors assessed this outcome using a five-point scale (0: worsening or unchanged, 1: mild improvement, 2: moderate improvement, 3: good improvement and 4: excellent improvement). Both treatments demonstrated significant moderate to excellent improvement, and there was no difference between groups in the long term (12 weeks after start of treatment) (RR 1.00, 95% CI 0.92 to 1.09; 1 study, 46 participants; Analysis 4.1). We assessed the evidence as low quality due to risk of bias and imprecision (Summary of findings 7).

Jaffary 2016 compared salicylic acid 30% peels with pyruvic acid 50% peels and the authors assessed this outcome using a four-point scale (excellent, good, fair, poor) in the medium term (8 weeks after start of treatment). Both treatments demonstrated significant good to excellent improvement, and there was no clear difference between groups (RR 1.12, 95% CI 0.68 to 1.84; 1 study, 86 participants; Analysis 4.1). We assessed the evidence as very low quality due to risk of bias and imprecision (Summary of findings 6).

Participants' global self-assessment of acne improvement (%) - split-face designs

Bae 2013 and Kessler 2008, using a split-face design, reported data for this outcome; however, the means and SDs or SDs alone were missing, so we presented the data in a table (see table in Analysis 4.2). Bae 2013 assessed this outcome using a four-point scale (3 = good improvement, 2 = moderate improvement, 1 = mild improvement, 0 = no improvement or worsening) showed that the percentage of participants with good to mild improvement in the short term was 92.3% in the 30% salicylic acid group and 84.6% in Jessner's solution group. Another study used patient self-questionnaires to assess this outcome at two months post-treatment (treatment duration of 10 weeks, measured at the post-treatment follow-up period) (Kessler 2008). The percentage of participants with 'more improved' was 35% in the 30% salicylic acid peel group and 41% in the 30% glycolic acid peel group.

Withdrawal for any reason

Jaffary 2016 compared salicylic acid 30% peels with pyruvic acid 50% peels in the medium term, and there was no clear difference between groups (RR 0.89, 95% CI 0.53 to 1.50; 1 study, 86 participants; Analysis 4.3). We assessed the evidence as low quality due to risk of bias and imprecision (Summary of findings 6).

When salicylic acid was compared with benzoyl peroxide, two trials reported no withdrawals in the short term (Draelos 2016; Shalita 1989), and Chantalat 2006 also reported no withdrawals in the medium term (Analysis 4.3). We assessed the evidence as very low quality due to risk of bias and imprecision (Summary of findings 5).

Babayeva 2011 and NilFroushzadeh 2009 compared salicylic acid with tretinoin; neither treatment group had any withdrawals in the long term (12 weeks after start of treatment) (Analysis 4.3). We assessed the evidence as low quality due to risk of bias and imprecision (Summary of findings 7).

One trial compared salicylic acid 30% peels with Jessner's solution (Dayal 2017); neither treatment group had any withdrawals in the long term (12 weeks after start of treatment) (Analysis 4.3).

Change in lesion counts

Total lesion (number of lesions post-intervention)

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion. the tretinoin group had a lower total lesion count than topical salicylic acid after intervention. The difference was significant in the short term (MD 7.70, 95% CI 1.89 to 13.51; 1 study, 46 participants; Analysis 4.4). However, the estimated RR had a very wide 95% CI which led to an imprecise result. The difference between topical salicylic acid and tretinoin in the medium term was uncertain due to the wide CI (MD 2.80, 95% CI -3.31 to 8.91; 1 study, 46 participants; Analysis 4.4), but showed greater certainty in the long term (12 weeks after start of treatment) (MD 3.60, 95% CI -0.06 to 7.26; 1 study, 46 participants; Analysis 4.4).

Draelos 2016 had no usable outcome data; the authors compared the short-term efficacy of salicylic acid 2% gel, benzoyl peroxide 3% gel and vehicle gel. The authors demonstrated the overall improvement in target lesion parameters of swelling, diameter and erythema from baseline, but there was no significant difference among these groups. In Chantalat 2007 (also with no usable outcome data), the authors stated that 0.5% salicylic acid in mild foaming cleaner formulations could significantly inhibit emerging acne lesions when compared to its vehicle. In Chen 2007 (again with no usable outcome data), the authors showed that salicylic acid in a microgel complex was superior to its vehicle in reducing total lesion counts and global acne severity.

Inflamed (number of lesions post-intervention)

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion. The tretinoin group had a lower inflamed lesion count than topical salicylic acid after intervention. The difference was significant in the short term (MD 4.30, 95% CI 0.50 to 8.10; 1 study, 46 participants; Analysis 4.5). There was no clear difference between topical salicylic acid and tretinoin in the medium term (MD 2.70, 95% CI -0.47 to 5.87; 1 study, 46 participants; Analysis 4.5), and long term (12 weeks after start of treatment) (MD 1.10, 95% CI -1.03 to 3.23; 1 study, 46 participants; Analysis 4.5).

Inflamed (mean counts or %)

Three studies reported data for this outcome; however, the SDs were missing, so we presented the data in a table (see table in Analysis 4.6). Babayeva 2011 reported the percentage reduction of inflamed lesions in the long term (12 weeks after start of treatment) was 77.6% in the salicylic acid 3% lotion group and 81.5% in the tretinoin 0.05 cream group; however, this difference was not significant. In one trial with a split-face design (Bae 2013), the author reported no difference in reduction of inflamed lesions between the salicylic acid 30% peel group and Jessner's solution group. Another split-face trial reported there no difference in mean inflamed lesion counts post-intervention in the long term (12 weeks after start of treatment) between the salicylic acid 20% or 30% peel group and the lipohydroxy acid 5% or 10% peel group (P = 0.111) (Levesque 2011). Chantalat 2005, with no usable outcome data, compared a proprietary 2% salicylic acid microgel with 10% benzoyl peroxide cream, and the authors found that the clinical resolution of target inflammatory lesions was more rapid with the novel 2% salicylic acid microgel than 10% benzoyl peroxide cream.

Papules (number of lesions post-intervention)

Jaffary 2016 reported no clear difference between salicylic acid 30% peels and pyruvic acid 50% peels in the short and medium term (Analysis 4.7). Short term: MD 0.87 (95% CI -2.48 to 4.22; 1 study, 52 participants) and medium term: MD 1.12 (95% CI -1.55 to 3.79; 1 study, 52 participants).

Pustules (number of lesions post-intervention)

Jaffary 2016 reported no clear difference between salicylic acid 30% peels and pyruvic acid 50% peels in the short and medium term (Analysis 4.8). Short term: MD -0.08 (95% CI -0.85 to 0.69; 1 study, 52 participants) and medium term: MD 0.31 (95% CI -0.53 to 1.15; 1 study, 52 participants).

Non-inflamed (number of lesions post-intervention)

Only one study that compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion contributed data for this outcome (Babayeva 2011). There was no statistically significant difference between topical salicylic acid and tretinoin in the short term (MD 3.90, 95% CI -0.03 to 7.83; 1 study, 46 participants; Analysis 4.9) and medium term (MD 0.30, 95% CI -3.55 to 4.15; 1 study, 46 participants; Analysis 4.9). However, there was a clear difference between topical salicylic acid and tretinoin in the long term (12 weeks after start of treatment) (MD 2.50, 95% CI 0.11 to 4.89; 1 study, 46 participants; Analysis 4.9), with less non-inflamed lesion counts in the tretinoin group.

Jaffary 2016 compared salicylic acid 30% peels with pyruvic acid 50% peels; participants receiving pyruvic acid 50% peels had fewer non-inflamed lesions, though there was no clear difference between groups in the short (MD 19.89, 95% CI -7.65 to 47.43; 1 study, 52 participants) and medium terms (MD 17.48, 95% CI -6.45 to 41.41; 1 study, 52 participants) (Analysis 4.9).

Non-inflamed (counts or percentage)

Three studies reported data for this outcome; however, the SDs were missing, so we presented the data in a table (see table in Analysis 4.10). Babayeva 2011 reported no difference in the long term (12 weeks after start of treatment) between the salicylic acid 3% lotion group and tretinoin 0.05% cream group (81.5% versus 87.2%). The split-face design trial of Bae 2013 reported a medium-term significant number reduction of non-inflamed lesion counts in the salicylic acid 30% peel group compared to the Jessner's solution group (average number reduction of non-inflamed counts 8 versus 4.3). In another split-face trial (Levesque 2011), there was no difference in percentage reduction of non-inflamed lesion

counts in the long term (12 weeks after start of treatment) between the salicylic acid 20% or 30% peel group and the lipohydroxy acid 5% or 10% peel group (P = 0.878).

Various types of acne lesions (counts or percentage)

Four studies reported data for this outcome; however, the SDs were missing, so we presented the data in a table (see table in Analysis 4.11). In a parallel trial (NilFroushzadeh 2009), 2% salicylic acid plus 1% clindamycin lotion showed a greater percentage reduction in closed comedones (P = 0.011), papules (P = 0.031), and total lesions (P = 0.039) in the long term (12 weeks after start of treatment) when compared to 0.025% tretinoin plus 1% clindamycin lotion. In a split-face trial that compared salicylic acid 30% peel with glycolic acid 30% peel (Kessler 2008), there was no statistically significant difference between groups in percentage reduction of total lesions at one month post-treatment (P > 0.05) (treatment duration of 10 weeks, measured at the post-treatment follow-up period). In Shalita 1989, with a cross-over design that compared salicylic acid 2% cleaner with 10% benzoyl peroxide wash, there was no statistically significant difference between groups in number of comedones post-intervention.

Physicians' global evaluation of acne improvement

Babayeva 2011 compared salicylic acid 3% gel with tretinoin 0.05% cream and reported long term data (12 weeks after start of treatment) (n = 46) and the authors assessed this outcome using a five-point scale (0: worsening or unchanged, 1: mild improvement, 2: moderate improvement, 3: good improvement and 4: excellent improvement). There was no difference between topical salicylic acid and tretinoin in moderate to excellent improvement (RR 1.00, 95% CI 0.92 to 1.09; 1 study, 46 participants; Analysis 4.12). Dayal 2017 reported data collected in the long term (12 weeks after start of treatment) (n = 40) and the authors assessed this outcome using percentage decrease in Michaelsson acne scores (MAS) (good improvement: > 50% decrease in MAS; fair improvement: 21% to 50% decrease in MAS; poor improvement: 11% to 20% decrease in MAS; no change: 0% to 10% decrease in MAS), and there was no clear difference between 30% salicylic acid peels and Jessner's solution peels (RR 1.11, 95% CI 0.93 to 1.31; 1 study, 40 participants; Analysis 4.12). Jaffary 2016 compared salicylic acid 30% peels with pyruvic acid 50% peels and the authors assessed this outcome using percentage decrease of acne severity index (ASI) (excellent = improved more than 75%, good = improved 50% to 75%, moderate = improved 25% to 50%, poor = improved < 25%), and there was no clear difference between salicylic acid 30% peels and pyruvic acid 50% peels (RR 1.20, 95% CI 0.70 to 2.06; 1 study, 86 participants; Analysis 4.12).

Physicians' global evaluation of acne improvement - split-face trials

In one split-face trial (Kessler 2008), the authors assessed this outcome using a five-point system (good: more than 50% improvement, fair: 21% to 50% improvement, poor: 10% to 20% improvement, no change, or worse) but did not report whether there was a statistical difference between the salicylic acid 30% peel group and glycolic acid 30% peel group at two months post-treatment (treatment duration of 10 weeks, measured at the post-treatment follow-up period). The SDs were missing, so we presented the data in a table (see table in Analysis 4.13).

In another study with a split-face design that included a total of 20 participants suffering from comedonal acne (Levesque 2011), each participant received salicylic acid peels (20% or 30%) on one side of the face and lipohydroxy acid peels (5% or 10%) on the other side of the face. The authors assessed this outcome using a three-point scoring system (1 = worse, 2 = stable, 3 = improved). There was a significant difference between groups in the short term (MD -0.40, 95% CI -0.67 to -0.13; 1 study; Analysis 4.14), which was in favour of lipohydroxy acid (5% or 10%) peel. However, there was no significant difference between groups in the medium term (MD 0.10, 95% CI -0.17 to 0.37; 1 study; Analysis 4.14) and long term (12 weeks after start of treatment) (MD 0.00, 95% CI -0.24 to 0.24; 1 study; Analysis 4.14).

Minor adverse events

Dryness - salicylic acid versus tretinoin

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion. There was no significant difference between topical salicylic acid and tretinoin (RR 1.17, 95% CI 0.70 to 1.94; 1 study, 46 participants; Analysis 4.15).

Peeling - salicylic acid versus tretinoin

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion. There was no significant difference between topical salicylic acid and tretinoin (RR 0.71, 95% CI 0.40 to 1.26; 1 study, 46 participants; Analysis 4.15).

Erythema - salicylic acid versus tretinoin

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion. There was no significant difference between topical salicylic acid and tretinoin (RR 0.88, 95% CI 0.38 to 2.01; 1 study, 46 participants; Analysis 4.15).

Burning - salicylic acid versus tretinoin

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion. There was no significant difference between topical salicylic acid and tretinoin (RR 1.14, 95% CI 0.50 to 2.63; 1 study, 46 participants; Analysis 4.15).

Itching - salicylic acid versus tretinoin

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion. The authors reported that three out of 23 people in the 3% alcohol-based salicylic acid plus clindamycin 1% lotion group versus five out of 23 people in the tretinoin 0.05% cream plus clindamycin 1% lotion group experienced itching (P = 0.70, Fisher's Exact test). There was no significant difference between treatment groups (RR 0.60, 95% CI 0.16 to 2.22; 1 study, 46 participants; Analysis 4.15).

Postpeel burning and stinging - salicylic acid versus Jessner's solution

Dayal 2017 compared salicylic acid 30% peel with Jessner's solution peel, and we found no clear difference between salicylic acid and Jessner's solution (RR 1.44, 95% CI 0.81 to 2.58; 1 study, 40 participants; Analysis 4.15).

Postpeel erythema - salicylic acid versus Jessner's solution

Dayal 2017 compared salicylic acid 30% peel with Jessner's solution peel, and we found no clear difference between salicylic acid and Jessner's solution (RR 1.50, 95% CI 0.50 to 4.52; 1 study, 40 participants; Analysis 4.15).

Postpeel hyperpigmentation - salicylic acid versus Jessner's solution

Dayal 2017 compared salicylic acid 30% peel with Jessner's solution peel. The authors reported that one out of 20 people in the salicylic acid 30% peel group versus three out of 20 people in the Jessner's solution peel group experienced postpeel hyperpigmentation (P = 0.61, Fisher's Exact test). There was no clear difference between salicylic acid and Jessner's solution (RR 0.33, 95% CI 0.04 to 2.94; 1 study, 40 participants; Analysis 4.15).

Total events - salicylic acid versus benzoyl peroxide

In one study with 90 people (Draelos 2016), the author compared the short-term efficacy of salicylic acid 2% gel, benzoyl peroxide 3% gel and vehicle gel. They reported that no adverse events were observed during this five-day study (30 participants in each treatment group) (Analysis 4.15).

Chantalat 2006 reported this outcome in the medium term. The authors reported that zero out of 20 people in the 2% salicylic acid microgel group versus two out of 21 people in the benzoyl peroxide 10% cream group experienced minor adverse events (P = 0.49, Fisher's Exact test). There was no clear difference between the 2% salicylic acid microgel group and benzoyl peroxide 10% cream group due to the wide CI (RR 0.21, 95% CI 0.01 to 4.11; 1 study, 41 participants; Analysis 4.15). We assessed the evidence as very low quality due to risk of bias and imprecision (Summary of findings 5).

Total events - salicylic acid versus tretinoin

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion and NilFroushzadeh 2009 compared 2% salicylic acid plus 1% clindamycin lotion with 0.025% tretinoin plus 1% clindamycin lotion. There was no clear difference between treatment groups due to the wide CI (RR 1.37, 95% CI 0.66 to 2.87; 2 studies, 74 participants; Analysis 4.15). We assessed the evidence as very low quality due to risk of bias and imprecision (Summary of findings 7).

Total events - salicylic acid versus lipohydroxy acid

Levesque 2011 was a split-face design that compared salicylic acid peel (20% or 30%) with lipohydroxy acid peel (5% or 10%), the authors did not report total number of participants who experienced at least one minor adverse event but evaluated minor adverse events using a 10 cm visual analogue scale. There was no difference for itching (P = 0.412), tightness (P = 0.108), and erythema (P = 0.103). Salicylic acid peels induced more desquamation (P = 0.007) and dryness (P < 0.05) but less stinging (P = 0.017) and burning (P = 0.021) when compared to lipohydroxy acid peels.

Quality of life - AQOL (score, post-intervention)

Babayeva 2011 compared 3% alcohol-based salicylic acid plus clindamycin 1% lotion with tretinoin 0.05% cream plus clindamycin 1% lotion. The study reported no statistically difference between groups for this outcome in the long term (12 weeks after start of treatment); however, the data were skewed, so we therefore could only present the data in a table (see table in Analysis 4.16).

We assessed the evidence as very low quality due to risk of bias and imprecision (Summary of findings 7). Chantalat 2006 did not provide means ± SDs, and the study compared salicylic acid 2% microgel with 10% benzoyl peroxide cream and found a significant improvement in quality of life with salicylic acid 2% microgel (Analysis 4.16). We assessed the evidence as very low quality due to risk of bias and imprecision (Summary of findings 5).

Comparison 5: topical salicylic acid versus placebo

Participants' global self-assessment of acne improvement

Participants' global self-assessment of acne improvement (score, high = well)

Only one study contributed data for this outcome assessed by a seven-point interval rating scale (Eady 1996). There was no significant difference between topical salicylic acid 2% lotion and placebo lotion in the short term (MD 0.30, 95% CI -0.12 to 0.72; 1 study, 106 participants; Analysis 5.1) or long term (12 weeks after start of treatment) (MD 0.40, 95% CI -0.05 to 0.85; 1 study, 99 participants; Analysis 5.1). However, in the medium term, participants in the salicylic acid group recorded a higher score for acne improvement than those in the placebo group, the difference was clearly significant (MD 0.50, 95% CI 0.23 to 0.77; 1 study, 102 participants; Analysis 5.1).

Withdrawal for any reason

One trial compared salicylic acid 2% gel with vehicle gel (Draelos 2016), and neither treatment group had any withdrawals in the short term (Analysis 5.2). Another two trials reported data in the long term (12 weeks after start of treatment) (Eady 1996; Shalita 1981), and there was no clear difference between salicylic acid and placebo due to the wide CI (RR 2.07, 95% CI 0.76 to 5.68; 2 studies, 163 participants; Analysis 5.2), but one study reported no events.

Change in lesion counts

Mean counts or percentage reduction

Three studies reported data for this outcome; however, the authors did not provide mean and/or SDs. Eady 1996 only reported the P values, and results showed that salicylic acid 2% lotion treatment had better efficacy in whitehead (long term, P < 0.002), papules (long term, P = 0.022), and total lesion (medium term, P < 0.043; and long term, P < 0.001) number reduction when compared to placebo. In Techapichetvanich 2011, the percentage reduction of non-inflamed lesions in the long term (10 weeks after start of treatment) was 84.0% for the salicylic acid (20% or 30%) peel group and 36.0% for the vehicle peel group (P = 0.001), and the percentage reduction of total lesions in the long term was 84.0% for the salicylic acid (20% or 30%) peel group and 26.0% for the vehicle peel group (P = 0.001), suggesting the benefits of salicylic acid treatment. The Shalita 1981 study also suggested the advantage of salicylic acid 0.5% solution over placebo in percentage reduction in total lesions in the long term, although the author did not state whether the difference was of statistical significant (Analysis 5.3).

Inflamed (counts or percentage)

Two studies reported data for this outcome; however, the authors did not provide mean and/or SDs, so we presented the data in a table (Analysis 5.4). Eady 1996 showed a statistically significant difference between topical salicylic acid 2% lotion and placebo lotion in the long term (12 weeks after start of treatment) (P <

0.022) in favour of salicylic acid, but no difference in the short and medium term for reduction in number of inflamed lesions. Shalita 1981 did not report the P value, but the data suggested the advantage of salicylic acid 0.5% solution over placebo for percentage reduction of inflamed lesions in the long term (12 weeks after start of treatment).

Non-inflamed (counts or percentage)

Two studies reported data for this outcome; however, the authors did not provide mean and/or SDs (Analysis 5.5). Eady 1996 showed that topical salicylic acid 2% lotion demonstrated a significant reduction in number of non-inflamed lesions in the medium (P = 0.047) and long term (12 weeks after start of treatment) (P < 0.001) compared to placebo lotion, but no difference in the short term (no exact P value reported). Shalita 1981 showed no significant difference between groups for percentage reduction of closed comedones in the long term (12 weeks after start of treatment) (no exact P value reported); however, the percentage reduction of open comedones was significant in the salicylic acid 0.5% solution group compared to placebo (no exact P value reported).

Physicians' global evaluation of acne improvement

Shalita 1981 compared salicylic acid 0.5% solution with placebo and reported long term data (12 weeks after start of treatment) (n = 49). The authors assessed this outcome using a four-point Likert-type scale (excellent, good, fair, poor). There were more participants rated as good or excellent improvement in the salicylic acid 0.5% solution group than participants in the placebo group (RR 2.16, 95% CI 1.17 to 4.0; 1 study, 49 participants; Analysis 5.6).

Minor adverse events

Total adverse events

Draelos 2016 included 90 participants and compared the short-term efficacy of salicylic acid 2% gel, benzoyl peroxide 3% gel and vehicle gel. They reported that no adverse events were observed during this five-day study (30 participants in each treatment group) (Analysis 5.7).

Shalita 1981 included 49 participants and compared 0.5% salicylic acid solution with placebo solution in the long term. However, there were no adverse events reported in either treatment group (Analysis 5.7); the authors only stated that side effects were minimal.

Quality of life

No study collected data for this outcome.

Comparison 6: topical salicylic acid versus no treatment (including studies with a co-intervention in both arms)

Participants' global self-assessment of acne improvement

For this outcome, there were no data reported in the short and medium term. Akarsu 2012 reported data in the long term (12 weeks after start of treatment) and the authors assessed this outcome using a five-point scale (0 = worsening or unchanged, 1 = mild improvement, 2 = moderate improvement, 3 = good improvement, 4 = excellent improvement). This trial compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel in moderate to excellent improvement. There was no significant difference between treatment groups (RR 0.96, 95% CI 0.86 to 1.07; 1 study, 50 participants; Analysis 6.1). We assessed the evidence as low quality due to risk of bias and imprecision (Table 6).

Withdrawal for any reason

Three relevant trials reported data for this outcome in the long term (treatment duration over 12 weeks) (Akarsu 2012; Kar 2013; NilFroushzadeh 2009). Two trials had no withdrawals during treatment (Kar 2013; NilFroushzadeh 2009). There was no clear difference between treatment groups due to the wide CI (RR 3.00, 95% CI 0.13 to 70.30; 3 studies, 138 participants, two of which reported no events, Analysis 6.2). We assessed the evidence as very low quality due to risk of bias and imprecision (Table 6).

Change in lesion counts

Total (percentage reduction from baseline)

Three studies reported data for this outcome (Akarsu 2012; Kar 2013; NilFroushzadeh 2009; however, the authors did not provide mean and/or SDs. Two studies reported higher percentage reduction of lesion counts in the salicylic acid group than that in the no treatment group (Akarsu 2012; NilFroushzadeh 2009), and authors stated the difference was statistically significant in the long term (12 weeks after start of treatment). Kar 2013 also reported higher percentage reduction of total lesion counts in the salicylic acid group in the long term (16 weeks after start of treatment), although the authors did not state whether the difference was statistically significant. (Analysis 6.3).

Inflamed (percentage reduction from baseline)

Two studies reported data for this outcome; however, the authors did not provide mean and/or SDs, so we presented the data in a table (see table in Analysis 6.4). Study authors compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel. The study reported higher percentage reduction of lesion counts in the salicylic acid group than in the no treatment group (98.2% versus 73.8%); the authors stated the difference was statistically significant in the long term (12 weeks after start of treatment) (Akarsu 2012). Another study also reported higher percentage reduction of papules and pustules in the salicylic acid group in the long term (12 weeks after start of treatment) (NilFroushzadeh 2009).

Non-inflamed (percentage reduction from baseline)

Akarsu 2012 compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel; however, the authors did not provide SDs. In Akarsu 2012 the percentage reduction of non-inflamed lesions in the long term (12 weeks after start of treatment) was significantly greater in participants receiving salicylic acid treatment (94.7%) than no treatment (81.1%), although the P value was unclear. Authors NilFroushzadeh 2009 compared 2% salicylic acid + 1% clindamycin lotion with 1% clindamycin lotion and results showed higher percentage reduction of comedones in the salicylic acid group (Analysis 6.5).

Physicians' global evaluation of acne improvement

Akarsu 2012 reported data collected in the long term (12 weeks after start of treatment). This trial compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel and assessed this outcome using a 5-point scale (0 = worsening or unchanged,

1 = mild improvement, 2 = moderate improvement, 3 = good improvement, 4 = excellent improvement). There was no significant difference between treatment groups in the moderate to excellent improvement categories (RR 0.96, 95% CI 0.86 to 1.07; 1 study, 50 participants; Analysis 6.6).

Minor adverse events

Dryness

Akarsu 2012 compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel. Results showed a higher risk of dryness in the salicylic acid/clindamycin/benzoyl peroxide group than control (16/25 versus 6/25). The difference was significant (RR 2.67, 95% CI 1.25 to 5.68; 1 study, 50 participants; Analysis 6.7).

Peeling

Akarsu 2012 compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel. There was no clear difference between treatment groups (RR 1.50, 95% CI 0.74 to 3.03; 1 study, 50 participants; Analysis 6.7).

Erythema

Akarsu 2012 compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel. The estimated RR had a very wide 95% CI resulting in imprecision (RR 4.00, 95% CI 0.94 to 17.00; 1 study, 50 participants; Analysis 6.7),

Burning

Akarsu 2012 compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel. There was no clear difference between treatment groups (RR 1.67, 95% CI 0.71 to 3.89; 1 study, 50 participants; Analysis 6.7).

Itching

Akarsu 2012 compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel. The authors reported that five out of 25 people in the salicylic acid/clindamycin/benzoyl peroxide group versus three out of 25 people in the clindamycin/benzoyl peroxide group experienced itching (P = 0.70, Fisher's Exact test). There was no significant difference between treatment groups (RR 1.67, 95% CI 0.45 to 6.24; 1 study, 50 participants; Analysis 6.7).

Total events

Akarsu 2012 and NilFroushzadeh 2009 compared salicylic acid with no treatment in the long term (12 weeks after start of treatment). There was no clear difference between treatment groups due to a wide CI (RR 3.43, 95% CI 0.14 to 82.00; 2 studies, 78 participants; Analysis 6.7). We assessed the evidence as very low quality due to risk of bias and imprecision (Table 6).

Quality of life - AQOL (score, post-intervention)

Akarsu 2012 compared 3% salicylic acid to 1% clindamycin lotion and 5% benzoyl peroxide gel with 1% clindamycin lotion and 5% benzoyl peroxide gel in the long term (12 weeks after start of treatment); however, the data were not available for meta-analysis (Analysis 6.8). At the end of the study, the median and 95% CI of the AQOL score was 0.5 (0.6 to 2.1) in the salicylic acid/clindamycin/benzoyl peroxide treatment group and 1 (1.5 to 4.3) in the clindamycin/benzoyl peroxide group, the study authors may have reported the wrong data as the median was not included in the 95% CI. The authors reported no "statistically significant" difference between treatment groups. We assessed the evidence as very low quality (Table 6).

Comparison 7: topical nicotinamide versus other topical treatments

Participants' global self-assessment of acne improvement

No study collected data for this outcome.

Withdrawal for any reason

We found three trials that compared nicotinamide with clindamycin (Khodaeiani 2013; Shahmoradi 2013; Shalita 1995), and there was no significant difference between the treatment groups in the medium term, two of which reported zero events, (RR 1.13, 95% CI 0.49 to 2.60; 3 studies, 216 participants; Analysis 7.1). We rated this as low-quality evidence due to risk of bias and imprecision (Summary of findings 8).

Only Weltert 2004 compared topical nicotinamide 4% gel with erythromycin 4% gel, and there was no significant difference between the treatment groups (RR 1.40, 95% CI 0.46 to 4.22; 1 study, 158 participants; Analysis 7.1). We rated this as low-quality evidence due to risk of bias and imprecision (Summary of findings 9).

Change in lesion counts

Inflamed (number of lesions post-intervention)

There were no long term data for this outcome. Khodaeiani 2013 reported short and medium term data (n = 80). There was no clear difference between topical nicotinamide 4% gel and clindamycin 1% gel in the short term (MD 0.97, 95% CI -0.92 to 2.86; 1 study, 80 participants; Analysis 7.2), or the medium term (MD 0.92, 95% CI -1.25 to 3.09; 1 study, 80 participants; Analysis 7.2).

Inflamed counts (counts or percentage)

Two studies reported data for this outcome; however, the data were not available for meta-analysis; they are presented in a table (see table in Analysis 7.3). Shalita 1995 compared nicotinamide 4% gel with clindamycin 1% gel, there was no difference in percentage reduction of inflamed lesions in the short (P = 0.06, no means ± SDs provided) and medium term (P = 0.17, skewed data). Weltert 2004 compared nicotinamide 4% gel with erythromycin 4% gel, but the study authors did not report the P value and the data were skewed.

Comedones (number of lesions post-intervention)

Weltert 2004 reported data collected in the medium term (n = 158). There was no clear difference between topical nicotinamide 4% gel and erythromycin 4% gel (MD -1.00, 95% CI -2.10 to 0.10; 1 study, 158 participants; Analysis 7.4).

Physicians' global evaluation of acne improvement

Shalita 1995 reported data collected in the short and medium term. The authors assessed this outcome using a 5-point scoring system (+3 = much better, +2 = moderately better, +1 = slightly better, 0 = no change, -1 = worse). There was no significant difference

between topical nicotinamide 4% gel and clindamycin 1% gel in the moderately better or much better categories in the short term (RR 0.93, 95% CI 0.53 to 1.66; 1 study, 76 participants) or medium term (RR 0.95, 95% CI 0.60 to 1.50; 1 study, 76 participants; Analysis 7.5).

Shalita 1995 also reported the P value for this outcome (Analysis 7.6). There was no statistically significant difference between topical nicotinamide 4% gel and clindamycin 1% gel in the percentage of participants in the moderately better or much better categories in the short term (P = 0.36) or medium term (P = 0.19) for physicians' global evaluation of acne improvement.

Minor adverse events

Itching - nicotinamide versus clindamycin

Khodaeiani 2013 reported that four out of 40 people in the nicotinamide 4% gel group versus three out of 40 people in the clindamycin 1% gel group experienced itching (P = 1.00, Fisher's Exact test). There was no significant difference between topical nicotinamide 4% gel and clindamycin 1% gel (RR 1.33, 95% CI 0.32 to 5.58; 1 study, 80 participants; Analysis 7.7).

Burning - nicotinamide versus clindamycin

Khodaeiani 2013 reported that seven out of 40 people in the nicotinamide 4% gel group versus two out of 40 people in the clindamycin 1% gel group experienced burning (P = 0.15, Fisher's Exact test). There was no clear difference between topical nicotinamide 4% gel and clindamycin 1% gel as the CI was wide (RR 3.50, 95% CI 0.77 to 15.83; 1 study, 80 participants; Analysis 7.7).

Crusting - nicotinamide versus clindamycin

Khodaeiani 2013 reported that two out of 40 people in the nicotinamide 4% gel group versus three out of 40 people in the clindamycin 1% gel group experienced crusting (P = 1.00, Fisher's Exact test). There was no significant difference between nicotinamide 4% gel and clindamycin 1% gel (RR 0.67, 95% CI 0.12 to 3.78; 1 study, 80 participants; Analysis 7.7).

Greasy skin - nicotinamide versus clindamycin

Khodaeiani 2013 reported that zero out of 40 people in the nicotinamide 4% gel group versus three out of 40 people in the clindamycin 1% gel group experienced greasy skin (P = 0.24, Fisher's Exact test). There was no clear difference between nicotinamide 4% gel and clindamycin 1% gel (RR 0.14, 95% CI 0.01 to 2.68; 1 study, 80 participants; Analysis 7.7).

Dermatitis - nicotinamide versus clindamycin

Khodaeiani 2013 reported that one out of 40 people in the nicotinamide 4% gel group versus zero out of 40 people in the clindamycin 1% gel group experienced dermatitis (P = 1.00, Fisher's Exact test). There was no clear difference between nicotinamide 4% gel and clindamycin 1% gel (RR 3.00, 95% CI 0.13 to 71.51; 1 study, 80 participants; Analysis 7.7), as the estimated RR had a very wide 95% CI resulting in imprecision.

Total events - nicotinamide versus clindamycin

Three trials compared nicotinamide with clindamycin (Khodaeiani 2013; Shahmoradi 2013; Shalita 1995). There was no significant difference between topical nicotinamide and clindamycin (RR 1.20, 95% CI 0.73 to 1.99; 3 studies, 216 participants; Analysis 7.7). We rated this as low-quality evidence due to risk of bias and imprecision (Summary of findings 8).

Pertinent clinical signs - nicotinamide versus erythromycin (short term)

Weltert 2004 found "no significant difference" between topical nicotinamide 4% gel and erythromycin 4% gel (RR 1.33, 95% CI 0.60 to 2.99; 1 study, 158 participants; Analysis 7.7).

Pertinent clinical signs - nicotinamide versus erythromycin (medium term)

Weltert 2004 found "no significant difference" between topical nicotinamide 4% gel and erythromycin 4% gel (RR 1.10, 95% CI 0.50 to 2.44; 1 study, 158 participants; Analysis 7.7).

Funtional or physical signs - nicotinamide versus erythromycin (short term)

Weltert 2004 found "no significant difference" between topical nicotinamide 4% gel and erythromycin 4% gel (RR 1.05, 95% CI 0.61 to 1.82; 1 study, 158 participants; Analysis 7.7).

Funtional or physical signs - nicotinamide versus erythromycin (medium term)

Weltert 2004 found "no significant difference" between topical nicotinamide 4% gel and erythromycin 4% gel (RR 0.75, 95% CI 0.38 to 1.48; 1 study, 158 participants; Analysis 7.7).

Quality of life

No study collected data for this outcome.

Comparison 8: topical sulphur versus other topical treatments

Participants' global self-assessment of acne improvement (numerical point system defined by investigator, high = well)

Vasarinsh 1969 assessed this outcome using a numerical point scoring system (greatly improved +2, somewhat improved +1, no change 0, worse -1); however, the SDs were missing (Analysis 8.1). The study authors compared topical sulphur 2% lotion to topical benzoyl peroxide 5% lotion, the average score (high = well) was 0.75 in the sulphur group and 0.66 in the benzoyl peroxide group. The authors did not state whether the difference was statistically significant. We assessed the evidence as very low-quality due to risk of bias and imprecision (Table 7).

Withdrawal for any reason

Vasarinsh 1969 reported that six out of 18 people in the topical sulphur 2% lotion group versus two out of 16 people in the benzoyl peroxide 5% lotion group withdrew from the trial (P = 0.23, Fisher's Exact test). There was no clear difference between the topical sulphur 2% lotion group and the topical benzoyl peroxide 5% lotion group in the medium term (RR 2.67, 95% CI 0.62 to 11.39; 1 study, 34 participants; Analysis 8.2). We assessed the evidence as very low-quality due to risk of bias and imprecision (Table 7).

Change in lesion counts (scores, high = well)

Vasarinsh 1969 compared topical sulphur 2% lotion with topical benzoyl peroxide 5% lotion; however, the SDs were missing, so we presented the data in a table (see table in Analysis 8.3). The average scores (high = well) of comedone-pustule and papule-cyst in participants receiving sulphur treatment were lower than in the

benzoyl peroxide group. The authors did not state whether the difference was statistically significant.

Physicians' global evaluation of acne improvement

Vasarinsh 1969 compared topical sulphur 2% lotion with topical benzoyl peroxide 5% lotion. Trial authors assessed this outcome by using a scoring system defined by investigators (unchanged or worse: -4 to 0, minimal improvement: 0.1 to 3.99, moderate improvement: 4 to 5.99, good improvement: 6 to 8). There was no significant difference between treatment groups in the moderate to good improvement categories in the medium term (RR 1.24, 95% CI 0.49 to 3.15; 1 study, 34 participants; Analysis 8.4).

Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high = well)

Vasarinsh 1969 compared topical sulphur 2% lotion with topical benzoyl peroxide 5% lotion; however, the SDs were missing, so we presented the data in a table (see table in Analysis 8.5). Trial authors assessed this outcome using a numerical point scoring system (complete improvement +3, moderate improvement +2, slight improvement +1, questionable 0, no change 0, worse -1). The average score (high = well) was 0.50 in the sulphur treatment group and 1.07 in the benzoyl peroxide group. However, the authors did not state whether the difference was statistically significant.

Minor adverse events

Erythema and drying - sulphur versus benzoyl peroxide

Vasarinsh 1969 reported that zero out of 18 people in the topical sulphur 2% lotion group versus five out of 16 people in the benzoyl peroxide 5% lotion group experienced erythema and drying (P = 0.02, Fisher's Exact test). We did not present the RR and 95% CI because the presence of zero events in one arm led to discordant results (Analysis 8.6).

Quality of life

No study collected data for this outcome.

Comparison 9: topical sulphur versus placebo

Participants' global self-assessment of acne improvement (numerical point system defined by investigator, high = well)

Vasarinsh 1969 compared sulphur 2% lotion with placebo lotion using a numerical point scoring system (greatly improved +2, somewhat improved +1, no change 0, worse -1); however, the SDs were missing (Analysis 9.1). The average score (high = well) was 0.75 in participants receiving sulphur treatment and 0.53 in the placebo group. The authors did not state whether the difference was statistically significant. We assessed the evidence as very low-quality due to risk of bias and imprecision (Table 8).

Withdrawal for any reason

Vasarinsh 1969 reported that six out of 18 people in the topical sulphur 2% lotion group versus four out of 19 people in the placebo group withdrew from the trial. There was no clear difference between topical sulphur 2% lotion and placebo in the medium term (RR 1.58, 95% CI 0.53 to 4.70; 1 study, 37 participants; Analysis 9.2). We assessed the evidence as very low-quality due to risk of bias and imprecision (Table 8).

Change in lesion counts (scores, high=well)

Only one study reported data for this outcome; however, the SDs were missing (Analysis 9.3). Vasarinsh 1969 compared sulphur 2% lotion with placebo lotion, the score (high = well) of comedone-pustule was - 0.70 in participants receiving sulphur treatment and 0.00 in the placebo group; the authors did not state whether this difference was statistically significant. In addition, the score (high = well) of papule-cyst was 0.30 in participants receiving sulphur treatment and 0.53 in the placebo group; the authors did not state whether this difference was statistically significant.

Physicians' global evaluation of acne improvement

Vasarinsh 1969 compared topical sulphur 2% lotion with placebo using a scoring system defined by investigators (unchanged or worse: -4 to 0, minimal improvement: 0.1 to 3.99, moderate improvement: 4 to 5.99, good improvement: 6 to 8). There was no significant difference between treatment groups in the moderate to good improvement categories in the medium term (RR 1.48, 95% CI 0.57 to 3.82; 1 study, 37 participants; Analysis 9.4).

Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high = well)

Vasarinsh 1969 compared sulphur 2% lotion with placebo lotion; however, the SDs were missing (Analysis 9.5). Trial authors assessed this outcome using a numerical point scoring system (complete improvement +3, moderate improvement +2, slight improvement +1, questionable 0, no change 0, worse -1). The average score (high = well) was 0.50 in participants receiving sulphur treatment and 0.94 in the placebo group. The authors did not state whether this difference was statistically significant.

Minor adverse events

Erythema and drying

Vasarinsh 1969 compared sulphur 2% lotion with placebo lotion. The authors reported that zero out of 18 people in the topical sulphur 2% lotion group versus two out of 19 people experienced erythema and drying (P = 0.49, Fisher's Exact test). There was no clear difference between treatment groups (RR 0.21, 95% CI 0.01 to 4.11; 1 study, 37 participants; Analysis 9.6).

Quality of life

No study collected data for this outcome.

Comparison 10: topical sulphur versus no treatment (including studies with a co-intervention in both arms)

Participants' global self-assessment of acne improvement (numerical point system defined by investigator, high = well)

Vasarinsh 1969 compared sulphur 2% + benzoyl peroxide 5% lotion with benzoyl peroxide 5% lotion using a numerical point scoring system (greatly improved +2, somewhat improved +1, no change 0, worse -1); however, the SDs were missing (Analysis 10.1). The average score (high = well) was 1.15 in participants receiving sulphur + benzoyl peroxide treatment and 0.66 in the benzoyl peroxide group. The authors did not state whether the difference was statistically significant.

Withdrawal for any reason

Vasarinsh 1969 reported that six out of 19 people in the topical sulphur 2% + benzoyl peroxide 5% lotion group versus two out of 16 people in the benzoyl peroxide 5% lotion group withdrew from the trial (P = 0.24, Fisher's Exact test). There was no clear difference between topical sulphur 2% + benzoyl peroxide 5% lotion and benzoyl peroxide 5% lotion in the medium term (RR 2.53, 95% CI 0.59 to 10.83; 1 study, 35 participants; Analysis 10.2).

Change in lesion counts (scores, high = well)

Only one study reported data for this outcome; however, the SDs were missing (Analysis 10.3). Vasarinsh 1969 compared sulphur 2% + benzoyl peroxide 5% lotion with benzoyl peroxide 5% lotion, the score (high = well) of comedone-pustule was 0.81 in participants receiving sulphur 2% + benzoyl peroxide 5% lotion and 0.55 in the benzoyl peroxide 5% lotion group, the score (high = well) of papule-cyst was 0.91 in participants receiving sulphur 2% + benzoyl peroxide 5% lotion treatment and 0.69 in the benzoyl peroxide 5% lotion group. The authors did not state whether this difference was statistically significant.

Physicians' global evaluation of acne improvement

Vasarinsh 1969 compared topical sulphur 2% + benzoyl peroxide 5% lotion with benzoyl peroxide 5% lotion using a scoring system defined by investigators (unchanged or worse: -4 to 0, minimal improvement: 0.1 to 3.99, moderate improvement: 4 to 5.99, good improvement: 6 to 8). There was no significant difference between treatment groups in the moderate to good improvement categories in the medium term (RR 1.52, 95% CI 0.64 to 3.61; 1 study, 35 participants; Analysis 10.4).

Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high = well)

Vasarinsh 1969 compared topical sulphur 2% + benzoyl peroxide 5% lotion with benzoyl peroxide 5% lotion; however, the SDs were missing (Analysis 10.5). Trial authors assessed this outcome by using a numerical point scoring system (complete improvement +3, moderate improvement +2, slight improvement +1, questionable 0, no change 0, worse -1). The average score (high = well) was 1.53 in participants receiving sulphur 2% + benzoyl peroxide 5% treatment and 1.07 in the benzoyl peroxide 5% group. The authors did not state whether this difference was statistically significant.

Minor adverse events

Erythema and drying

Vasarinsh 1969 reported that four out of 19 people in the topical sulphur 2% + benzoyl peroxide 5% lotion group versus five out of 16 people in the benzoyl peroxide 5% lotion group experienced erythema and drying (P = 0.70, Fisher's Exact test). There was no clear difference between treatment groups (RR 0.22, 95% CI 0.22 to 2.09; 1 study, 35 participants; Analysis 10.6).

Quality of life

No study collected data for this outcome.

Comparison 11: topical zinc versus other topical treatments

Participants' global self-assessment of acne improvement

No study collected data for this outcome.

Withdrawal for any reason

Sharquie 2008 reported that three out of 23 people in the 5% zinc sulphate solution group versus four out of 24 people in the 2% tea lotion group withdrew from the trial (P = 1.00, Fisher's Exact test). There was no significant difference between the 5% zinc sulphate solution group and the 2% tea lotion group in the medium term (RR 0.78, 95% CI 0.20 to 3.12; 1 study, 47 participants; Analysis 11.1). We rated the quality of evidence as very low due to risk of bias and imprecision (Table 9).

Change in lesion counts

Papules (number of lesions post-intervention)

Sharquie 2008 reported data collected in the medium term. There was no clear difference between 5% zinc sulphate solution and 2% tea lotion (MD -2.44, 95% CI -7.80 to 2.92; 1 study, 40 participants; Analysis 11.2).

Pustules (number of lesions post-intervention)

Sharquie 2008 reported data collected in the medium term. There was no significant difference between 5% zinc sulphate solution and 2% tea lotion (MD -0.70, 95% CI -6.97 to 5.57; 1 study, 40 participants; Analysis 11.3).

Physicians' global evaluation of acne improvement

For this outcome, there were no data reported in the short and long term; Sharquie 2008 reported data collected in the medium term and assessed this outcome using a three-point system defined by the trial authors (reduction of more than 50% inflamed lesion count: good; 10% to 50% reduction: moderate; less than 10% reduction: no response). There was no significant difference between 5% zinc sulphate solution and 2% tea lotion in the good or moderate response categories (RR 0.80, 95% CI 0.51 to 1.24; 1 study, 47 participants; Analysis 11.4).

Minor adverse events - total events

Zinc versus tea

Sharquie 2008 reported no significant difference between 5% zinc sulphate solution and 2% tea lotion (RR 1.46, 95% CI 0.54 to 3.95; 1 study, 47 participants; Analysis 11.5). We rated the quality of evidence as very low due to risk of bias and imprecision (Table 9).

Quality of life

No study collected data for this outcome.

Comparison 12: topical zinc versus no treatment (including studies with a co-intervention in both arms)

Participants' global self-assessment of acne improvement (visual analogue scale)

Only one study that compared zinc/clindamycin 1% gel with clindamycin 1% gel reported data for this outcome (Cunliffe 2005); however, the data were not available for meta-analysis due to no reporting of means ± SDs (Analysis 12.1). The study authors only reported that there was no significant difference between treatment groups for this outcome in the long term (16 weeks after start of treatment) but they did not report the visual analogue scale or P values. We assessed the evidence as low quality due to risk of bias and imprecision (Table 10).

Withdrawal for any reason

Cunliffe 2005 compared zinc/clindamycin 1% gel with clindamycin 1% gel. There was no significant difference between treatment groups in the long term (16 weeks after start of treatment) (RR 1.21, 95% CI 0.43 to 3.45; 1 study, 163 participants; Analysis 12.2). We assessed the evidence as low quality due to risk of bias and imprecision (Table 10).

Change in lesion counts

Total (lesion counts reduction)

Only one study that compared zinc/clindamycin 1% gel with clindamycin 1% gel reported data for this outcome (Cunliffe 2005); however, the data were not available for meta-analysis due to no reporting of means and SDs; instead we presented the data in a table (see table in Analysis 12.3). There was no significant difference between treatment groups in the medium and long term (16 weeks after start of treatment) (P = 0.707), but the authors did not report the data in each group.

Inflamed (lesion counts reduction)

Two studies reported data for this outcome; however, the data were not available for meta-analysis due to no reporting of means and SDs Analysis 12.4. Bojar 1994 compared 1.2% zinc/4% erythromycin with 4% erythromycin in the long term (12 weeks after start of treatment) and reported an improvement in both groups after intervention; however, they did not state whether there was a difference between groups. In another trial that compared zinc/clindamycin 1% gel with clindamycin 1% gel (Cunliffe 2005), the results demonstrated no difference in the long term (16 weeks after start of treatment) between groups (P = 0.626); the authors also did not report the values of reduction in inflamed lesion counts.

Non-inflamed (lesion count reduction)

Two studies reported data for this outcome; however, the data were not available for meta-analysis due to no reporting of means and SDs; we presented the data in a table instead (see table in Analysis 12.5). Bojar 1994 compared 1.2% zinc/4% erythromycin with 4% erythromycin in the long term (12 weeks after start of treatment), the study authors did not report the values of reduction in non-inflamed lesion counts or the P value. In another trial that compared zinc/clindamycin 1% gel with clindamycin 1% gel (Cunliffe 2005), the results demonstrated no difference in the medium and long term (16 weeks after start of treatment) between groups (P = 0.769); the authors also did not report the values of reduction in non-inflamed lesion counts.

Physicians' global evaluation of acne improvement (visual analogue scale)

Cunliffe 2005 compared zinc/clindamycin 1% gel with clindamycin 1% gel; however, the data were not available for meta-analysis due to no reporting of means or SDs; we presented the data in a table (see table in Analysis 12.6). There was no significant difference between groups in the long term (16 weeks after start of treatment) but the study authors did not report the visual analogue scale or P values.

Minor adverse events

We did not find any studies that reported total number of participants experiencing at least one minor adverse event. Cunliffe 2005 compared zinc/clindamycin 1% gel with clindamycin 1% gel, but the study authors did not report the P value and showed results as count data (Analysis 12.7). The total number of adverse events was 91 in 80 participants receiving zinc/clindamycin 1% gel and 117 in 83 participants receiving clindamycin 1% gel. We assessed the evidence as low quality due to risk of bias and imprecision (Table 10).

Quality of life

No study collected data for this outcome.

Comparison 13: topical alpha-hydroxy acid versus other topical treatments

Participants' global self-assessment of acne improvement

ElRefaei 2015 and Garg 2009 compared 35% glycolic acid peels with 20% salicylic - 10% mandelic acid peels. ElRefaei 2015 used a visual analogue scale (poor < 30% improvement; fair 30% to 60% improvement; and good > 60% improvement); Garg 2009 also used a visual analogue scale (good > 60%; fair 31% to 60%; poor < 30%; no change, worse). Both treatments demonstrated significant fair to good improvement, and there was no clear difference between groups in the long term (12 weeks after start of treatment) (RR 1.06, 95% CI 0.88 to 1.26; 1 study, 40 participants; Analysis 13.1). We assessed the evidence as low quality due to imprecision (Summary of findings 10). In Garg 2009, the authors collected data in the post-treatment follow-up period and reported that 20 out of 22 people in the 35% glycolic acid peel group versus 20 out of 22 people in the 20% salicylic - 10% mandelic acid peel group demonstrated fair to good improvement at three months post-treatment (treatment duration of 12 weeks, measured in the post-treatment follow-up period).

Withdrawal for any reason

Hunt 1992 compared topical alpha-hydroxy acid (gluconolactone 14% in solution) and benzoyl peroxide 5% lotion. There was no significant difference between treatment groups in the long term (12 weeks after start of treatment) (RR 0.83, 95% CI 0.27 to 2.55; 1 study, 100 participants; Analysis 13.2). We assessed the evidence as low quality due to risk of bias and imprecision (Table 11).

ElRefaei 2015 and Garg 2009 compared 35% glycolic acid peels with 20% salicylic - 10% mandelic acid peels; neither treatment group had any withdrawals in the long term (12 weeks after start of treatment) (Analysis 13.2). We assessed the evidence as low quality due to risk of bias and imprecision (Summary of findings 10).

Change in lesion counts

Non-inflamed (number of lesions post-intervention)

ElRefaei 2015 compared 35% glycolic acid peels with 20% salicylic - 10% mandelic acid peels in the short and medium term; there was a clear significant difference between groups at both treatment terms in favour of 20% salicylic - 10% mandelic acid peels. Short term: MD 10.00 (95% CI 4.41 to 15.59; 1 study, 40 participants) and medium term: MD 11.90 (95% CI 7.17 to 16.63; 1 study, 40 participants) (Analysis 13.3). The authors also reported data collected at two months post-treatment (treatment duration of 12 weeks, measured at the post-treatment follow-up period); the 20% salicylic - 10% mandelic acid peels was favoured (1.8 ± 1.99 in 20% salicylic - 10% mandelic acid peels group versus 14.3 ± 10.03 in the 35% glycolic acid peels group).

Papules (number of lesions post-intervention)

ElRefaei 2015 compared 35% glycolic acid peels with 20% salicylic - 10% mandelic acid peels in the long term; there was a clear significant difference between groups in favour of 20% salicylic - 10% mandelic acid peels (MD 1.25, 95% CI 0.36 to 2.14; 1 study, 40 participants) (Analysis 13.4). The authors also reported data collected at two months post-treatment (treatment duration of 12 weeks, measured at the post-treatment follow-up period); the 20% salicylic - 10% mandelic acid peels group was favoured (2.45 ± 1.28 in 20% salicylic - 10% mandelic acid peels group versus 3.4 ± 1.57 in the 35% glycolic acid peels group).

Pustules (number of lesions post-intervention)

ElRefaei 2015 compared 35% glycolic acid peels with 20% salicylic - 10% mandelic acid peels in the long term; there was a clear significant difference between groups in favour of 20% salicylic - 10% mandelic acid peels (MD 1.20, 95% CI 0.44 to 1.96; 1 study, 40 participants) (Analysis 13.5). The authors also reported data collected at two months post-treatment (treatment duration of 12 weeks, measured at the post-treatment follow-up period); the 20% salicylic - 10% mandelic acid peels group was favoured (2.2 ± 1.47 in 20% salicylic - 10% mandelic acid peels group versus 3.75 ± 1.997 in the 35% glycolic acid peels group).

Total (counts or percentage)

Hunt 1992, a parallel study, reported data for this outcome; however, the data were not available for meta-analysis due to no reporting of means and SDs (Analysis 13.6). The study authors only stated there was no significant difference in total lesion count reduction between alpha-hydroxy acid (gluconolactone 14% in solution) and benzoyl peroxide 5% lotion in the short, medium, and long term (12 weeks after start of treatment), but they did not report data in each group.

Kessler 2008, a split-face design, also reported data for this outcome. The study authors compared 30% glycolic acid peels with 30% salicylic acid peels; there was no statistically significant difference between groups in percentage reduction of total lesions at one month post-treatment (P > 0.05) (treatment duration of 10 weeks, measured at the post-treatment follow-up period) (Analysis 13.6).

Inflamed (counts)

Two studies reported data for this outcome. Hunt 1992 did not provide means and SDs, and in Ilknur 2010, data were skewed, so we could only present the data in a table (see table in Analysis 13.7). In the parallel Hunt 1992 trail that compared alpha-hydroxy acid (gluconolactone 14% in solution) with benzoyl peroxide 5% lotion, there was significant difference in the medium (P < 0.05) and long term (12 weeks after start of treatment) (P < 0.05), indicating that benzoyl peroxide can lead to a greater reduction in lesion counts, but no difference was observed in the short term. In the split-face Ilknur 2010 trial that compared alpha-hydroxy acid (glycolic acid) 20% to 70% peels with amino fruit acid 20% to 60% peels, there was no significant difference between groups in number of inflamed lesions in the short, medium, and long term (6 months after start of treatment) (P > 0.05). The mean number of inflamed lesions post-intervention in the alpha-hydroxy acid (glycolic acid) peel group was close to that in the amino fruit acid peels group for the same time period, but the data were skewed (e.g. mean ± SD: 10.08 ± 5.72 in the alpha-hydroxy acid group; 8.67 ± 4.48 in the amino fruit acid peels group).

Non-inflamed (counts)

Two studies reported data for this outcome; however, Hunt 1992 did not provide means and SDs and in Ilknur 2010, data were skewed (Analysis 13.8). In the parallel Hunt 1992 trial that compared alpha-hydroxy acid (gluconolactone 14% in solution) with benzoyl peroxide 5% lotion, there was no significant difference between groups in lesion count reduction in the short, medium, and long term (12 weeks after start of treatment) (no exact P value reported). In the split-face Ilknur 2010 trial that compared alpha-hydroxy acid (glycolic acid) 20% to 70% peels with amino fruit acid 20% to 60% peels, there was no significant difference between groups in number of non-inflamed lesions in the short, medium, and long term (6 months after start of treatment) (P > 0.05). The mean number of non-inflamed lesions post-intervention in the alpha-hydroxy acid (glycolic acid) peel group was close to that in the amino fruit acid peels group for the same time period, but the data were skewed (e.g. mean ± SD: 36.29 ± 37.37 in the alpha-hydroxy acid group; 36.00 ± 40.42 in the amino fruit acid peels group).

Physicians' global evaluation of acne improvement

ElRefaei 2015 and Garg 2009 compared 35% glycolic acid peels with 20% salicylic - 10% mandelic acid peels using the same five-point visual analogue scale (worse; no change; poor: < 30% improvement; fair: 31% to 60% improvement; good: > 60% improvement). ElRefaei 2015 reported that two out of 20 people in the 35% glycolic acid peels group versus five out of 20 people in the 20% salicylic - 10% mandelic acid peels group demonstrated fair to good improvement in the short term (P = 0.41, Fisher's Exact test). The 35% glycolic acid peels group showed fewer numbers of participants with fair to good improvement for all treatment terms; the difference was statistically significant in the medium (RR 0.29, 95% CI 0.11 to 0.72; 1 study, 40 participants) but not in the short term (RR 0.40, 95% CI 0.09 to 1.83; 1 study, 40 participants) or long term (RR 0.95, 95% CI 0.79 to 1.13; 1 study, 40 participants) (Analysis 13.9). In ElRefaei 2015, the authors also collected data at the post-treatment follow-up period and reported that 16 out of 20 people in the 35% glycolic acid peels group versus 19 out of 20 people in the 20% salicylic - 10% mandelic acid peels group demonstrated fair to good improvement at two months post-treatment (treatment duration of 12 weeks, measured at the post-treatment follow-up period). Garg 2009 reported that 20 out of 22 people in the 35% glycolic acid peels group versus 21 out of 22 people in the 20% salicylic - 10% mandelic acid peels group demonstrated fair to good improvement at three months post-treatment (treatment duration of 12 weeks, measured at the post-treatment follow-up period).

Physicians' global evaluation of acne improvement (percentage) - split-face design

Only one study reported data for this outcome at two months post-treatment (treatment duration of 10 weeks, measured at the post-treatment follow-up period); however, the SDs were missing, so we presented the data in a table (see table in Analysis 13.10). The trial authors assessed this outcome using a five-point system (good: more than 50% improvement; fair: 21% to 50% improvement; poor: 10% to 20% improvement; no change; or worse). In this split-face trial (Kessler 2008), the authors did not report whether there was a difference between the alpha-hydroxy acid (glycolic acid 30% peel) group and the salicylic acid 30% peel group.

Minor adverse events

Total events - gluconolactone (alpha-hydroxy acid) versus benzoyl peroxide

Hunt 1992 compared alpha-hydroxy acid (gluconolactone 14% in solution) with benzoyl peroxide 5% lotion and showed that alpha-hydroxy acid had a lower risk of minor adverse events than benzoyl peroxide (12/50 versus 25/50). There was a significant difference (RR 0.48, 95% CI 0.27 to 0.85; 1 study, 100 participants; Analysis 13.11). We assessed the evidence as low quality due to risk of bias and imprecision (Table 11).

Total events - glycolic acid versus salicylic - mandelic acid

Garg 2009 compared 35% glycolic acid peels with 20% salicylic - 10% mandelic acid peels; there was no difference between groups (RR 1.80, 95% CI 0.72 to 4.52; 1 study, 44 participants; Analysis 13.11). We assessed the evidence as very low quality due to risk of bias and imprecision (Summary of findings 10).

In one split-face study with no usable outcome data (Kim 1999), the authors compared 70% glycolic acid peels with Jessner's solution peels. The authors demonstrated the equal treatment effect and lesser degree of exfoliation in the glycolic acid arm.

Burning or sensation

ElRefaei 2015 reported that two out of 20 people in the 35% glycolic acid peels group versus four out of 20 people in the 20% salicylic - 10% mandelic acid peels group experienced burning or sensation (P = 0.66, Fisher's Exact test). There was no difference between groups (RR 0.50, 95% CI 0.10 to 2.43; 1 study, 40 participants; Analysis 13.11).

Desquamation

ElRefaei 2015 and Garg 2009 compared 35% glycolic acid peels with 20% salicylic - 10% mandelic acid peels; there was no difference between groups (RR 1.03, 95% CI 0.11 to 9.60; 2 studies, 84 participants; Analysis 13.11).

Dryness

ElRefaei 2015 reported that two out of 20 people in the 35% glycolic acid peels group versus three out of 20 people in the 20% salicylic - 10% mandelic acid peels group experienced dryness (P = 1.00, Fisher's Exact test); there was no difference between groups (RR 0.67, 95% CI 0.12 to 3.57; 1 study, 40 participants; Analysis 13.11).

Hunt 1992 compared alpha-hydroxy acid (gluconolactone 14% in solution) with benzoyl peroxide 5% lotion but with no numerical data. The authors only reported that the number of participants who experienced dryness in the benzoyl peroxide group was significantly greater than that in the alpha-hydroxy acid (gluconolactone 14% in solution) group (P < 0.02).

Acne flare

ElRefaei 2015 and Garg 2009 reported that three out of 42 people in the 35% glycolic acid peels group versus three out of 42 people in the 20% salicylic - 10% mandelic acid peels group experienced acne flare (P = 1.00, Fisher's Exact test); there was no difference between groups (RR 1.00, 95% CI 0.22 to 4.63; 2 studies, 84 participants; Analysis 13.11).

Quality of life

No study collected data for this outcome.

Comparison 14: topical alpha-hydroxy acid versus placebo

Participants' global self-assessment of acne improvement

No study collected data for this outcome.

Withdrawal for any reason

For this outcome, we only found one relevant trial that compared alpha-hydroxy acid (gluconolactone 14% in solution) with placebo. Hunt 1992 reported data in the long term (12 weeks after start of treatment). The authors reported that five out of 50 people in the gluconolactone 14% solution group versus four out of 50 people in the placebo group withdrew from the trial (P = 1.00, Fisher's Exact test). There was no significant difference between topical alpha-hydroxy acid and placebo (RR 1.25, 95% CI 0.36 to 4.38; 1 study, 100 participants; Analysis 14.1). We assessed the evidence as low quality due to risk of bias and imprecision (Table 12).

Change in lesion counts

No study collected data for this outcome.

Physicians' global evaluation of acne improvement

No study collected data for this outcome.

Minor adverse events - total events

For this outcome, there were no data reported in the short term and medium term. We only found one relevant trial that compared alpha-hydroxy acid (gluconolactone 14% in solution) with its placebo. Hunt 1992 reported data collected in the long term (12 weeks after start of treatment). There was no "significant" difference between topical alpha-hydroxy acid and placebo (RR 2.40, 95% CI 0.91 to 6.31; 1 study, 100 participants; Analysis 14.2). We assessed the evidence as low quality due to risk of bias and imprecision (Table 12).

Quality of life

No study collected data for this outcome.

Assessment of reporting bias

We did not conduct funnel plots for primary outcomes, as the number of included studies in each forest plot was fewer than 10.

Sensitivity analysis

We were unable to perform sensitivity analyses due to the small numbers of studies.

DISCUSSION

Summary of main results

We evaluated six test interventions in this review (topical azelaic acid, topical salicylic acid, topical nicotinamide, topical sulphur, topical zinc, and topical fruit acid (alpha-hydroxy acid). The most-assessed treatments were salicylic acid and azelaic acid (assessed by 73.5% of the included studies). The least assessed treatment was sulphur (1 study). With regard to the primary outcomes, 38.8% of the studies measured 'participants global self-assessment of acne improvement', and 85.7% measured 'withdrawal for any reason'.

Minor side effects were well-reported, but the total number was not always reported in each study; some studies only reported the number of individual side effects. Quality of life was least reported, with only 12.2% of the studies measuring this outcome.

Although certain outcomes and interventions were well-assessed, evidence quality ranged from very low to moderate, with most of the evidence deemed very low or low quality, meaning we cannot draw definitive conclusions about the treatments in question.

The following results were measured at the end of treatment, which was long-term (except for 2 studies where it was medium-term) for the outcome 'participants' global self-assessment of acne improvement' and mixed length (medium-term mainly) for minor adverse events. We assessed minor adverse events as total number of participants who experienced at least one minor adverse event.

Azelaic acid

For participants' global self-assessment of acne improvement, there is probably little or no difference between treatments when azelaic acid is compared to tretinoin (moderate-quality evidence; Summary of findings 4), and there may be little or no difference between treatments when azelaic acid is compared to clindamycin (low-quality evidence; Summary of findings 3). We are uncertain if there is a difference between azelaic acid and adapalene (very low-quality evidence; Summary of findings 1). Azelaic acid is probably less effective than benzoyl peroxide (moderate-quality evidence; Summary of findings 2).

When assessing our other primary outcome, withdrawal (for any reason), low-quality evidence showed there may be no difference between azelaic acid versus benzoyl peroxide, clindamycin, or tretinoin (Summary of findings 2; Summary of findings 3; Summary of findings 4). When comparing azelaic acid to adapalene, we are uncertain of the effect on number of withdrawals due to very low-quality evidence (Summary of findings 1).

Most adverse events reported were mild in nature and were limited to the application sites. Based on results of single small studies, we are not certain of total minor adverse events when comparing azelaic acid with adapalene or benzoyl peroxide (very low-quality evidence; Summary of findings 1; Summary of findings 2). There may be no difference between groups in total minor adverse events when comparing azelaic acid to clindamycin (low-quality evidence; Summary of findings 3). In the studies comparing azelaic acid to tretinoin, the total number of minor adverse events were not reported, but the study authors did report individual application site reactions, such as scaling (Summary of findings 4).

Quality of life was not well-assessed by the studies evaluating azelaic acid, and we are uncertain of the effect of azelaic acid compared to adapalene due to very low-quality evidence (Summary of findings 1).

Salicylic acid

For participants' global self-assessment of acne improvement, results may be similar with salicylic acid compared to pyruvic acid tretinoin (low-quality evidence; Summary of findings 7). We are not certain of the effect of salicylic acid compared to pyruvic acid (very low-quality evidence; Summary of findings 6). This outcome was not assessed in the study comparing salicylic acid to benzoyl peroxide (Summary of findings 5).

When comparing salicylic acid to benzoyl peroxide, we are uncertain of the effect on number of withdrawals due to very low-quality evidence (Summary of findings 5). There may be no difference between groups in the number of withdrawals when comparing salicylic acid and pyruvic acid (low-quality evidence; Summary of findings 6). There were no withdrawals when salicylic acid was compared to tretinoin (low-quality evidence; Summary of findings 7).

All side effects reported were of mild to moderate intensity and transient. The incidence of total minor adverse events when comparing salicylic acid with benzoyl peroxide or tretinoin was uncertain due to very low-quality evidence (Summary of findings 5; Summary of findings 7). Total minor adverse events were not reported in the trial comparing salicylic acid to pyruvic acid (Summary of findings 6), but individual application site reactions were reported, such as scaling and redness.

Quality of life was not well-assessed by the studies evaluating salicylic acid, and we are uncertain of the effect of salicylic acid compared to benzoyl peroxide or tretinoin due to very low-quality evidence (Summary of findings 5; Summary of findings 7).

Nicotinamide

Out of the four studies which assessed nicotinamide against clindamycin or erythromycin, none reported data for participants' global self-assessment of acne improvement. There may be no differences in rate of withdrawals when comparing nicotinamide to clindamycin or erythromycin, based on low-quality evidence (Summary of findings 8; Summary of findings 9). Most adverse events reported were local application site reactions. Based on the results of three studies, there may be no difference in the incidence of total minor adverse events when comparing nicotinamide with clindamycin (low-quality evidence; Summary of findings 8). The total number of minor adverse events was not reported for nicotinamide versus erythromycin. No studies collected data for quality of life.

Alpha-hydroxy (fruit) acid

Glycolic acid peels may make no difference to participants' global self-assessment of acne improvement when compared with salicylic-mandelic acid peels, and there were no withdrawals in this comparison (both low-quality evidence; Summary of findings 10). We are uncertain if there is a difference between the two groups in total minor adverse events due to very low-quality evidence (Summary of findings 10). Adverse events associated with alpha-hydroxy acid treatment were always mild in nature. This comparison did not assess quality of life.

Overall completeness and applicability of evidence

The eligible evidence included in this review is not sufficient to address all of our prespecified objectives. The limited number of randomised controlled trials (RCTs) concerning the use of the review's topical treatments of interest make it hard to evaluate their efficacy, and combining study results for meta-analysis was challenging due to the variability in conducting and reporting of trials.

Of the 49 included studies, 47 studies had a total of 3880 participants, and two studies did not report the sample size (Chantalat 2007; Chen 2007). All eligible trials investigated

participants with different forms or severity of acne vulgaris. Of the total included participants in this review, 75.7% (2939 participants from 33 trials) had mild to moderate acne, 10.3% (399 participants from 5 trials) probably also had mild to moderate acne, 4.8% (188 participants from 3 trials) had unknown acne severity, and only a part of the remaining 9.1% (354 participants from 6 trials) had a severe form of acne.

The age of participants from 41 studies ranged from 10 years old to 45 years old; the other eight studies did not report these data. Based on what the trials reported, most participants were aged 12 to 30 years, and there were more female than male participants, which is reflective of the age group and sex in which acne is most prevalent.

Treatment was overwhelmingly of medium- to long-term duration. Medium-term treatment was classed as treatment applied for four to eight weeks, and long-term treatment was deemed as any intervention applied for more than eight weeks. The length of treatment duration in some studies (e.g. a 5-day treatment duration in Draelos 2016) could have been too short to detect a significant difference between treatment groups.

We identified RCTs for all of the six test interventions. Most studies assessed salicylic acid and azelaic acid; four studies investigated nicotinamide; three studies tested the efficacy and safety of zinc; and six studies investigated the efficacy and safety of alpha-hydroxy acid. Sulphur was the least-assessed intervention, with only one study testing its efficacy and safety. However, the least-assessed treatments (sulphur, zinc, and gluconolactone) are no longer used in common current clinical practice. Thirty-one studies compared the above interventions with active treatments, such as clindamycin, erythromycin, tretinoin, and benzoyl peroxide. Fourteen studies compared the interventions with placebo control or no treatment. Four studies compared the interventions with both active treatments and placebo. This means that for some of the core comparisons we found no evidence. For example, we did not identify any studies comparing azelaic acid with placebo that assessed the outcome of participants' global self-assessment of acne improvement; neither did we identify any studies comparing nicotinamide with placebo or no treatment that assessed any of the outcomes.

Less than half of the trials assessed the primary outcome 'participants' global self-assessment of acne improvement' (19/49). In terms of safety, 42/50 trials measured 'withdrawal for any reason', and although the total number of minor adverse events was not always reported, individual side effects were. The least-reported outcome was quality of life, which was measured by six studies.

Quality of the evidence

Limitations in study design and implementation

Our assessments of risk of bias revealed considerable variations in study design and implementation among the included studies. Only eight studies clearly addressed how the randomisation was performed (Cunliffe 1989; Dayal 2017; ElRefaei 2015; Ilknur 2010; Kar 2013; Kim 1999; Schaller 2016; Thielitz 2015), and only one study author stated how to conceal the allocation (ElRefaei 2015). Thirty-nine studies had a double- or single-blind design, but more than half of the studies did not report sufficient information about their methods to confirm blinding of participants/personnel and assessors. The remaining 10 studies did not mention blinding information. We rated 11 of the included trials to be at high risk of attrition bias. It should be noted that a significant proportion of the outcome data were of skewed distribution, and we presented them in additional tables in the Data and analyses section. In addition, the study authors frequently did not report SDs and the continuous data could not be analysed in meta-analysis in such instances. For most of the comparisons, it was only possible to get pooled estimates with limited number of trials. Therefore, we downgraded all of the outcomes assessed via GRADE by at least one level for study limitations due to high/unclear risk of bias (we downgraded a small minority of outcomes by two levels for very serious study limitations).

Indirectness of the evidence

The included studies in our review assessed representative populations, though no studies included participants with neonatal and infantile acne. In our review, we included both active- and placebo-controlled trials, rendering it applicable to assess the efficacy of most of the interventions. However, we failed to include some trials that compared nicotinamide to placebo/no treatment. The evidence provided by the included head-to-head trials was both relevant and direct. We did not downgrade the 'indirectness' domain in all GRADE assessments.

Inconsistency of the results

We failed to find high levels of heterogeneity in all cases, mainly because the evidence for many comparisons/outcomes was based on a single study. Therefore, we did not downgrade for 'inconsistency' in any of our GRADE assessments.

Imprecision of the results

The very limited number of included studies examining six test interventions did not allow us to substantively evaluate the degree of precision of the effect estimates. In most instances, there was only a single study in each comparison, and wide confidence intervals (CIs), small sample sizes (optimal sample size is not met) or total number of events (< 300) were responsible for the imprecision. Therefore, we downgraded the majority of outcomes assessed via GRADE by one level for serious imprecision.

Publication bias

We were unable to assess publication bias because none of the comparisons had more than 10 studies. Therefore, it is meaningless to create funnel plots. We did not downgrade the 'Publication bias' domain in any GRADE assessments.

Potential biases in the review process

As shown in Electronic searches, we conducted a systematic electronic search of databases. In addition, we also checked the bibliographies of included studies for further references to relevant trials. However, the fact that 15 potentially eligible studies have not yet been incorporated may be a source of potential bias. We were unable to contact some study authors for further data due to the lack of a correspondence email address. We contacted study authors in order to obtain additional data, but only a few replied and not all provided us with the requested data.

Although there were some departures from the protocol (see Differences between protocol and review), these changes are unlikely to be a potential source of bias. We did not make

any a posteriori decisions about the analysis or investigation of heterogeneity after seeing the data.

Our inclusion of studies investigating a synergistic salicylic acid microgel complex could be questioned (Chantalat 2005; Chantalat 2006; Chantalat 2007; Chen 2007). These four studies were published as abstracts with no contact emails; thus, based on this insufficient information, we did not know the components and the drug delivery system of the intervention.

Agreements and disagreements with other studies or reviews

There have been no reviews published which evaluated these topical treatments in a systematic way. Our review substantially updates and improves the previous work in this area. The findings of this review generally agree with the findings in previous summary reviews (Gamble 2012; Haider 2004; Purdy 2011).

AUTHORS' CONCLUSIONS

Implications for practice

Presently, clinicians often choose topical retinoids and antimicrobials as the first choice of treatment for mild and moderate acne (Akhavan 2003; Titus 2012; Well 2013). The data in this review show there is no high-quality evidence to determine the effects of the topical treatments azelaic acid, salicylic acid, nicotinamide, sulphur, zinc, and alpha-hydroxy acid over the commonly used topical drugs. In some cases, the comparative studies suggest no difference between these topical treatments and commonly used retinoids or antimicrobials, but we cannot draw definitive conclusions due to very low- to low-quality evidence. The limited number of trials and other issues (e.g. inadequate reporting) make it hard to obtain high-quality evidence.

We cannot draw conclusions about the effect of the following comparisons on the outcome 'participants' global self-assessment of acne improvement', as the quality of evidence is very low or the outcome was not reported.

- Azelaic acid compared to adapalene
- Salicylic acid compared to pyruvic acid
- Salicylic acid compared to benzoyl peroxide
- Nicotinamide compared to clindamycin
- Nicotinamide compared to erythromycin

In terms of treatment response (participants' global self-assessment of acne improvement; PGA), azelaic acid is probably less effective than benzoyl peroxide (moderate-quality evidence), and there may be little or no difference in PGA when comparing azelaic acid to clindamycin (low-quality evidence). There is probably little or no difference when comparing azelaic acid to tretinoin (moderate-quality evidence). There may be little or no difference in PGA between salicylic acid and tretinoin (low-quality evidence). There may be no difference in PGA when comparing glycolic acid peel to salicylic-mandelic acid peel (low-quality evidence).

We cannot draw conclusions about the effect of the following comparisons on the outcome 'withdrawal for any reason', as the quality of evidence is very low or the outcome was not reported.

- Azelaic acid compared to adapalene
- Salicylic acid compared to benzoyl peroxide

Based on low-quality evidence, there may be no differences in rates of withdrawal for any reason when comparing the following.

- Azelaic acid with benzoyl peroxide, clindamycin, or tretinoin
- Salicylic acid with pyruvic acid
- Nicotinamide with clindamycin or erythromycin

There were no withdrawals in the comparisons of salicylic acid versus tretinoin and glycolic acid versus salicylic-mandelic acid.

We cannot draw conclusions about the effect of the following comparisons on minor adverse events, assessed as total number of participants who experienced at least one minor adverse event, as the quality of evidence is very low or the outcome was not reported.

- Azelaic acid compared to adapalene
- Azelaic acid compared to benzoyl peroxide
- Azelaic acid compared to tretinoin
- Salicylic acid compared to benzoyl peroxide
- Salicylic acid with pyruvic acid
- Salicylic acid was compared to tretinoin
- Nicotinamide compared to erythromycin
- Glycolic acid (alpha-hydroxy acid) compared to salicylic-mandelic acid (peel)

There may be no difference in minor adverse events when comparing azelaic acid to clindamycin.

The adverse events caused by these treatments included mainly application site reactions such as erythema, scaling, dry skin, burning, peeling, and itching, and the risk of specific adverse events (e.g. erythema) was mostly similar between treatment groups.

We do not have sufficient evidence to determine the efficacy and safety of sulphur, zinc, and gluconolactone, which are no longer used in clinical practice.

In the absence of high-quality evidence for these treatments, clinical decisions may continue to be guided by clinical experiences and patients' preferences.

Implications for research

There is a need for further head-to-head comparisons of the topical treatments azelaic acid, salicylic acid, nicotinamide, and glycolic acid with commonly used active drugs (topical retinoids and antimicrobials). Moreover, trials comparing these topical treatments with vehicle/placebo or no treatment are also required. This will confirm their efficacy for treating mild to moderate acne.

Randomised trials with a parallel or cross-over design are necessary. With respect to cross-over trials, study authors should report the outcome data as previously suggested (Elbourne 2002). Study authors should clearly report the severity of illness. Participants irrespective of age, severity, or gender need to be included. Study authors should clearly report the co-interventions in each treatment arm. A long-term treatment duration (over 8 weeks) for future trials is suggested. We do not recommend trials authors measure the drug efficacy in the post-treatment follow-up

period as these topical medications most probably have no long-lasting effect after withdrawal of therapy.

The variability in conducting and reporting of trials significantly hampered combining study results for meta-analysis. We recommend standardisation of outcome reporting in future trials. The trial authors should use a standardised scale (e.g. measured by a four-point scale: excellent, good, fair, and poor) to measure participants' global self-assessment of acne improvement, and the authors should provide a clear description of how the outcome was measured. Study authors should also report the number of withdrawals from the trial and the reasons for withdrawals. In addition, development of a standardised scale for physicians' global evaluation of acne improvement is necessary, and the report of number of participants would be better. We recommend study authors report the total number of participants who experienced at least one adverse event, but not report adverse events as count data. It would also be useful if study authors presented the total number of participants who experienced individual side effects, e.g. redness. Assessment of quality of life using a validated instrument (e.g. Acne-Specific Quality of Life Questionnaire; Acne-QoL) is highly desirable. Adherence to recommendations from the Cochrane Skin - Core Outcome Set Initiative would improve and standardise outcome measurement (CS-COUSIN 2019).

Unfortunately, the study authors often presented inadequate data or information, for example, randomisation was not clearly described, allocation concealment was not reported, it was unclear who was blinded, results were presented in figures with no raw data, standard deviations (SDs) were not mentioned and could not be obtained in any way, and exact P values were not reported. Furthermore, 11/49 studies had high attrition bias; therefore, efforts should be made to ensure participants remain in the study. We have to acknowledge that many included studies in this review predate the CONSORT recommendations (Begg 1996; Moher 2001), but future studies should ensure they adhere to the CONSORT recommendations on trials to guarantee the full availability of all data. Many of our analyses were limited to single study data. These studies had small sample sizes; hence, we downgraded the majority of our evidence for imprecision. Future studies should ensure a sample size calculation is used. We could not assess publication bias because of the limited number of studies in each comparison.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akarsu 2012

Study characteristics	
Methods	**Aim of study:** to evaluate the efficacy and safety of the addition of 3% SA in 70% alcohol treatment to 1% CDP lotion and 5% BPO gel and compare it with the addition of only 70% alcohol to 1% CDP lotion and 5% BPO gel in the treatment of mild to moderate facial AV **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details of sequence generation methods

Akarsu 2012 *(Continued)*

	Blinding: only single-blind (assessors as following) was used **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** one withdrawal because of change of city
Participants	**Population description:** mild to moderate facial AV **Setting:** not described **Randomised number:** 50 **Age (years):** 18 to 28 in treatment group; 18 to 29 in control group **Sex (M/F):** 7/17 in treatment group; 6/19 in control group **Severity of illness:** mild to moderate Total lesion counts: 80.50 (72.83 to 94.84) in treatment group; and 77.00 (76.06 to 95.14) in control group; Inflammatory lesion counts: 25.50 (21.01 to 29.24) in treatment group; and 28.00 (21.64 to 29.40) in control group; Non-inflammatory lesion counts: 60.00 (49.39 to 68.02) in treatment group; and 59.00 (50.43 to 67.33) in control group
Interventions	**Name of treatment group:** SA and CDP + BPO group **n** = **25** **Description:** the addition of 3% SA in 70% alcohol treatment to 1% CDP lotion and 5% BPO gel **Treatment period:** 12 weeks **Timing:** twice-daily (morning and evening) **Name of treatment group:** CDP + BPO group **n** = **25** **Description:** combination of CDP and BPO **Treatment period:** 12 weeks **Timing:** twice-daily (morning and evening)
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor) (week 12; 5-point scale: 0 = worsening or unchanged, 1 = mild improvement, 2 = moderate improvement, 3 = good improvement, 4 = excellent improvement) • Withdrawal for any reason (1 withdrawal, week 2) **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately) • Percentage reduction in lesion counts, from baseline to week 12 • Physicians' global evaluation of acne improvement (week 12; 5-point scale: 0 = worsening or unchanged, 1 = mild improvement, 2 = moderate improvement, 3 = good improvement, 4 = excellent improvement) • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event) (symptoms assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe); number of participants who experienced minor adverse event, week 12) • Quality of life (AQOL questionnaire) **Other outcomes that were not analysed in this review**

Akarsu 2012 *(Continued)*

- Time to 50% reduction in total lesion counts
- Skin barrier functions

Notes	**Funding:** not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive topical treatments for AV with one of the two treatment protocols...". Comment: no details of random methods were described
Allocation concealment (selection bias)	Unclear risk	No details of concealment were described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This 12-week study was designed as a single-blind, randomised, 1:1 parallel group comparative investigation...". Comment: only single-blind (assessors as following) was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Evaluations were performed by a blinded investigator to avoid subjective bias at baseline and after 2, 4, 8 and 12 weeks of treatment." Comment: insufficient information about method to ensure blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient voluntarily withdrew from the study after the first visit because of change of city." Comment: 4% of dropouts happened in the intervention group. Although no ITT analysis was used and imbalance rates of dropouts presented in the study, this withdrawal was unlikely to influence the effect.
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Aksakal 1997

Study characteristics

Methods	**Aim of study:** to compare the efficacy and skin tolerance of metronidazole 1% cream and AZA 20% cream in the treatment of moderate to severe acne **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details of sequence generation methods **Blinding:** unclear **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** none

Aksakal 1997 *(Continued)*

Participants	**Population description:** moderate to severe AV **Setting:** not described **Randomised number:** 40 **Age (years):** average 19.2 (range 14 to 27) **Sex (M/F):** 2/18 in treatment group; 14/6 in control group **Severity of illness:** moderate to severe acne
Interventions	**Name of treatment group:** AZA **n** = **20** **Description:** AZA 20% **Treatment period:** 12 weeks **Timing:** twice-daily **Name of treatment group:** metronidazole **n** = **20** **Description:** metronidazole 1% **Treatment period:** 12 weeks **Timing:** twice-daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (inflamed and non-inflamed). Authors reported P value, week 12 • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Only mentioned but no usable data. • Quality of life Authors did not report this outcome
Notes	**Funding**: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Forty patients with only moderate to severe acne participated in this randomised, comparative study". Comment: no details of random methods was described
Allocation concealment (selection bias)	Unclear risk	No details of concealment were described
Blinding of participants and personnel (performance bias)	Unclear risk	Not mentioned

Aksakal 1997 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Forty patients...participated in...", "the study was completed with 40 patients". Comment: no missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient baseline data reported
Other bias	Low risk	No other potential bias identified

Babayeva 2011

Study characteristics	
Methods	**Aim of study:** to evaluate the efficacy and safety of combination therapy with all-TRA 0.05% cream plus CDP 1% lotion (all-TRA + CDP group) in comparison with the combination of 3% alcohol-based SA plus CDP 1% lotion (SA + CDP group) in the treatment of mild to moderate facial AV **Design:** parallel **Unit of allocation:** patients **Allocation:** randomised; no details of random methods were provided **Blinding:** single-blinding; open label for assessors **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** none
Participants	**Population description:** mild to moderate facial AV **Setting:** not described **Randomised number:** 46 **Age:** 18 to 31 in treatment group; 18 to 26 in control group **Sex (M/F):** 5/18 in treatment group; 5/18 in control group **Severity of illness:** mild to moderate Total lesion counts: 66.52 ± 8.04 in treatment group; and 66.52 ± 8.04 in control group; Inflammatory lesion counts: 21.95 ± 7.18 in treatment group; and 20.65 ± 7.73 in control group; Non-inflammatory lesion counts: 44.78 ± 6.12 in treatment group; and 45.43 ± 6.38 in control group
Interventions	**Name of treatment group:** SA + CDP group **n** = 23 **Description:** combination of 3% alcohol-based SA plus CDP 1% lotion **Treatment period:** 12 weeks **Timing:** twice-daily

Babayeva 2011 *(Continued)*

	Name of treatment group: all-TRA + CDP group **n** = 23 **Description:** all-TRA 0.05% cream plus CDP 1% lotion **Treatment period:** 12 week **Timing:** twice-daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor; week 12; 5-point scale, 0: worsening or unchanged, 1: mild improvement, 2: moderate improvement, 3: good improvement and 4: excellent improvement) • Withdrawal for any reason (no withdrawals) **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately) • Percentage reduction in lesion counts, baseline and week 2, 4, 8, and 12 • Physicians' global evaluation of acne improvement (week 12; 5-point scale, 0: worsening or unchanged, 1: mild improvement, 2: moderate improvement, 3: good improvement and 4: excellent improvement) • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event; symptoms evaluated using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe; reported number of participants who experienced minor adverse event) • Quality of life. AQOL questionnaire, week 12 **Other outcomes that were not analysed in this review** • Time to 50% reduction in total lesion counts • Skin surface barrier
Notes	**Funding**: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This 12-week study was designed as a single-blind, randomised, 1:1 parallel group and comparative investigation..."; Quote: "Patients were randomised to receive topical treatments for AV with one of two topical agent combinations..." Comment: no details of random methods were provided
Allocation concealment (selection bias)	Unclear risk	No detail of concealment approach was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "This 12-week study was designed as a single-blind, randomised, 1:1 parallel group and comparative investigation...", Comment: unclear which side was blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Evaluations were performed by an investigator aware of the treatment allocation at baseline and after 2, 4, 8 and 12 weeks of treatment." Comment: outcome assessment was not blinded
Incomplete outcome data (attrition bias)	Low risk	Quote: "The 12-week treatment periods were completed by all subjects."

Babayeva 2011 *(Continued)*

All outcomes		Comment: no missing outcome data
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Bae 2013

Study characteristics	
Methods	**Aim of study:** to compare the effectiveness and side effects of SA peels and Jessner's solution peels in the treatment of acne using a split-face model **Design:** within subjects, split-face design **Unit of allocation:** split-face **Allocation:** randomised; no details of random sequence generation methods **Blinding:** evaluator blinded only **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** none
Participants	**Population description:** mild to moderate acne according to the Cunliffe grading system **Setting:** university setting in Korea **Randomised number:** 13 **Age:** mean: 22.6; range: 20 to 28 **Sex (M/F):** 13/0 **Severity of illness:** mild to moderate Non-inflammatory lesion counts: 18.6 ± 20.9 in one side of face versus 22.7 ± 26.2 in other side; Inflammatory lesion counts: 14.2 ± 6.0 versus 12.5 ± 7.8
Interventions	**Name of treatment group:** 30% SA **n** = 13 faces **Description:** 30% SA **Treatment period:** 4 weeks **Timing:** three times every 2 weeks **Name of treatment group:** Jessner's solution **n** = 13 faces **Description:** 14 g of resorcinol, 14 g of SA, 14 mL of lactic acid, and ethanol quantum satis 100 mL **Treatment period:** 4 weeks **Timing:** three times every 2 weeks
Outcomes	**Primary outcomes (see notes)**

Bae 2013 *(Continued)*

- Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor; week 6; 4-point scale: 3 = good improvement, 2 = moderate improvement, 1 = mild improvement, 0 = no improvement or worsening)
- Withdrawal for any reason (no withdrawals)

Secondary outcomes

- Change in lesion counts (total or inflamed and non-inflamed separately). Mean lesion counts at baseline, week 2, 4, and 6
- Physicians' global evaluation of acne improvement. Authors did not report this outcome
- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Only mentioned but data not usable
- Quality of life. Authors did not report this outcome.

Notes	**Funding**: not described This was a 'split-face'. According to the protocol of this review, only summary statistics were used to conduct analysis using the generic inverse variance method and it was separate from parallel trials.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Split-face, within-subjects design study. No randomisation method was described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Double blinding was impossible because the two chemical peels showed different acute responses" Comment: blinding probably insufficient
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the evaluator blinding method was used" Comment: insufficient information about method to ensure blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the 13 participants completed the study, no missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient data regarding subject global assessment
Other bias	Low risk	No other potential bias identified

Barbareschi 1991

Study characteristics

Methods	**Aim of study:** to investigate the activity against comedones of 20% AZA cream compared with 0.05% RA cream and placebo cream using clinical and scanning electron microscopy evaluation **Design:** parallel

Barbareschi 1991 *(Continued)*

	Unit of allocation: individuals **Allocation:** randomised; authors did not describe their sequence generation methods **Blinding:** unclear **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** none
Participants	**Population description:** comedonal acne **Setting:** not described **Randomised number:** 30 **Age:** AZA group: 15 to 27; RA group: 16 to 25; Placebo group: 15 to 28 **Sex (M/F):** 5/5 (AZA group); 6/4 (RA group); 3/7 (placebo group) **Severity of illness:** comedonal acne
Interventions	**Name of treatment group 1:** 20% AZA cream **n** = 10 **Description:** 20% AZA cream (Skinoren, Schering) **Treatment period:** 4 months **Timing:** twice-daily **Name of control group 2:** 0.05% RA **n** = 10 **Description:** 0.05% RA **Treatment period:** 4 months **Timing:** twice-daily **Name of control group 3:** placebo cream **n** = 10 **Description:** placebo cream **Treatment period:** 4 months **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). (comedone numbers, baseline, week 16) • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Authors did not report this outcome • Quality of life. Authors did not report this outcome
Notes	• Funding: not described • 20% AZA cream versus 0.05% RA was presented in comparison of AZA versus any topical treatments; 20% AZA cream versus placebo cream was presented in comparison of AZA versus placebo

Barbareschi 1991 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly allocated to three groups...". Comment: no details of random methods were described
Allocation concealment (selection bias)	Unclear risk	No information of allocation concealment was described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The same observer made the clinical assessment..." Comment: insufficient detail reported about method used to ensure blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the 30 participants completed the study, no missing outcome data
Selective reporting (reporting bias)	High risk	"Side effects" not reported
Other bias	Low risk	No other potential bias identified

Bojar 1994

Study characteristics

Methods	**Aim of study:** This double-blind study was carried out to assess the ability of 4% w/v erythromycin with and without 1.2% w/v zinc acetate to reduce the numbers of erythromycin-resistant propionibacterium in vivo, and also to monitor the acquisition of resistant strains de novo during therapy **Design:** parallel, active-control **Unit of allocation:** individuals **Allocation:** randomised; no further detail **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** 7 in total
Participants	**Population description:** mild to moderate AV (grades 0.5 to 3.0 on the Burke and Cunliffe Scale) **Setting:** not described **Randomised number:** 52 **Age (years):** treatment group: 17.9 years, 13 to 27 years; control group: 20.4 years, 15 to 37 years

Bojar 1994 *(Continued)*

	Sex (M/F): 30/15 in both groups **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** erythromycin with zinc acetate n = 20 (number of participants completed the study, number of randomised participants was unknown) **Description:** topical 4% w/v erythromycin with 1.2% w/v zinc acetate, in a base consisting of 26% w/v di-isopropyl sebacate and 57% w/v ethanol. Applied with a plain soap for skin cleansing **Treatment period:** 12 weeks **Timing:** twice daily **Name of treatment group:** erythromycin n = 25 (number of participants completed the study, number of randomised participants was unknown) **Description:** topical 4% w/v erythromycin, in a base consisting of 26% w/v di-isopropyl sebacate and 57% w/v ethanol. Applied with a plain soap for skin cleansing **Treatment period:** 12 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. 7 in total, unknown in each group **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Baseline and week 4, 8 and 12. Authors only reported no difference between groups without P value and other summary statistics • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Authors did not report this outcome • Quality of life. Authors did not report this outcome. **Other outcomes that were not analysed in this review** • Microbiological evaluations
Notes	**Funding** Brocades Pharma for financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to treatment with either...". Comment: no details of random methods were described
Allocation concealment (selection bias)	Unclear risk	We judged an unclear risk of bias because the authors did not report this issue.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.

Bojar 1994 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Seven of the original 52 patients failed to attend one or more follow-up appointments, and have been excluded from the data analysis". Comment: the author did not report which of the seven participants belonged to which group, number of missing data considered enough to introduce bias
Selective reporting (reporting bias)	High risk	"Side effects" not reported
Other bias	Low risk	No other potential bias identified

Cavicchini 1989

Study characteristics	
Methods	**Aim of study:** to compare the activity of topical AZA with that of BPO in participants suffering from papulopustular acne **Design:** parallel **Unit of allocation:** patients **Allocation:** unclear **Blinding:** single-blinding for participants **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** not described
Participants	**Population description:** papulopustular acne **Setting:** not described **Randomised number:** 30 **Age:** not described **Sex:** either sex **Severity of illness:** papulopustular acne
Interventions	**Name of treatment group:** AZA group **n** = unclear (see notes) **Description:** topical 20% AZA cream **Treatment period:** 6 months **Timing:** initially nightly (firstly 2 weeks) and subsequently twice a day **Name of treatment group:** BPO group **n** = unclear (see notes) **Description:** 5% BPO gel **Treatment period:** 6 months

Cavicchini 1989 *(Continued)*

	Timing: initially nightly (firstly 2 weeks) and subsequently twice a day
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). "Global assessment: good and excellent results" was reported in the trial; we did not know whether it meant participants global self-assessment. Therefore, we did not consider this outcome. • Withdrawal for any reason. Authors did not report this outcome. **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of inflamed lesions, from baseline to month 6, no usable data. • Physicians' global evaluation of acne improvement. "Global assessment: good and excellent results" was reported in the trial; we did not know whether it meant physician global self-assessment. Therefore, we did not consider this outcome. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported percentage of participants who experienced minor adverse event. • Quality of life. Authors did not report this outcome
Notes	The study authors did not report the number of participants allocated to each treatment group. **Funding:** not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A group of 30 patients...were randomly assigned to treatment with.." Comment: no detail of random sequence generation was provided
Allocation concealment (selection bias)	Unclear risk	We judged an unclear risk of bias because the authors did not report this issue.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote "AZA cream and BPO gel were stored in identical tubes." Comment: participants were blinded to treatment group, blinding of personnel unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single blinding for participants was used rather than outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study did not address this outcome.
Selective reporting (reporting bias)	Unclear risk	No reporting baseline characteristics
Other bias	Low risk	No other potential bias identified

Chantalat 2005

Study characteristics	
Methods	**Aim of study:** to evaluate the efficacy of twice daily application of the novel 2% SA acne treatment compared to twice daily application of 10% BPO treatment or untreated (control) **Design:** parallel **Unit of allocation:** patients **Allocation:** unclear **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** not described
Participants	**Population description:** mild to moderate acne **Setting:** not described **Randomised number:** unclear **Age:** not described **Sex:** either sex **Severity of illness:** mild to moderate acne
Interventions	**Name of treatment group:** 2% SA group **n** = unclear (see notes) **Description:** novel 2% SA acne treatment **Treatment period:** unclear **Timing:** twice daily **Name of treatment group:** BPO group **n** = unclear (see notes) **Description:** 10% BPO gel **Treatment period:** unclear **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). "Subject self-assessments" was reported in the trial, but not this outcome • Withdrawal for any reason. Authors did not report this outcome **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Only mentioned resolution of lesions at week 1 but no numerical data were reported. • Physicians' global evaluation of acne improvement. "Subject self-assessments" was reported in the trial, but not this outcome. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Mentioned minor adverse events but no numerical data reported. • Quality of life. Authors did not report this outcome
Notes	The study authors did not report the number of participants allocated to each treatment group.

Chantalat 2005 *(Continued)*

Funding: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment were described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors only reported the number of participants who completed trial but did not report total number of randomised participants.
Selective reporting (reporting bias)	Unclear risk	Study published as abstract only
Other bias	Low risk	No other potential bias identified

Chantalat 2006

Study characteristics

Methods	**Aim of study:** to evaluate the clinical efficacy of a formulation containing the microgel complex with 2% SA (n = 20) versus a 10% BPO cream (n = 21) **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomised without further details **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** no withdrawal
Participants	**Population description:** mild to moderate facial AV **Setting:** not described **Randomised number:** 41 **Age (years):** 12 to 30 years **Sex (M/F):** not reported

Chantalat 2006 *(Continued)*

	Severity of illness: mild to moderate acne
Interventions	**Name of treatment group:** 2% SA **n** = **20** **Description:** a novel treatment containing a synergistic microgel complex was developed to have sebum solubilising properties, enhanced delivery of SA, and skin moisturisation and conditioning properties **Treatment period:** 6 weeks **Timing:** twice daily **Name of treatment group:** 10% BPO cream **n** = **21** **Description:** 10% BPO is a widely used topical agent to treat inflammatory acne **Treatment period:** 6 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome. • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Only mentioned, but no data • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse event • Quality of life. Authors reported AQOL, but no data
Notes	**Funding:** 100% of this poster funded by Johnson & Johnson Consumer and Personal Products Worldwide

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A 6-week, double-blind, randomised, controlled clinical study was conducted..." Comment: but no details of random sequence were reported
Allocation concealment (selection bias)	Unclear risk	We judged an unclear risk of bias because the authors did not report this issue.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.
Incomplete outcome data (attrition bias)	Low risk	All the participants completed the study, no missing outcome data

Chantalat 2006 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Study published as abstract only
Other bias	Low risk	No other potential bias identified

Chantalat 2007

Study characteristics	
Methods	**Aim of study:** a second cleanser (cleanser B) containing the microgel complex with 0.5% SA was evaluated **Design:** double-blind, randomised, vehicle controlled design **Unit of allocation:** patients **Allocation:** unclear **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** not described
Participants	**Population description:** acne participants **Setting:** not described **Randomised number:** unclear **Age:** not described **Sex:** unclear **Severity of illness:** not described
Interventions	**Name of treatment group:** 0.5% SA group **n** = unclear (see notes) **Description:** a cleanser containing the microgel complex with 0.5% SA **Treatment period:** unclear **Timing:** unclear **Name of treatment group:** vehicle group **n** = unclear (see notes) **Description:** vehicle group **Treatment period:** unclear **Timing:** unclear
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). 'Global acne severity' was reported in the trial, but probably not this outcome • Withdrawal for any reason. Authors did not report this outcome **Secondary outcomes**

Chantalat 2007 *(Continued)*

- Change in lesion counts (total or inflamed and non-inflamed separately). Day 1, but no numerical data were reported
- Physicians' global evaluation of acne improvement. "Global acne severity" was reported in the trial, but probably not this outcome
- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Mentioned minor adverse events but no numerical data reported
- Quality of life. Authors did not report this outcome

Notes	The study authors did not report the number of participants allocated to each treatment group. **Funding:** 100% is sponsored by Johnson & Johnson Consumer & Personal Products Worldwide

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.
Allocation concealment (selection bias)	Unclear risk	We judged an unclear risk of bias because the authors did not report this issue.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was 'double-blinded' and vehicle controlled, blinding probably sufficient.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This study was 'double-blinded' and vehicle controlled. Insufficient information about how blinding of outcome assessor was ensured.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors did not report the total number of randomised participants.
Selective reporting (reporting bias)	Unclear risk	Study published as abstract only
Other bias	Low risk	No other potential bias identified

Chen 2007

Study characteristics

Methods	**Aim of study:** the acne treatment benefits of this oil-free cleanser (SA microgel complex) were evaluated **Design:** double-blind, randomised, vehicle controlled design **Unit of allocation:** patients **Allocation:** unclear **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** not described

Chen 2007 *(Continued)*

	Dropouts: not described
Participants	**Population description:** subjects of Fitzpatrick skin types I-V **Setting:** not described **Randomised number:** unclear **Age:** 12 through 35 years **Sex:** either sex **Severity of illness:** mild to moderate acne
Interventions	**Name of treatment group:** SA group **n** = unclear **Description:** the cleanser containing the SA microgel complex **Treatment period:** unclear **Timing:** unclear **Name of treatment group:** vehicle group **n** = unclear **Description:** vehicle group (no detailed information provided) **Treatment period:** unclear **Timing:** unclear
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). "Global acne severity" was mentioned in the trial, but probably not this outcome • Withdrawal for any reason. Authors did not report this outcome **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Time points not reported and no usable data. • Physicians' global evaluation of acne improvement. "Global acne severity" was mentioned in the trial, but probably not this outcome. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). No minor adverse events occurred, sample size unclear • Quality of life. Authors did not report this outcome
Notes	**Funding:** supported by Neutrogena Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation
Allocation concealment (selection bias)	Unclear risk	We judged an unclear risk of bias because the authors did not report this issue.
Blinding of participants and personnel (performance bias)	Low risk	This study was 'double-blinded' and vehicle controlled, blinding probably sufficient

Chen 2007 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This study was 'double-blinded' and vehicle controlled. Insufficient information about how blinding of outcome assessor was ensured
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors did not report total number of randomised participants.
Selective reporting (reporting bias)	Unclear risk	Study published as abstract only
Other bias	Low risk	No other potential bias identified

Cunliffe 1989

Study characteristics	
Methods	**Aim of study:** the present investigation was concerned with, for the first time, comparing AZA with placebo therapy for acne **Design:** parallel **Unit of allocation:** individuals **Allocation:** allocation was randomised (FORTRAN 77 RANDT program) **Blinding:** double-blinding; this is a placebo control trial **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** no
Participants	**Population description:** AV **Setting:** not described **Randomised number:** 40 **Age (years):** unclear **Sex (M/F):** 26/14 **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** AZA **n** = **20** **Description:** AZA 20% **Treatment period:** 12 weeks **Timing:** twice daily **Name of treatment group:** placebo **n** = **20** **Description:** placebo **Treatment period:** 12 weeks **Timing:** twice daily

Cunliffe 1989 *(Continued)*

Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of inflamed and non-inflamed lesions, week 4, 8, and 12 • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). 6-point scale 0 (none) to 5 (severe) and 3-point scale (no, mild, severe) used to assess severity but no usable data • Quality of life. Authors did not report this outcome.
Notes	Funding not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was randomised (FORTRAN 77 RANDT program)
Allocation concealment (selection bias)	Unclear risk	We judged an unclear risk of bias because the authors did not report this issue.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was 'double-blinded' and placebo-controlled, blinding probably sufficient
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This study was 'double-blinded' and placebo-controlled. Insufficient information about how blinding of outcome assessor was ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients returned for clinical assessment..." Comment: no missing outcome data
Selective reporting (reporting bias)	Unclear risk	No baseline data for each group reported. Insufficient reporting "adverse events"
Other bias	Low risk	No other potential bias identified

Cunliffe 2005

Study characteristics

Methods	**Aim of study:** to compare the efficacy and safety of a 1% clindamycin/zinc gel when applied to the face once daily or twice daily with a 1% clindamycin lotion applied twice daily for 16 weeks in participants with mild to moderate AV **Design:** parallel **Unit of allocation:** individuals

Cunliffe 2005 *(Continued)*

	Allocation: unclear **Blinding:** observer-blind **Duration of trial (from recruitment to last follow-up):** the study ran through autumn, winter and early spring **Dropouts:** 10/83 for clindamycin/zinc gel qd; 7/80 for clindamycin/zinc gel bid; 6/83 for clindamycin lotion bid
Participants	**Population description:** mild to moderate acne **Setting:** 8 centres in the UK, 1 in France and 1 in Germany **Randomised number:** 163 **Age:** 12 to 40 years **Sex:** either sex **Severity of illness:** mild to moderate acne graded between 2 and 7 with at least 15 inflammatory and 10 non-inflammatory lesions, but fewer than 75 lesions of either type
Interventions	**Name of treatment group:** clindamycin/zinc gel **n** = 80 **Description:** a topical acne treatment in which CDP equivalent to 1% clindamycin ('clindamycin/zinc gel') presented in a gel formulation has received marketing authorisations in a number of EU and non-EU countries **Treatment period:** 16 weeks **Timing:** twice daily **Name of treatment group:** clindamycin lotion bid **n** = 83 **Description:** 1% clindamycin lotion **Treatment period:** 16 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Visual analogue scale, week 16 • Withdrawal for any reason. 23 withdrawals during 16 weeks' study **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). From baseline to week 16, but no usable data, P value reported • Physicians' global evaluation of acne improvement. Visual analogue scale, week 16 • Minor adverse events (assessed as total number of participants who experienced at least 1 minor adverse event). A 10-point scale from zero (0) to severe (7–9) used but no usable data; reported number of minor adverse events • Quality of life. Authors did not report this outcome
Notes	**Funding:** this study was sponsored by Strakan Pharmaceuticals Ltd. **For interventions:** authors also used a 'clindamycin/zinc gel qd [three times/day]' group, in which timing was different from control group (twice/day). Therefore, reviewers did not consider it in the analysis.

Cunliffe 2005 *(Continued)*

	Regarding outcomes: all primary and secondary efficacy variables at 16 weeks had conclusions based upon an analysis of the last observation carried forward (LOCF) for the ITT population only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation
Allocation concealment (selection bias)	Unclear risk	We judged an unclear risk of bias because the authors did not report this issue.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "An observer-blind design was used due to the difficulty in blinding the two different topical formulations". Comment: blinding probably insufficient
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The investigator and assessors of all clinical variables were blinded to treatment allocation to avoid bias" Comment: insufficient information about blinding method
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twenty-three (9%) patients failed to complete the study, withdrawal rates were similar across the treatment groups..." "All primary and secondary efficacy variables at 16 weeks had conclusions based upon an analysis of the last observation carried forward (LOCF) for the intention-to-treat (ITT) population". Comment: ITT analysis. similar withdrawal rates across treatment groups, and missing data sufficiently addressed
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Dayal 2017

Study characteristics

Methods	**Aim of study:** to compare the efficacy and safety of 30% SA versus JS peels in treatment of mild to moderate facial acne in Indian participants **Design:** parallel **Unit of allocation:** individuals **Allocation:** computerised randomisation was used **Blinding:** observer-blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** no dropouts
Participants	**Population description:** mild to moderate acne **Setting:** Department of dermatology, Pt. BD Sharma, Universitiy of Health Sciences, Rohtak, India

Dayal 2017 *(Continued)*

	Randomised number: 40 **Age:** SA: 17.8 ± 1.88; Jessner's solution: 16.8 ± 2.09 **Sex (M/F):** SA (12/8); Jessner's solution (14/6) **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** SA **n** = 20 **Description:** SA 30% peel **Treatment period:** 12 weeks **Timing:** peels were performed 2 weeks apart with total of six peels **Name of treatment group:** Jessner's solution **n** = 20 **Description:** a combination of SA (14%), resorcinol (14%), and lactic acid (14%) in 95% ethanol **Treatment period:** 12 weeks **Timing:** peels were performed 2 weeks apart with total of six peels
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of inflamed and non-inflamed lesions, from baseline to week 12, SDs were missing. • Physicians' global evaluation of acne improvement (week 12; 3-point scale, good: > 50% decrease in MAS, fair: 21% to 50% decrease in MAS, poor: 11% to 20% decrease in MAS, and no change: 0% to 10% decrease in MAS) • Minor adverse events (assessed as total number of participants who experienced at least 1 minor adverse event). Authors reported number of participants who experienced adverse event • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • MAS
Notes	**Funding:** not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients with grade I and II acne vulgaris were randomly divided into two groups of 20 each, based on computerized randomisation". Comment: computerized randomisation was used
Allocation concealment (selection bias)	Unclear risk	We judged an unclear risk of bias because the authors did not report this issue.
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement

Dayal 2017 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A certified dermatologist, who was kept blinded throughout the study, evaluated…" Comment: outcome assessor was kept blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the participants completed the study, no missing outcome data
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Draelos 2016

Study characteristics	
Methods	**Aim of study:** to evaluate the short-term effect of a BPO 3% gel on acne lesions **Design:** parallel **Unit of allocation:** individuals **Allocation:** no details of concealment was described **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** no dropouts
Participants	**Population description:** mild to moderate acne **Setting:** single centre in USA **Randomised number:** 90 **Age:** 12 to 45 years; BPO 22.1 ± 9.90; SA 17.8 ± 6.22; vehicle 20.3 ± 7.47 **Sex (M/F):** BPO (12/18); SA (18/12); vehicle (13/17) **Severity of illness:** participants with mild to moderate acne
Interventions	**Name of treatment group:** SA **n** = 30 **Description:** SA 2% gel **Treatment period:** four days **Timing:** once daily **Name of treatment group:** BPO **n** = 30 **Description:** BPO 3% gel **Treatment period:** four days **Timing:** once daily

Draelos 2016 *(Continued)*

	Name of treatment group: vehicle **n** = 30 **Description:** vehicle **Treatment period:** four days **Timing:** once daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). 5-point scale, 0 (very dissatisfied) to 5 (very satisfied), data not shown • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Authors did not report this outcome. • Physicians' global evaluation of acne improvement. Authors did not report this outcome. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). No adverse events occurred. • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Target lesion swelling, diameter, erythema • Skin clarity
Notes	**Funding**: this study was funded by GlaxoSmithKline Consumer Healthcare Ltd; Zoe Diana Draelos MD and Dror Rom PhD received remuneration for consultancy services, and Keith Ertel PhD was an employee of GSK at the time the study was conducted. The sponsor reviewed the final manuscript before submission.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " Eligible subjects were randomised to use one of three test articles…". Comment: no details of random methods were described
Allocation concealment (selection bias)	Unclear risk	No details of concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "A 5-day, double-blind, randomised clinical trial was conducted..." Comment: although 'double-blind' was mentioned, no details were reported for its identification
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "A 5-day, double-blind, randomised clinical trial was conducted..." Comment: although 'double-blind' was mentioned, no details were reported for its identification
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Ninety subjects were enrolled and all completed the study". Comment: no missing outcome data
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the study protocol.

Draelos 2016 *(Continued)*

Other bias	Unclear risk	Quote: "This study was funded by GlaxoSmithKline Consumer Healthcare Ltd; Zoe Diana Draelos MD and Dror Rom PhD received remuneration for consultancy services, and Keith Ertel PhD was an employee of GSK at the time the study was conducted. The sponsor reviewed the final manuscript before submission". Comment: unclear whether an important risk of bias exists

Dunlap 1997

Study characteristics	
Methods	**Aim of study:** to compare a 3% erythromycin/5% BPO combination in gel versus 20% AZA cream in the treatment of AV **Design:** parallel **Unit of allocation:** individuals **Allocation:** unclear **Blinding:** investigator-blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** not reported
Participants	**Population description:** people with acne **Setting:** not described **Randomised number:** 150 **Age:** 13 to 30 years **Sex:** either sex **Severity of illness:** grade II or III, Pillsbury classification
Interventions	**Name of treatment group:** AZA **n** = unclear (see notes) **Description:** 20% AZA cream **Treatment period:** 8 weeks **Timing:** twice daily **Name of treatment group:** erythromycin/BPO **n** = unclear (see notes) **Description:** 3% erythromycin/5% BPO **Treatment period:** 8 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. Authors did not report this outcome

Dunlap 1997 *(Continued)*

	Secondary outcomes • Change in lesion counts (total or inflamed and non-inflamed separately). Week 2, 4, and 8. But no numeric data were reported. • Physicians' global evaluation of acne improvement. Week 2, 4, and 8. Scales not described and no numeric data were reported. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Authors did not report this outcome • Quality of life Authors did not report this outcome
Notes	The study authors did not report the number of participants allocated to each group. **Funding:** not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was with a "investigator-blind" design, blinding of participants probably insufficient
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was with a "investigator-blind" design, we were not sure whether assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants randomised to each group was not reported
Selective reporting (reporting bias)	Unclear risk	Study published as abstract only
Other bias	Low risk	No other potential bias identified

Eady 1996

Study characteristics

Methods	**Aim of study:** not described **Design:** parallel **Unit of allocation:** patients **Allocation:** randomisation; no details **Blinding:** placebo-control, double-blind

Eady 1996 *(Continued)*

	Duration of trial (from recruitment to last follow-up): not described **Dropouts:** 15
Participants	**Population description:** mild-moderate facial acne **Setting:** not described **Randomised number:** 114 **Age:** 16 to 25 years **Sex (M/F):** 86/28 **Severity of illness:** mild to moderate
Interventions	**Name of treatment group: SA** group **n** = **56** **Description:** A 2% SA and 10% hydroalcoholic lotion **Treatment period:** 12 weeks **Timing:** twice daily **Name of treatment group:** placebo group **n** = **58** **Description:** 10% hydroalcoholic lotion **Treatment period:** 12 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Week 4, 8, and 12; 7-point interval rating scale (details not described); Mean ± SE was reported and we converted SE to SD • Withdrawal for any reason. 15 dropouts during 12 weeks' study **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Week 4, 8, and 12 • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Mentioned minor adverse events with no usable data • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Change in acne severity by Leeds technique
Notes	**Funding:** this study is supported by Proctor and Gamble

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was a stratified, randomised, double-blind parallel-group clinical study" Comment: but no details of random sequence were reported

Eady 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details of concealments were reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was a 'double-blind', 'placebo-controlled' trial, binding probably sufficient
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was a 'double-blind', 'placebo-controlled' trial. Insufficient information about how blinding of outcome assessor was ensured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 15 (13%) patients dropped out during the course of study." Comment: no ITT analysis, but number of missing data not considered to introduce bias
Selective reporting (reporting bias)	Unclear risk	No baseline data for each group reported. Insufficient reporting "adverse events"
Other bias	Low risk	No other potential bias identified

ElRefaei 2015

Study characteristics	
Methods	**Aim of study:** to evaluate the efficacy and the tolerability of a combination of 20% salicylic–10% mandelic acid peel against a 35% glycolic acid peel in the treatment of active AV **Design:** parallel **Unit of allocation:** individuals **Allocation:** sealed envelope method was used **Blinding:** assessor-blind **Duration of trial (from recruitment to last follow-up):** conducted from March 2012 to March 2013 **Dropouts:** no dropouts
Participants	**Population description:** participants with facial AV **Setting:** Dermatology and Andrology Department of Beha University hospital, Egypt **Randomised number:** 40 **Age:** 14 to 29 years; 35% glycolic acid peel: 19.55 ± 4.19; 20% salicylic–10% mandelic acid peel: 19.8 ± 4.02 **Sex (M/F):** 35% glycolic acid peel (5/15); 20% salicylic–10% mandelic acid peel (3/17) **Severity of illness:** moderate to severe, 20 participants in 20% salicylic–10% mandelic acid peel had moderate acne compared with 19 participants with moderate acne and one with severe acne in GAP
Interventions	**Name of treatment group:** glycolic acid **n** = 20 **Description:** 35% glycolic acid peel **Treatment period:** 12 weeks

ElRefaei 2015 *(Continued)*

	Timing: seven peeling sessions were conducted for each group every two weeks **Name of treatment group:** 20% salicylic–10% mandelic acid peel **n** = 20 **Description:** 20% salicylic–10% mandelic acid peel **Treatment period:** 12 weeks **Timing:** seven peeling sessions were conducted for each group every two weeks
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Week 12; a 3-point visual analogue scale: poor < 30% improvement, fair 30% to 60% improvement, and good > 60% improvement • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of inflamed and non-inflamed lesions, from baseline to week 20. • Physicians' global evaluation of acne improvement. Week 4, 8, 12, and 20; a five-point visual analogue scale (VAS): (1) worse, (2) no change, (3) poor (< 30% improvement), (4) fair (31% to 60% improvement), and (5) good (> 60% improvement) • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported total number of participants who experienced adverse events • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Post-acne hyperpigmentation and scars • Michaelsson severity index
Notes	**Funding**: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " This randomised clinical trial was carried out on 40 patients who were divided randomly, by the sealed envelope method…". Comment: sealed envelope method was used
Allocation concealment (selection bias)	Low risk	Quote: " This randomised clinical trial was carried out on 40 patients who were divided randomly, by the sealed envelope method…". Comment: sealed envelope method was used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Two uninvolved dermatologists made a subjective assessment…". Comment: blinding probably sufficient
Incomplete outcome data (attrition bias)	Low risk	Quote: "All of them (32 females and eight males) completed the study." Comment: no missing outcome data

ElRefaei 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Garg 2009

Study characteristics	
Methods	**Aim of study:** to compare the therapeutic efficacy and tolerability of 35% glycolic acid peels and 20% salicylic–10% mandelic acid peels in active acne **Design:** parallel **Unit of allocation:** individuals **Allocation:** no details **Blinding:** not described **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** no dropouts
Participants	**Population description:** Indian participants with Fitzpatrick skin types IV to VI with AV **Setting:** hospital in India, all participants were Indian **Randomised number:** 44 **Age:** mean: 22 ± 3.0; range 16 to 27 **Sex (M/F):** 11/33 **Severity of illness:** participants with AV and post-acne scarring and hyperpigmentation not responding to conventional treatment for 3 or more months
Interventions	**Name of treatment group:** glycolic acid peels **n** = 22 **Description:** 35% glycolic peels **Treatment period:** 12 weeks **Timing:** fortnightly intervals for six sessions **Name of treatment group:** 20% salicylic–10% mandelic acid peels **n** = 22 **Description:** 20% salicylic–10% mandelic acid peels **Treatment period:** 12 weeks **Timing:** fortnightly intervals for six sessions
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Week 4, 8, 12, and 24; a 5-point visual analogue scale: good > 60%, fair 31% to 60%, poor < 30%, no change, worse • Withdrawal for any reason. No withdrawals

Garg 2009 *(Continued)*

Secondary outcomes

- Change in lesion counts (total or inflamed and non-inflamed separately). Week 2, 4, 6, 8, 10, 12, 24. SDs were missing
- Physicians' global evaluation of acne improvement. Week 4, 8, 12, and 24; a 5-point visual scale: good > 60%, fair 31% to 60%, poor < 30%, no change, worse
- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported total number of participants who experienced adverse events
- Quality of life. Authors did not report this outcome

Other outcomes that were not analysed in this review

- Post-acne hyperpigmentation and scars
- Michaelsson severity index

Notes	**Funding**: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: " The treating physician made an objective assessment of..." Comment: blinding probably insufficient
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All 44 patients (33 women and 11 men) completed the study." Comment: no missing outcome data
Selective reporting (reporting bias)	Unclear risk	No baseline data for each group reported. Insufficient data regarding "subjective assessment of response".
Other bias	Low risk	No other potential bias identified

Gollnick 2004a

Study characteristics

Methods	**Aim of study:** to clinically test 15% AZA gel against 5% BPO in participants with mild to moderate AV **Design:** parallel, double-blind, randomised, multicentre, phase III trial **Unit of allocation:** patients **Allocation:** randomisation; no details **Blinding:** double-blinded study; no details

Gollnick 2004a *(Continued)*

	Duration of trial (from recruitment to last follow-up): 1997 to 2000 **Dropouts:** 5 participants in the AZA group and 10 participants in the BPO group discontinued the study due to adverse events. 38 participants in the AZA group and 43 participants in the BPO group did not complete the scheduled 4 months treatment.
Participants	**Population description:** mild to moderate AV **Setting:** multicentres, recruitment in Germany, Netherlands, Norway, and Greece **Randomised number:** 351; 176 to AZA group and 175 to BPO group **Age, median years (range):** AZA group: 20 (13 to 45); BPO group: 19 (11 to 42) **Sex, numbers male/female (% male):** AZA group: 68/108 (63%); BPO group: 67/108 (62%) **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** AZA group, N = 176 **Description:** 15% AZA in hydro gel (brand: Skinoren 15% gel) topical application 2 times per day for 4 months **Treatment period:** 4 months **Timing:** 2 times per day **Name of control group:** BPO group, N = 175 **Description:** 5% BPO in hydro gel (brand: Scherogel) topical application 2 times per day for 4 months **Treatment period:** 4 months **Timing:** 2 times per day
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Week 16; a four-point Likert-type rating scale (very good, good, moderate, poor) • Withdrawal for any reason (81 withdrawals during the 4 months treatment) **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reported median of percent reduction of the lesions, week 16 • Physicians' global evaluation of acne improvement. Week 16; a four-point Likert-type rating scale (very good, good, moderate, poor) • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Adverse drug-related events • Quality of life. Authors did not report this outcome.
Notes	**Funding:** not reported; two authors were employees of the pharmaceutical company Schering

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.

Gollnick 2004a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment were described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants continuously dropped out, which is shown in Table 2 (of the paper) for the time points 1, 2, 3, ≥ 4 months from 100% down to 75%. 15 participants dropped out because of minor local adverse events. Number of missing data considered enough to introduce bias.
Selective reporting (reporting bias)	High risk	Additionally reported outcome (subjective global evaluations) that were not mentioned in the Method section
Other bias	Unclear risk	The study reported on the statistical approach that they used non-inferiority borders of 15%. The reporting appears not fully clear whether they describe an equivalence trial or an inferiority trial. Local adverse events were compared between Gollnick 2004a (BPO) and Gollnick 2004b (Clinda) in an indirect fashion. In Table 1, the total number of participants with acne of the face was incorrectly reported 351, but should be 251. Conflict of interest: authors are employees of a pharmaceutical company that marketed AZA

Gollnick 2004b

Study characteristics	
Methods	**Aim of study:** to clinically test 15% AZA gel against 1% clindamycin gel in participants with mild to moderate AV **Design:** parallel, double-blind, randomised, multicentre, phase III trial **Unit of allocation:** patients **Allocation:** randomisation; no details **Blinding:** double-blinded study; no details **Duration of trial (from recruitment to last follow-up):** 1997 to 2000 **Dropouts:** 5 participants in the AZA group and 1 participant in the clindamycin group discontinued the study due to adverse events. 20 participants in the AZA group and 10 participants in the clindamycin group did not complete the scheduled 4 months treatment.
Participants	**Population description:** mild to moderate AV **Setting:** multicentres, recruitment in Germany, Netherlands, Norway, and Greece **Randomised number:** 229; 114 to azelaic group and 115 to clindamycin group

Gollnick 2004b *(Continued)*

	Age, median years (range): AZA group: 19 (14 to 50); clindamycin group: 19 (13 to 38) **Sex, numbers male/female (% male):** AZA group: 47/67 (41%); clindamycin group: 55/60 (48%) **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** AZA group, N = 114 **Description:** 15% AZA in hydro gel (brand: Skinoren 15% Gel) topical application 2 times per day for 4 months **Treatment period:** 4 months **Timing:** 2 times per day **Name of control group:** clindamycin group, N = 115 **Description:** 1% clindamycin in hydro gel (brand: Basocin Acne Gel) topical application 2 times per day for 4 months **Treatment period:** 4 months **Timing:** 2 times per day
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Week 16; a four-point Likert-type rating scale (very good, good, moderate, poor) • Withdrawal for any reason (30 withdrawals during the 4 months treatment) **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reported median of percent reduction of the lesions, week 16 • Physicians' global evaluation of acne improvement. Week 16; a four-point Likert-type rating scale (very good, good, moderate, poor) • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Adverse drug-related events • Quality of life. Authors did not report this outcome.
Notes	**Funding:** not reported; two authors were employees of the pharmaceutical company Schering

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment were described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.

Gollnick 2004b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants continuously dropped out, which is shown in Table 2 for the time points 1, 2, 3, ≥ 4 months from 100% down to 83%. Six participants dropped out possibly because of minor local adverse events. Number of missing data considered enough to introduce bias
Selective reporting (reporting bias)	High risk	Additionally reported outcome (Subjective global evaluations) that were not mentioned in the Method section
Other bias	Unclear risk	Minor local adverse events were compared between Gollnick 2004a and Gollnick 2004b in an indirect fashion. In study 2, the duration of therapy differed between test and control arm. An advantage was reported for AZA, although the difference was not significant. Conflict of interest: authors are employees of a pharmaceutical company that marketed AZA

Hayashi 2012

Study characteristics	
Methods	**Aim of study:** to evaluate AZA 20% cream efficacy in Japanese participants with AV **Design:** randomised placebo-controlled investigator-blinded split-face study **Unit of allocation:** face **Allocation:** randomisation; no details **Blinding:** blinding for investigators **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** not described
Participants	**Population description:** Japanese participants with AV **Setting:** multicentres in Japan, all participants were Japanese **Randomised number:** 66 **Age:** ≥ 16 years old **Sex:** unclear **Severity of illness:** AV with more than 30 total lesion counts
Interventions	**Name of treatment group:** 20% AZA cream **n** = unclear (see notes) **Description:** 20% AZA cream **Treatment period:** 12 weeks **Timing:** twice daily **Name of treatment group:** placebo **n** = unclear (see notes) **Description:** placebo group

Hayashi 2012 *(Continued)*

	Treatment period: 12 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. Authors did not report this outcome **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Week 12 • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Authors reported subjective symptoms, but with no numerical data • Quality of life. Authors did not report this outcome
Notes	The study authors did not report the number of participants allocated to each group. **Funding:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment were described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was an 'investigator-blinded', 'placebo-controlled' study. Blinding probably sufficient
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This study was an 'investigator-blinded', 'placebo-controlled' study. Insufficient information about how blinding of outcome assessor was ensured.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This was not stated.
Selective reporting (reporting bias)	Unclear risk	Study published as poster only
Other bias	Low risk	No other potential bias identified

Hunt 1992

Study characteristics

Methods	**Aim of study:** to compare the efficacy and skin tolerance of a topical alpha hydroxy acid preparation gluconolactone 14% in solution, with its vehicle alone (placebo) and 5% BPO lotion in treatment of mild to moderate acne

Hunt 1992 *(Continued)*

	Design: parallel **Unit of allocation:** patients **Allocation:** randomisation; no details **Blinding:** blinding for participants, investigators and assessors **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** 15 dropouts with reasons; 4 discontinued due to irritation of the skin
Participants	**Population description:** mild to moderate acne **Setting:** not described **Randomised number:** 150 **Age:** 20.1 (13 to 36) years **Sex:** 76/74 **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** alpha-hydroxy acid group. **n** = 50 **Description:** alpha hydroxy acid preparation gluconolactone 14% in aqueous solution (formulation developed by Narhex Australia Pty Ltd) **Treatment period:** not described **Timing:** not described **Name of control group 1:** placebo group. **n** = 50 **Description:** the vehicle of treatment group **Treatment period:** not described **Timing:** not described **Name of control group 2:** BPO group. **n** = 50 **Description:** 5% BPO water-based lotion **Treatment period:** not described **Timing:** not described
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome. • Withdrawal for any reason (15 withdrawals during 12 weeks' study) **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). From baseline to week 12, percentage reduction of lesion counts. • Physicians' global evaluation of acne improvement. Authors did not report this outcome. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event) • Skin reactions were graded using a 4-point scale (0-nil, 1-mild, 2-moderate to 3-severe). Reported number of participants who experienced minor adverse events.

Hunt 1992 *(Continued)*

- Quality of life. Authors did not report this outcome.

Notes	**Funding:** Narhex Australia Pty Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were randomised into three treatment groups..." Comment: but no details of random methods were described
Allocation concealment (selection bias)	Unclear risk	Although "identical numbered packages" were used here, no more details for enough concealment were described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All treatments were supplied in 100 ml aliquots, pre-packed in identical numbered packages...both doctor and patients were blinded". Comment: blinding probably sufficient
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...and patients were instructed not to describe to the assessing doctor any characteristics of the product such as colour, smell or consistency" Comment: blinding probably sufficient
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 15 (10%) dropouts with reasons; number of missing data not considered enough to introduce bias significantly
Selective reporting (reporting bias)	Unclear risk	Insufficient data regarding "adverse events"
Other bias	High risk	Suspicious baseline imbalance in total lesion counts among groups (76.8 ± 7.5 in gluconolactone group; 94.7 ± 11.1 in placebo group; 76.5 ± 7.0 in BPO group); the use of a Student's t-test with no posthoc analysis to compare the means of lesions of three treatment groups

Ilknur 2010

Study characteristics

Methods	**Aim of study:** to compare the therapeutic effects of glycolic acid and amino fruit acids peels in participants with AV **Design:** single-blind, randomised, right - left comparison study **Unit of allocation:** split-face **Allocation:** randomisation; drawing **Blinding:** single blinding; assessors **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** 6
Participants	**Population description:** 0.25 to 2 grades AV

Ilknur 2010 *(Continued)*

	Setting: not described **Randomised number:** 30 **Age:** 18.96 (13 to 30) years **Sex:** 7/17 (completed data) **Severity of illness:** grades of 0.25 to 2, Leeds technique
Interventions	**Name of treatment group:** glycolic acid **n** = 24 sides of faces **Description:** GA solution was applied (glycolic acid peels; Neostrata, Princeton, NJ, USA) at concentrations from the lowest to the highest (20%, 35%, 50%, 70%). It is a type of fruit acid. **Treatment period:** 6 months **Timing:** 2 to 6 minutes/peel; entire period is 6 months **Name of treatment group:** amino fruit acids gel group; **n** = 24 sides of faces **Description:** amino fruit acid gel was applied (amino fruit acid peels; exCel Cosmeceuticals, Bloomfield Hills, MI, USA) at concentrations from the lowest to the highest (20%, 30%, 40%, 50%, 60%) **Treatment period:** 6 months **Timing:** 2 to 6 minutes/peel; entire period is 6 months
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome. • Withdrawal for any reason. Six dropouts during the 6-month study. Split-face design **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of non-inflamed and inflamed lesion counts, baseline, week 4, 8, 12, 16, 20, and 24 • Physicians' global evaluation of acne improvement. Authors did not report this outcome. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Mentioned minor adverse events and no summary statistics. • Quality of life. Authors did not report this outcome.
Notes	**Funding:** not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "In order to determine which therapy would be performed on which side of the face, randomisation was conducted by drawing." Comment: drawing is reliable for random sequence generation
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment were described.
Blinding of participants and personnel (performance bias)	High risk	This study is single-blind which was applied to the outcome investigators and method to ensure blinding was not described. Blinding of participants probably insufficient

Ilknur 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "In the clinical assessment, each side of the face was evaluated by a doctor blinded to the study..." Comment: the method to ensure blinding of outcome assessor throughout the study was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	6 dropouts (20%) with reasons; no ITT analysis was used. Number of missing data considered enough to introduce bias significantly
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Iraji 2007

Study characteristics	
Methods	**Aim of study:** our objective in this study was to evaluate the efficacy of 20% AZA gel in the treatment of mild to moderate AV. **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** double-blind; participants and investigators **Duration of trial:** not described **Dropouts:** no
Participants	**Population description:** mild to moderate acne **Setting:** not described **Randomised number:** 60 **Age:** average 18.3 in AZA group; 16.93 in placebo group **Sex:** 10/20 in AZA group; 13/17 in placebo group **Severity of illness:** mild to moderate acne
Interventions	**Name of treatment group:** AZA group; **n** = 30 **Description:** 20% AZA gel **Treatment period:** 6 weeks **Timing:** twice daily **Name of treatment group:** vehicle gel; **n** = 30 **Description:** composed of carbopol 934 (1%), glycerin (5%) and triethanolamine (0.2% to 0.5%) **Treatment period:** 6 weeks

Iraji 2007 *(Continued)*

	Timing: twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome. • Withdrawal for any reason. No withdrawals. **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Percentage reduction of total, non-inflamed and inflamed lesion counts, week 2, 4 and 6 • Physicians' global evaluation of acne improvement. Authors did not report this outcome. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse events • Quality of life. Authors did not report this outcome. **Other outcomes that were not analysed in this review** • Acne severity index
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment were described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both physicians and patients were blinded to the type of treatment". Comment: this study was 'vehicle-controlled', 'double-blinded', blinding probably sufficient
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both physicians and patients were blinded to the type of treatment. The same dermatologist counted the number of comedones, papules and pustules on the face at each visit." Comment: this study was 'vehicle-controlled', 'double-blinded', blinding probably sufficient
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All 60 patients completed the study." Comment: no missing outcome data
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Jaffary 2016

Study characteristics

Jaffary 2016 *(Continued)*

Methods	**Aim of study:** to compare the efficacy of pyruvic acid 50% and SA 30% peeling in the treatment of mild to moderate acne **Design:** parallel **Unit of allocation:** individuals **Allocation:** no details of concealment **Blinding:** one-blind **Duration of trial (from recruitment to last follow-up):** recruited within the second 6 months of 2010 **Dropouts:** SA group: 16; pyruvic acid group: 18
Participants	**Population description:** mild to moderate acne **Setting:** Al-Zahra Hospital Dermatology Clinic and Isfahan Skin Research Centre, Iran **Randomised number:** 86 **Age:** 15 to 40 years; SA group: 23.05 ± 5.7; pyruvic acid group: 25.07 ± 6 **Sex (M/F):** SA group (4/39); pyruvic acid group (3/40) **Severity of illness:** participants with mild to moderate acne
Interventions	**Name of treatment group:** SA **n** = 43 **Description:** SA 30% peels **Treatment period:** eight weeks **Timing:** applied every two weeks **Name of treatment group:** pyruvic acid **n** = 43 **Description:** pyruvic acid 50% peels **Treatment period:** eight weeks **Timing:** applied every two weeks
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Week 8; 4-point scale was used, patient satisfaction (excellent, good, fair, poor) were recorded using a checklist. • Withdrawal for any reason. 34 withdrawals during the 8-week study **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of non-inflamed and inflamed lesion counts, week 2, 4, 6 and 8. • Physicians' global evaluation of acne improvement. Week 8; a 4-point system defined by the author (excellent, good, moderate, poor), initial acne severity index improved more than 75%: excellent, improved 50% to 75%: good, improved 25% to 50%: moderate, and improved < 25%: poor response. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Mentioned this outcome but no usable data • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review**

Jaffary 2016 *(Continued)*

- Acne severity index

Notes	**Funding**: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: " The patients randomly allocated in one of the two groups under study". Comment: no details of random methods were described
Allocation concealment (selection bias)	Unclear risk	No details of concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: " In a prospective `one-blinded` clinical trial..." Comment: unclear which side was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: " In a prospective `one-blinded` clinical trial..." Comment: unclear which side was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	'As-treated' analysis was used with substantial withdrawals in treatment groups.
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section.
Other bias	High risk	Suspicion of fraudulent data reporting (20 participants in group one completed treatment period reported in the text, but 25 reported in Figure and 27 reported in Table)

Kar 2013

Study characteristics

Methods	**Aim of study:** to compare the efficacy of oral isotretinoin and oral isotretinoin with 20% SA peels in participants with moderate to severe acne **Design:** parallel **Unit of allocation:** patients **Allocation:** unclear **Blinding:** investigator-blinded **Duration of trial (from recruitment to last follow-up):** carried out between April 2012 and March 2013 **Dropouts:** no
Participants	**Population description:** moderate to severe acne

Kar 2013 *(Continued)*

	Setting: Department of Skin and VD of a Tertiary Care Hospital of Eastern India **Randomised number:** 60 **Age:** range 18 to 25 years; mean ± SD 20 ± 1.9 years in combination group; 20.6 ± 1.9 years in isotretinoin group **Sex:** 16/14 in combination group; 13/17 in isotretinoin group **Severity of illness:** moderate to severe MAS score 64.1 ± 4.4 in combination group; 63 ± 5.1 in isotretinoin group
Interventions	**Name of treatment group:** salicyclic acid and isotretinoin group; **n** = 30 **Description:** 20 mg oral isotretinoin once daily along with 20% SA peels every two weeks **Treatment period:** 16 weeks **Timing:** 20 mg oral isotretinoin once daily along with 20% SA peels every two weeks **Name of treatment group:** Isotretinoin group; **n** = 30 **Description:** 20 mg oral isotretinoin **Treatment period:** 16 weeks **Timing:** once daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Percentage reduction of total lesions, week 16, SDs were missing • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Only mentioned 'drying of lips', no usable data • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • MAS
Notes	**Funding:** SA peel (Vedasol - 20 gel from Vedaderm Inc. Chicago) used in this study was supplied by Percos India. Isotretinoin (Cap Tretiva 20 mg) was supplied by Intas Pharmaceuticals bearing lot number S12B018 and expiry date January 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised using a random number table." Comment: random number table is reliable for random sequence generation
Allocation concealment (selection bias)	Unclear risk	No details

Kar 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Investigator 1 (1st author) did the group allocation of the patients using a random number table. Investigator 2 (2nd author) performed the chemical peeling on patients in the second group using 20% SA." Comment: blinding of participants probably insufficient
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The 3rd investigator (3rd author) was blinded from the group allocation and treatment modalities. She did the MASI scoring and evaluation of all patients at all the visits." Comment: binding of investigator probably sufficient
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study, no missing outcome data
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Katsambas 1989a

Study characteristics	
Methods	**Aim of study:** to test whether AZA is an active drug in acne therapy (i.e. is a 20% AZA cream clinically superior to its vehicle?) **Design:** parallel **Unit of allocation:** patients **Allocation:** randomisation; no details **Blinding:** placebo design, double-blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** 12 (13%) of dropouts with reasons
Participants	**Population description:** papulo-pustular acne (degree 2 or 3 of Plewig-Kligmann) **Setting:** not described **Randomised number:** 92 **Age:** 19 (13 to 27) years in treatment group and 19 (14 to 34) years **Sex:** 17/26 in treatment group and 10/39 in control group **Severity of illness:** moderate inflammatory acne
Interventions	**Name of treatment group:** AZA group; **n** = **43** **Description:** 20% AZA cream provided by Schering AG, West Berlin **Treatment period:** 3 months **Timing:** twice daily

Katsambas 1989a *(Continued)*

	Name of treatment group: placebo group; **n** = **49** **Description:** cream base of AZA group **Treatment period:** 3 months **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. 12 withdrawals during the 3-month study **Secondary outcomes** • Change in lesion count (total or inflamed and non-inflamed separately). Median percentage reduction of non-inflamed and inflamed lesion counts, baseline, weeks 4, 8, and 12 • Physicians' global evaluation of acne improvement. Week 12; 4-point system defined by the author (excellent, good, moderate, poor), 75% to 100% reduction of the initial total lesion counts: excellent, 50% to 75% reduction: good, 25% to 50% reduction: moderate, less than 25%: poor response • Minor adverse events (assessed as total number of participants who experienced at least 1 minor adverse event). Reported number of participants who experienced minor adverse events • Quality of life. Authors did not report this outcome
Notes	**Funding:** not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Allocation to treatment with 20% azelaic acid cream or with the cream base was random." Comment: no details of randomisation were described
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "92 patients with papulo-pustular acne were enrolled in a 3-month, double-blind study". Comment: this was a 'double-blind', 'vehicle-controlled' study, blinding probably sufficient
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "92 patients with papulo-pustular acne were enrolled in a 3-month, double-blind study". Comment: this was a 'double-blind', 'vehicle-controlled' study, insufficient information about how blinding of outcome assessor was ensured
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 10% dropout rates in each group with reasons; loss to follow-up is not balanced between groups
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Katsambas 1989b

Study characteristics	
Methods	**Aim of study:** to test how effective AZA cream is against comedonal acne (e.g. as compared with topical tretinoin) **Design:** parallel **Unit of allocation:** patients **Allocation:** unclear **Blinding:** unclear **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** 23 withdrawals due to adverse events; 84 withdrawals (29%) without reasons
Participants	**Population description:** comedonal acne **Setting:** multicentres, no further details **Randomised number:** 289 **Age:** 18 (12 to 38) years in treatment group and 17 (11 to 47) years **Sex:** 71/72 in treatment group and 66/80 in control group **Severity of illness:** comedonal acne
Interventions	**Name of treatment group:** AZA group; **n** = 143 **Description:** 20% AZA cream **Treatment period:** 6 months **Timing:** once a day for the first 2 weeks then twice daily **Name of treatment group:** tretinoin group; **n** = 146 **Description:** 0.05% tretinoin cream **Treatment period:** 6 months **Timing:** once a day for the first 2 weeks then twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Week 24; 4-point system (excellent, good, moderate, poor) • Withdrawal for any reason. 23 withdrawals due to adverse events; 84 withdrawals during the 6-month study **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Median number reduction of non-inflamed and total lesion counts, from baseline to week 24. • Physicians' global evaluation of acne improvement. 4-point system defined by the author; week 24 4-point system defined by the author (excellent, good, moderate, poor), 75% to 100% reduction of initial comedone count: excellent, 50% to 75% reduction: good, 25% to 50% reduction: moderate, less than 25%: poor

Katsambas 1989b *(Continued)*

- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse events
- Quality of life. Authors did not report this outcome

Notes	**Funding:** not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were randomly assigned to treatments..." Comment: no details of random methods were provided
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	84 dropouts (29%) without reasons; all participants analysed but no imputation method reported
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Kessler 2008

Study characteristics

Methods	**Aim of study:** to compare the efficacy of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial AV **Design:** split-face, double-blind, randomised, controlled study **Unit of allocation:** faces **Allocation:** randomisation; no details **Blinding:** double-blind; but only assessors were blinded clearly **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** 3
Participants	**Population description:** mild to moderately severe facial AV **Setting:** University School of Medicine, USA

Kessler 2008 *(Continued)*

	Randomised number: 20 **Age:** 24 (13 to 38) years **Sex:** 7/13 **Severity of illness:** mild to moderately severe
Interventions	**Name of treatment group:** glycolic acid; **n** = 20 faces **Description:** 30% glycolic acid (Glyderm, Valeant Pharmaceuticals Inc. Costa Mesa, CA, formerly ICN Pharmaceuticals Inc.) **Treatment period:** 10 weeks **Timing:** every 2 weeks; 4 to 5 minutes each treatment **Name of treatment group:** SA; **n** = 20 faces **Description:** 30% SA (B-LIFTx, Bradley Pharmaceuticals, Inc., Fairfield, NJ, formerly Bioglan Pharmaceuticals) **Treatment period:** 10 weeks **Timing:** every 2 weeks; 4 to 5 minutes each treatment
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Assessed by completing a questionnaire at the 1-month post-treatment follow-up visit. Split-face design • Withdrawal for any reason. Three dropouts during the 10-week treatment period; split-face design **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Weeks 2, 4, 6, 8, 10 and post-treatment follow-up (weeks 14, and 18), no usable data • Physicians' global evaluation of acne improvement. Five-point system (good: more than 50% improvement, fair: 21% to 50% improvement, poor: 10% to 20% improvement, no change, or worse) assessed at the 1- and 2-month post-treatment follow-up visits. Split-face design • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Authors reported this outcome but no data provided • Quality of life (QoL). Authors did not report this outcome
Notes	**Funding:** not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Treatment sites were randomly assigned before the first treatment visit by assigning one side of the face to receive the 30% glycolic acid...". Comment: no details of random methods were described
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias)	Unclear risk	Although 'double-blind' was mentioned, no details were reported for its identification.

Kessler 2008 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A blinded evaluator performed the quantitative and clinical assessment from baseline through the 2-month follow-up." Comment: blinding probably sufficient
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 dropouts (15%) with reasons and ITT analysis was used
Selective reporting (reporting bias)	Unclear risk	Insufficient data regarding investigator and patient assessment of acne improvement
Other bias	Low risk	No other potential bias identified

Khodaeiani 2013

Study characteristics	
Methods	**Aim of study:** to compare efficacy of the topical 4% nicotinamide and 1% clindamycin gels in participants with AV **Design:** parallel, randomised, double-blind clinical trial **Unit of allocation:** patients **Allocation:** unclear **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** recruited from July 2010 through July 2011 **Dropouts:** none
Participants	**Population description:** moderate inflammatory facial AV (grade III) **Setting:** teaching clinic of dermatology in Iran **Randomised number:** 80 **Age:** 23.88 ± 3.67 in nicotinamide group; 23.25 ± 3.77 in clindamycin group **Sex:** 15/25 in nicotinamide group; 13/27 in clindamycin group **Severity of illness:** moderate inflammatory acne Duration of disease (years): 2.65 ± 0.98 in nicotinamide group; 2.38 ± 0.98 in clindamycin group
Interventions	**Name of treatment group:** nicotinamide group; **n** = **40** **Description:** topical 4% nicotinamide carbomer as a gelling agent, water with methyl alcohol and propyl paraben, glycerin and polyethylene glycol, as well as 4% nicotinamide **Treatment period:** 8 weeks **Timing:** twice daily **Name of treatment group:** clindamycin group; **n** = **40**

Khodaeiani 2013 *(Continued)*

	Description: carbomer as a gelling agent, water with methyl alcohol and propyl paraben, glycerin and polyethylene glycol, as well as 1% clindamycin; triethanolamine as an extra-agent **Treatment period:** 8 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals. **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of inflamed lesion counts, weeks 4 and week 8 • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse events • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Cook's acne grade score
Notes	**Funding:** there was no funding or financial source in support of the present work

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomised in two equal groups to receive either topical 1% clindamycin gel, or topical 4% nicotinamide gel twice daily for eight consecutive weeks." Comment: no details of randomisation method was provided
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both preparations were provided in similar 80 mg tubes marked A or B, known only to the trial coordinator and pharmacy staff." Comment: blinding probably sufficient
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study, no missing outcome data
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Kim 1999

Study characteristics	
Methods	**Aim of study:** to compare the effectiveness of treatment and side effects in the treatment of facial acne by two agents, 70% glycolic acid and Jessner's solution **Design:** split-face **Unit of allocation:** body part **Allocation:** random permuted block method was used **Blinding:** assessor - blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** none
Participants	**Population description:** participants with acne grades of 0.25 to 2.0 (mild to moderate acne by Dr. Cunliffe's grading system) **Setting:** Department of Dermatology, Seoul National University Hospital (Seoul, Korea) **Randomised number:** 26 **Age:** 16 to 27 years old; median age: 19 **Sex (M/F):** 4/22 **Severity of illness:** participants with acne grades of 0.25 to 2.0 (mild to moderate acne by Dr. Cunliffe's grading system)
Interventions	**Name of treatment group:** glycolic acid **n** = 26 **Description:** 70% glycolic acid peel **Treatment period:** six weeks **Timing:** the procedures were repeated 3 times every 2 weeks **Name of treatment group:** Jessner's solution **n** = 26 **Description:** Jessner's solution (resorcinol, SA, lactic acid in ethanol; Delasco, Council Bluffs, IA) **Treatment period:** six weeks **Timing:** the procedures were repeated 3 times every 2 weeks
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Assessed by preference test questions, week 6. No usable data. • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Authors did not report this outcome. • Physicians' global evaluation of acne improvement. Authors did not report this outcome. • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Authors reported minor adverse events with no usable data • Quality of life. Assessed by preference test questions, week 6. No usable data

Kim 1999 *(Continued)*

	Other outcomes that were not analysed in this review • Cunliffe's acne grade score
Notes	**Funding**: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: " For randomisation, we used the random permuted block method to make random allocation of two treatment methods." Comment: random permuted block method was used
Allocation concealment (selection bias)	Unclear risk	Quote: " For randomisation, we used the random permuted block method to make random allocation of two treatment methods." Comment: the authors did not report this issue
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "…the evaluator binding method was used for our study". Comment: insufficient information about how blinding of outcome assessor was ensured throughout the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Twenty-six patients (22 females and 4 males) aged from 16 to 27 years old, completed the clinical trial." Comment: no missing outcome data
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Levesque 2011

Study characteristics

Methods	**Aim of study:** the goal of this study was to compare the safety and efficacy of peels with LHA (lipohydroxy acid) and peels with SA in subjects with comedonal acne **Design:** split-face **Unit of allocation:** body parts **Allocation:** sequentially numbered envelops **Blinding:** investigator-blind **Duration of trial (from recruitment to last follow-up):** recruited between August 2007 and January 2008 **Dropouts:** three

Levesque 2011 *(Continued)*

Participants	**Population description:** adult subjects with at least five non-inflammatory acne lesions on each side of the face and < 30 inflammatory lesions on the entire face **Setting:** Hamzavi Dermatology, USA **Randomised number:** 20 **Age:** 29.0 **Sex:** 1/19 **Severity of illness:** comedonal acne non-inflammatory lesions per hemi-face at Day 14 (baseline) 13.3 ± 7.7 (range 5 to 33)
Interventions	**Name of treatment group:** SA peel; **n** = 20 sites **Description:** 20% or 30%, Biomedic Micropeel Plus; LRP **Treatment period:** 12 weeks (every other week for a total of 6 peels) **Timing:** every other week for a total of six peels **Name of treatment group:** LHA peel; **n** = 20 sites **Description:** LHA: 2-hydroxy 5-octanoyl benzoic acid; 5% or 10%, Biomedic LHA-PEEL, La Roche-Posay Pharmaceutical Laboratories (LRP, Asnieres, France) **Treatment period:** 12 weeks (every other week for a total of 6 peels) **Timing:** every other week for a total of six peels
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. Three dropouts during the 12-week treatment period; split-face design **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of non-inflamed and inflamed lesion counts, weeks 2, 4, 6, 8, 10, and 12 • Physicians' global evaluation of acne improvement. Global acne assessment (1 = worse, 2 = stable, 3 = improved), weeks 2, 4, 6, 8, 10, and 12 • Minor adverse events (assessed as total number of participants who experienced at least 1 minor adverse event). Assessed severity using visual analogue scale • Quality of life. Authors did not report this outcome
Notes	**Funding:** not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation list was prepared manually by the sponsor". Comment: no details of random methods were provided
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were assigned to treatments with sequentially numbered envelopes". Comment: it did not describe whether "sealed" method was used

Levesque 2011 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Board-certified dermatologists who enrolled the subjects and performed the efficacy and tolerance evaluation were kept blinded throughout the study". Comment: whether participants were blinded to treatment was unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Board-certified dermatologists who enrolled the subjects and performed the efficacy and tolerance evaluation were kept blinded throughout the study". Comment: blinding probably sufficient
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three dropouts with reasons, missing data have been imputed using appropriate methods
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

NilFroushzadeh 2009

Study characteristics	
Methods	**Aim of study:** to compare the efficacy of combination treatment of clindamycin + SA, versus clindamycin + tretinoin versus **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** single-blind **Duration of trial (from recruitment to last follow-up):** recruited from September 06 to August 07 **Dropouts:** none
Participants	**Population description:** mild-to moderate AV **Setting:** Skin Disease and Leishmaniasis Research Center and Isfahan University of Medical Sciences clinics, Iran **Randomised number:** 42 **Age:** 15 to 25 years **Sex: (M/F):** 0/42 **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** 1% clindamycin + 2% SA lotion; **n** = 14 **Description:** 1% clindamycin + 2% SA lotion **Treatment period:** 12 weeks **Timing:** twice daily

NilFroushzadeh 2009 *(Continued)*

	Name of control group 1: 1% clindamycin + 0.025% tretinoin; **n** = 14 **Description:** 1% clindamycin + 0.025% tretinoin **Treatment period:** 12 weeks **Timing:** once nightly **Name of control group 2:** 1% clindamycin lotion; **n** = 14 **Description:** 1% clindamycin **Treatment period:** 12 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Week 12, only summary statistics were reported. • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse event • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Acne Severity Index
Notes	**Funding:** not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was a single-blinded clinical trial, no details of randomisation methods were provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients were blinded to the type of treatment". Comment: It did not describe how "blinding" method was used. This study was 'single-blinded', blinding of personnel probably insufficient
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was a 'single-blinded' (patient-blinded) trial, blinding of investigator probably insufficient
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients completed the study." Comment: no missing outcome data

NilFroushzadeh 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No baseline data for each group reported
Other bias	Low risk	No other potential bias identified

Ozkan 2000

Study characteristics	
Methods	**Aim of study:** we investigated the emergence of resistant CNS after 8 weeks of topical therapy with AZA and CDP, and we compared their clinical efficacy **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** no details **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** none
Participants	**Population description:** participants with acne **Setting:** Hospital of Medical Faculty of Osmangazi University, Turkey **Randomised number:** 40 **Age:** 20.85 ± 3.0 in AZA group; 21.75±2.6 in clindamycin group **Sex (M/F):** 5/15 in AZA group; 6/14 in clindamycin group **Severity of illness:** having an acne grade ≤ 3.0 according to the Leeds' acne assessment technique
Interventions	**Name of treatment group:** azelaic acid group; **n** = 20 **Description:** AZA **Treatment period:** 8 weeks **Timing:** twice daily **Name of treatment group:** clindamycin; **n** = 20 **Description:** CDP **Treatment period:** 8 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals. **Secondary outcomes**

Ozkan 2000 *(Continued)*

- Change in lesion counts (total or inflamed and non-inflamed separately). Authors did not report this outcome.
- Physicians' global evaluation of acne improvement. Authors did not report this outcome
- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported skin reactions but no numerical data
- Quality of life. Authors did not report this outcome

Other outcomes that were not analysed in this review

- Microbiological evaluations
- Acne grades, assessed by the Leeds' technique

Notes	**Funding:** not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This study was designed as a randomised and controlled trial". Comment: no details of random methods were described
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment were described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study, no missing outcome data
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Pazoki-Toroudi 2010

Study characteristics

Methods	**Aim of study:** we evaluated the effects of a combination of AA 5% and erythromycin 2% (AzE) on mild to moderate AV **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** double-blind

Pazoki-Toroudi 2010 *(Continued)*

	Duration of trial (from recruitment to last follow-up): recruited between March 2008 and February 2009 **Dropouts:** 21 dropouts
Participants	**Population description:** mild to moderate facial AV **Setting:** three dermatology clinics in Tehran, Iran **Randomised number:** 147 **Age:** placebo group, AA 20% group, erythromycin 2% group and the AzE group was 20.75 ±1.83, 19.24 ± 2.45, 22.1 ± 1.89 and 20.33 ± 2.43 **Sex (M/F):** 86/61 **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** AZA; **n** = 35 **Description:** 20% AA **Treatment period:** 12 weeks. **Timing:** twice daily **Name of treatment group:** Erythromycin; **n** = 31 **Description:** erythromycin 2% **Treatment period:** 12 weeks **Timing:** twice daily **Name of treatment group:** AZA + erythromycin (AzE); **n** = 40 **Description:** AZA 5% + erythromycin 2% **Treatment period:** 12 weeks **Timing:** twice daily **Name of treatment group:** placebo; **n** = 20 **Description:** hydroxypropyl cellulose, propylene glycol, ethyl alcohol, and deionised water **Treatment period:** for 4 weeks and then returned to routine treatment determined by the dermatologist **Timing:** unclear
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Week 12, a five-point Likert-type scale (very satisfied, satisfied, moderately satisfied, unsatisfied, very unsatisfied) • Withdrawal for any reason. 21 dropouts in non-placebo groups (number in each group unknown) during the 12-week treatment period **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Mean non-inflamed and inflamed lesion counts at baseline, weeks 4, 8, and 12 • Physicians' global evaluation of acne improvement. Authors did not report this outcome

Pazoki-Toroudi 2010 *(Continued)*

- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse event
- Quality of life (QoL). Authors did not report this outcome

Notes	**Funding:** not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to four treatment groups". Comment: no details of random methods were provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Both the patients and their dermatologists blinded about the type of treatment". Comment: it did not describe how "blinding" method was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Both the patients and their dermatologists blinded about the type of treatment". Comment: it did not describe how "blinding" method was used. Blinding of outcome assessor unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 21 (14%) dropouts. No ITT analysis. Sufficient reporting of attrition and the number of missing outcome data not considered enough to introduce bias
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Pazoki-Toroudi 2011

Study characteristics

Methods	**Aim of study:** we evaluated the effect of a combination of AA 5% and clindamycin 2% (AA-Clin) on mild to moderate AV **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** recruited from April 2009 to November 2009 **Dropouts:** 6 participants did not refer to the centre in week 8 (3 from AA 5%, 1 from clindamycin 2%, and 2 from AA-Clin group), and 18 participants did not refer to the centre in week 12 (5 from AA 5%, 7 from clindamycin 2%, and 6 from AA-Clin group). For participants who did not refer to the centre at weeks 8 or 12, data for patient's satisfaction were collected from them by calling or inviting for a final

Pazoki-Toroudi 2011 *(Continued)*

	evaluation. Two of these participants did not refer to the centre because of the lack of effect (AA 5% group), and the rest of them for other reasons.
Participants	**Population description:** mild to-moderate facial AV **Setting:** three clinics in Tehran, Iran **Randomised number:** 150 **Age:** clindamycin 2%, AA 5%, and AA-Clin: 23.39 ± 2.69, 22.48 ± 2.50, and 22.1 ± 1.89 **Sex (M/F):** unclear **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** AZA-clindamycin gel (AA-Clin); **n** = 50 **Description:** AZA 5% and clindamycin 2% **Treatment period:** 12 weeks **Timing:** twice daily **Name of control group 1:** topical AZA; **n** = 50 **Description:** AZA 5% **Treatment period:** 12 weeks **Timing:** twice daily **Name of control group 2:** topical Clin; **n** = 50 **Description:** Clin 2% **Treatment period:** 12 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Week 12, a five-point Likert-type scale (very satisfied, satisfied, moderately satisfied, unsatisfied, very unsatisfied) • Withdrawal for any reason. Reported withdrawals at weeks 8 and 12. **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Percentage reduction of total, inflamed, and non-inflamed lesions, weeks 4, 8, and 12 • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse event. • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Acne Severity Index
Notes	**Funding:** all parts of present work was funded by Tehran University of medical Sciences. Comparison of AZA versus Clin was analysed in 'Topical AZA versus any topical treatment'; comparison of AZA-clindamycin gel (AZA-Clin) versus clindamycin was presented in 'Topical AZA versus no treatment'

Pazoki-Toroudi 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were assigned randomly to one of the three treatment groups". Comment: no details of random methods were provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Both patients and their dermatologists were blinded regarding the type of treatment". Comment: no details of blinding methods were provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Both patients and their dermatologists were blinded regarding the type of treatment". Comment: no details of blinding methods were provided. Blinding of outcome assessor unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis used. Missing data have been imputed using appropriate methods.
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Picosse 2015

Study characteristics	
Methods	**Aim of study:** evaluate the efficacy of AZA 15% gel for maintenance treatment for 1 year after oral isotretinoin **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** unclear **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** 7 in AZA group; 12 in control group
Participants	**Population description:** participants with AV who were about to complete the treatment of isotretinoin **Setting:** not described **Randomised number:** 50 **Age:** 14 to 35 (mean 20.2)

Picosse 2015 *(Continued)*

	Sex: not reported **Severity of illness:** not described
Interventions	**Name of treatment group:** AZA; **n** = 25 **Description:** AZA 15% gel **Treatment period:** 12 months **Timing:** twice daily **Name of control group:** control group; **n** = 25 **Description:** control group **Treatment period:** 12 months **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. 19 withdrawals during the 10-month treatment period **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Authors did not report this outcome • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Mentioned minor adverse events but no data available • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Sebum production
Notes	**Funding:** not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned

Picosse 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient reporting of attrition, and the number of missing data considered enough to introduce bias
Selective reporting (reporting bias)	Unclear risk	Study published as abstract only
Other bias	Low risk	No other potential bias identified

Schaller 2016

Study characteristics	
Methods	**Aim of study:** to compare the efficacy, tolerability and safety of a combination of BPO 3% and clindamycin 1% (BPO + CLN) with AZA 20% for the topical treatment of mild to moderate AV **Design:** parallel **Unit of allocation:** individuals **Allocation:** computer-generated schedule was used **Blinding:** assessor-blind **Duration of trial (from recruitment to last follow-up):** recruited between 21 February 2014 and 2 June 2014 **Dropouts:** 7 in AZA group; 4 in BPO + CLN group
Participants	**Population description:** mild to moderate acne **Setting:** 11 study centres in Germany **Randomised number:** 221 **Age:** 12 to 45 years; AZA 20.0 ± 6.9; BPO + CLN 20.1 ± 7.1 **Sex (M/F):** AZA (51/58); BPO + CLN (47/61) **Severity of illness:** participants with mild to moderate acne
Interventions	**Name of treatment group:** AZA **n** = 109 **Description:** AZA 20% cream **Treatment period:** 12 weeks **Timing:** twice daily **Name of treatment group:** BPO + clindamycin **n** = 30 **Description:** BPO 3% + clindamycin 1% gel **Treatment period:** 12 weeks **Timing:** once daily
Outcomes	**Primary outcomes**

Schaller 2016 *(Continued)*

- Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Weeks 2, 4, 8, and 12; 7-point scale, 0 = very much improved, 1 = much improved, 2 = minimally improved, 3 = no change, 4 = minimally worse, 5 = much worse, 6 = very much worse
- Withdrawal for any reason. 11 withdrawals during the 12-week treatment period

Secondary outcomes

- Change in lesion counts (total or inflamed and non-inflamed separately). Percentage reduction of inflamed, non-inflamed, total lesion counts, weeks 2, 4, 8 and 12.
- Physicians' global evaluation of acne improvement. Weeks 2, 4, 8, and 12; a 6-point scale, 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe and 5 = very severe
- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Assessed using a 4-point scale (0-none, 1-slight, 2-moderate, 3-strong); reported number of participants who experienced adverse events
- Quality of life; assessed using the 10-question Children's and Adult Dermatology Life Quality Indices, scored on a 4-point scale, weeks 2, 4, 8, and 12

Other outcomes that were not analysed in this review

- Time to 50% reduction of total lesions

Notes	**Funding**: the study (GSK200398) was funded by Stiefel, a GSK company. MSch has been a member of the advisory board of Bayer Healthcare and Galderma for the past 2 years and has received lecture fees from AbbVie, Bayer Healthcare, Galderma and La Roche-Posay. MSeb has been an advisor or investigator for AbbVie, Novartis, Janssen-Cilag, Lilly, Amgen, Celgene, Galderma, Leo Pharma, GSK, and Pfizer. Three authors are employees of GSK and hold stocks/shares in GSK.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation (1: 1) to treatments was performed using a computer-generated schedule". Comment: computer-generated schedule method was described
Allocation concealment (selection bias)	Unclear risk	We judged an unclear risk of bias because the authors did not report this issue.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients, site staff responsible for distribution and drug accountability and individuals involved in the conduct, analysis and reporting of clinical study data were not blinded to treatment assignment." Comment: we judged a high risk of bias because the authors reported that participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Acne lesion assessors were blinded to treatment. Patients were instructed not to use the study treatments in the presence of the acne assessor". Comment: blinding of outcome assessor probably sufficient
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The drop-out rate was low, with only 15 out of 221 (6.8%) patients leaving the study post-randomisation". Comment: we judged a low risk of bias because the attrition rate was low and similar in both treatment arms. And because the authors performed an ITT analysis including the data of all but four of the randomised participants.
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the study protocol

Schaller 2016 *(Continued)*

Other bias	Unclear risk	Comment: three authors are employees of GSK and hold stocks/shares in GSK. Unclear whether an important risk of bias exists

Shahmoradi 2013

Study characteristics	
Methods	**Aim of study:** this randomised clinical trial evaluated the efficacy of 5% nicotinamide gel versus 2% clindamycin gel in the treatment of mild-moderate AV **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** performed 2009 to 2010 **Dropouts:** none
Participants	**Population description:** mild or moderate AV **Setting:** St-Alzahra hospital, Isfahan University of Medical Sciences, Isfahan, Iran **Randomised number:** 60 **Age:** nicotinamide gel and clindamycin gel: 20.83 ± 3.34 years and 21.17 ± 3.53 years **Sex (M/F):** 0/60 **Severity of illness:** mild or moderate
Interventions	**Name of treatment group:** 5% nicotinamide; **n** = **30** **Description:** 5% nicotinamide gel provided by Isfahan Pharmacy School in the same containers **Treatment period:** 8 weeks **Timing:** twice daily **Name of treatment group:** 2% clindamycin; **n** = **30** **Description:** 2% clindamycin provided by Isfahan Pharmacy School in the same containers **Treatment period:** 8 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Authors did not report this outcome • Physicians' global evaluation of acne improvement. Authors did not report this outcome

Shahmoradi 2013 *(Continued)*

- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Only mentioned that no side effects observed
- Quality of life. Authors did not report this outcome

Other outcomes that were not analysed in this review

- Acne severity index

Notes	**Funding:** not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was a randomised controlled clinical trial. No details of randomisation methods were provided.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Both physicians and patients were blinded to the type of treatment" Comment: the study author did not report blinding method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No one was excluded from the study and all of the participants completed the study.
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Shalita 1981

Study characteristics

Methods	**Aim of study:** to evaluate the treatment of mild and moderate AV with SA in an alcohol-detergent vehicle **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** not described **Duration of trial (from recruitment to last follow-up):** conducted from early March to 6 June 1980 **Dropouts:** none
Participants	**Population description:** mild to moderate acne

Shalita 1981 *(Continued)*

	Setting: not described **Randomised number:** 49 **Age:** 12 to 20 **Sex (M/F):** 17/32 **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** SA; **n** = **25** **Description:** 0.5 % SA in an alcoholic detergent solution (Stri-Dex Medicated pads) **Treatment period:** 12 weeks **Timing:** not reported **Name of treatment group:** placebo; **n** = **24** **Description:** pads soaked in buffered water **Treatment period:** 12 weeks **Timing:** not reported
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. No withdrawals **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Percentage reduction of lesion counts, weeks 4, 8 and 12 • Physicians' global evaluation of acne improvement. Week 12; a 4-point Likert-type scale (excellent, good, fair, poor) • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). No adverse events reported and authors only said side effects were minimal. • Quality of life. Authors did not report this outcome
Notes	**Funding:** none known

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The test products were randomised and coded by the sponsor of the study". Comment: no details of random methods were provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned

Shalita 1981 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	It reported all the 45 participants' results, no missing outcome data
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Shalita 1989

Study characteristics	
Methods	**Aim of study:** to compare the efficacy of a widely used BPO wash with a product incorporating 2% SA in a detergent-based vehicle system **Design:** cross-over **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** not described **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** none
Participants	**Population description:** mild to moderate acne **Setting:** not mentioned **Randomised number:** 30 **Age:** 13 to 31 years **Sex (M/F):** 15/15 **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** SA; **n** = **15** **Description:** SA 2% **Treatment period:** 2 weeks **Timing:** once or twice daily **Name of treatment group:** BPO; **n** = **15** **Description:** 10% BPO wash **Treatment period:** 2 weeks **Timing:** once or twice daily
Outcomes	**Primary outcomes**

Shalita 1989 *(Continued)*

- Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome
- Withdrawal for any reason. No withdrawals

Secondary outcomes

- Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of non-inflamed and inflamed lesion counts, week 2
- Physicians' global evaluation of acne improvement. Authors did not report this outcome
- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Authors did not report this outcome
- Quality of life. Authors did not report this outcome

Notes	**Funding:** this research was supported by a grant from GenDerm Corporation, Northbrook, Illinois

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details of random sequence generation were described
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment were described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study, no missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient reporting data regarding change in inflammatory lesions
Other bias	High risk	No washout period between the first and second phases of the study

Shalita 1995

Study characteristics

Methods	**Aim of study:** to determine the efficacy and safety of topically applied 4% nicotinamide gel compared to 1% clindamycin gel, in treating inflammatory AV **Design:** parallel, active-control **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** double-blinding

Shalita 1995 *(Continued)*

	Duration of trial (from recruitment to last follow-up): not described **Dropouts:** 9 in nicotinamide group; 8 in clindamycin group
Participants	**Population description:** moderate inflammatory AV **Setting:** multicentres in USA **Randomised number:** 76 **Age:** 13 to 35 years (mean age 21.3 years) **Sex (M/F):** 23/53 **Severity of illness:** moderate inflammatory acne; defined by the presence of at least 15 papules and/or pustules on the face
Interventions	**Name of treatment group:** 4% nicotinamide gel; **n** = **38** **Description:** 4% nicotinamide gel **Treatment period:** 8 weeks **Timing:** twice daily **Name of treatment group:** 1% clindamycin gel; **n** = **38** **Description:** 1% clindamycin gel **Treatment period:** 8 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. 17 withdrawals during the 8-week treatment period **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Percentage reduction of inflamed lesions, weeks 4 and 8 • Physicians' global evaluation of acne improvement. Weeks 4 and 8; 5-point scale (+3 = much better, +2 = moderately better, +1 = slightly better, 0 = no change, -1 = worse) • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse event • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Acne severity rating (Allen-Smith Scale)
Notes	**Funding:** supported in part by Genderm Corporation, Lincolnshire, IL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients who met...in a double-blind, randomised manner" Comment: but no details of random sequence generation were described

Shalita 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients who met...in a double-blind, randomised manner" Comment: but no details of blinding method were described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Patients who met...in a double-blind, randomised manner" Comment: but no details of blinding method were described
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Reasons for premature withdrawal included adverse experience (nicotinamide 2), lost to follow-up (nicotinamide 7, clindamycin 5), non-medical reasons (clindamycin 5) or condition unchanged/worsened from baseline (clindamycin 1)". Comment: no ITT analysis with substantial withdrawals, number of missing data considered enough to introduce bias
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the methods section
Other bias	Low risk	No other potential bias identified

Sharquie 2008

Study characteristics	
Methods	**Aim of study:** to evaluate the effectiveness of 2% tea lotion in comparison with 5% zinc sulphate solution in the treatment of AV **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** single-blind **Duration of trial (from recruitment to last follow-up):** conducted from June 2006 to December 2007 **Dropouts**: 7
Participants	**Population description:** mild to moderate facial AV **Setting:** Department of Dermatology and Venereology, Baghdad Teaching Hospital, Baghdad, Iraq **Randomised number:** 47 **Age (years):** both groups 13 to 27 years, mean ± SD 19.5 ± 3.5 years **Sex (M/F):** 14/33 **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** zinc sulphate; **n** = **23**

Sharquie 2008 *(Continued)*

	Description: 5% zinc sulphate solution was prepared by dissolving 5 grams of zinc sulphate crystals in 95 mL of distilled water preservative **Treatment period:** 8 weeks **Timing:** twice daily **Name of treatment group:** tea; **n** = **24** **Description:** the tea leaves (Apple brand mark) were extracted with distilled water (35 gm of tea was mixed with 100 mL boiling hot distilled water for 30 min), then we allowed the tea extract to cool down, and took 100 mL of tea extract and 100 mL of distilled water, and it was weighed. The 2% tea lotion (100 mL) was prepared by adding 75 mL of the tea extract to 25 mL of ethanol, which was used as a preservative. **Treatment period:** 8 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. 7 withdrawals during the 8-week treatment period **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Mean inflamed lesions at baseline and week 8 • Physicians' global evaluation of acne improvement. Week 8; a three-point system (good, moderate, no response) defined by the author, reduction of more than 50% inflamed lesion counts: good; 10% to 50%: moderate; less than 10%: no response • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse events • Quality of life. Authors did not report this outcome
Notes	**Funding**: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were divided randomly into 2 groups. Group A: 24 participants were treated with 2% tea lotion. Group B used 5% zinc sulphate solution. No details of randomisation methods were provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This is a 'single-blind' trial. Unclear which side was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This is a 'single-blind' trial. Unclear which side was blinded
Incomplete outcome data (attrition bias)	High risk	40 participants completed the course of treatment. No ITT analysis, but per protocol analysis performed

Sharquie 2008 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Insufficient data regarding change in inflamed lesion counts
Other bias	Low risk	No other potential bias identified

Stinco 2007

Study characteristics	
Methods	**Aim of study:** to evaluate the sebostatic effect of three anti-acneic ingredients AZA, adapalene and BPO) conveyed in cream and to determine whether there is a correlation with the therapeutic results **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; not reported **Blinding:** not reported **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** four
Participants	**Population description:** mild or moderate comedonal or papulopustular acne **Setting:** not described **Randomised number:** 65 **Age:** 12 to 24 years **Sex:** 35/50 **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** AZA; **n** = **25** **Description:** not reported **Treatment period:** not reported **Timing:** once daily **Name of treatment group:** BPO; **n** = **20** **Description:** not reported **Treatment period:** not reported **Timing:** once daily **Name of treatment group:** adapalene; **n** = **20** **Description:** not reported **Treatment period:** not reported **Timing:** once daily

Stinco 2007 *(Continued)*

	Name of treatment group: volunteers; **n** = **20** **Description:** the same mild detergent **Treatment period:** not reported **Timing:** once daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. Four withdrawals at week 2 **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of inflamed and non-inflamed lesions, week 8 • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse event. Symptoms assessed using a 0-3 scale (0-non, 1-mild, 2-moderate, 3-severe) • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Sebaceous secretion
Notes	**Funding:** not reported Data from the volunteers group was excluded from the analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to one of three groups of treatment". Comment: no details of randomisation methods were provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Sixty-one participants and 16 volunteers completed the study, reasons for attrition reported, the dropouts not considered enough to introduce bias
Selective reporting (reporting bias)	Unclear risk	Insufficient data regarding change in non-inflamed and inflamed lesion counts

Stinco 2007 *(Continued)*

Other bias	Low risk	No other potential bias identified

Techapichetvanich 2011

Study characteristics	
Methods	**Aim of study:** to evaluate efficacy and tolerability of a combination of serial SA peels and topical standard regimen consisting of 5% BPO and 1% clindamycin lotion comparing with topical regimen alone in the treatment of mild to moderately severe facial AV **Design:** parallel, randomised, placebo controlled study **Unit of allocation:** individuals **Allocation:** randomisation; not reported **Blinding:** double-blind **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** unclear
Participants	**Population description:** participants with mild or moderate acne **Setting:** not described **Randomised number:** 37 **Age:** not described **Sex:** not described **Severity of illness:** mild to moderate
Interventions	**Name of treatment group:** SA group; **n** = unclear **Description:** 20% or 30% SA peels **Treatment period:** six weeks **Timing:** once a week **Name of treatment group:** vehicle group; **n** = unclear **Description:** vehicle group **Treatment period:** six weeks **Timing:** once a week
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. Authors did not report this outcome **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of total and non-inflamed lesions, week 10 • Physicians' global evaluation of acne improvement. Authors did not report this outcome

Techapichetvanich 2011 *(Continued)*

- Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Only mentioned side effects from both groups were comparable but no numerical data
- Quality of life. Authors did not report this outcome

Notes	**Funding:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This is a 'double-blind', 'placebo-controlled' trial, blinding probably sufficient.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This is a 'double-blind', 'placebo-controlled' trial, insufficient information about how blinding of assessor was ensured throughout the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This was not stated
Selective reporting (reporting bias)	Unclear risk	Study published as abstract only
Other bias	Low risk	No other potential bias identified

Thielitz 2015

Study characteristics

Methods	**Aim of study**: to evaluate the efficacy of AZA 15% gel versus no treatment during maintenance therapy of female adult acne and to compare its efficacy and safety versus adapalene 0.1% gel (AD) during a 9-month period (3-month treatment and 6-month maintenance treatment) **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; not reported **Blinding:** investigator-blind **Duration of trial (from recruitment to last follow-up):** study period was between August 2011 and October 2012 **Dropouts at the end of treatment phase:** AZA9M (AZA gel twice/day for 9 months): n = 3; AZA3M (AZA gel twice/day for 3 months followed by a 6-month observational phase): n = 2; AD9M (adapalene 0.1% gel once daily for 9 months): n = 1
Participants	**Population description:** adult female participants with mild to moderate acne

Thielitz 2015 *(Continued)*

	Setting: industry-sponsored single-site study in university, Germany
	Randomised number: 55
	Age: AZA9M: 30.58 ± 9.28; AZA3M: 28.14 ± 4.56; AD9M: 28.94 ± 6.71
	Sex: all subjects are females of European origin
	Severity of illness: mild to moderate acne
Interventions	**Name of treatment group:** AZA9M; **n** = 17
	Description: AZA 15% gel twice daily for 9 months
	Treatment period: 36 weeks
	Timing: twice daily
	Name of treatment group: AZA3M; **n** = 19
	Description: AZA gel for three months followed by a six-month observational phase
	Treatment period: 12 weeks
	Timing: twice daily
	Name of treatment group: AD9M; **n** = 19
	Description: adapalene 0.1% gel once daily for nine months
	Treatment period: 36 weeks
	Timing: once daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a 4-point scale: excellent, good, fair, and poor). Weeks 6 and 12; seven grades system 1: very much improved, 2: much improved, 3: improved, 4: unchanged, 5: worse, 6: much worse, 7: very much worse • Withdrawal for any reason. 6 dropouts during the 12-week treatment period **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of total, non-inflamed, and inflamed lesions. Weeks 6 and 12, post-treatment follow-up for 6 months • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Assessed using a 0-3 scale (0-none, 1-slight, 2-moderate, 3-strong). Reported number of participants who experienced minor adverse event • Quality of life (QoL). Dermatology Life Quality Index questionnaire (DLQI) **Other outcomes that were not analysed in this review** • Change in acne severity grade (Leeds Revised Acne Grading Scale)
Notes	**Funding**: Intendis GmbH, Max-Dohrn-Str. 10, 10589 Berlin, Germany. This was an investigator-initiated trial. The funder was not involved in the development of the study protocol, the data collection or analysis and the preparation of the manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement

Thielitz 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "The three arms were randomised in the ratio 1 : 1: 1, using the minimization method of Pocock and Simon and a stratification for age (18–29 years; 30–45 years) and severity classification at study entry..." Comment: minimisation method is reliable for random sequence generation
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study materials were dispensed by a designated person other than the investigator and the subjects were instructed not to discuss the study materials, treatment schedule and potential side-effects with the investigator". Comment: the subjects are not blinded and the investigators seemed blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The study materials were dispensed by a designated person other than the investigator and the subjects were instructed not to discuss the study materials, treatment schedule and potential side-effects with the investigator". Comment: unclear whether outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	The author performed both ITT and per-protocol analysis, reasons for attrition reported
Selective reporting (reporting bias)	Low risk	Results reported for all prespecified outcomes in the study protocol
Other bias	Low risk	No other potential bias identified

Vasarinsh 1969

Study characteristics	
Methods	**Aim of study:** in order to avoid a number of the pitfalls that detract from the value of previous published reports, the present controlled study utilised a variety of criteria, in an attempt to assess several major aspects of a multifaceted condition **Design:** parallel **Unit of allocation:** individuals **Allocation:** randomisation; not reported **Blinding:** double-blind, no details **Duration of trial (from recruitment to last follow-up):** conducted from September 1966 to May 1967 **Dropouts:** 18 dropouts
Participants	**Population description:** consecutive participants applying for acne therapy **Setting:** Wayne State University Health Service, USA **Randomised number:** 72 **Age:** not reported

Vasarinsh 1969 *(Continued)*

	Sex (M/F): 30/42 **Severity of illness:** not reported
Interventions	**Name of treatment group:** sulfur + BPO; **n** = **19** **Description:** sulfur2% and BPO 5% **Treatment period:** minimum four weeks, maximum 14 weeks, average 6.2 weeks **Timing:** overnight or twice daily **Name of treatment group:** BPO; **n** = **16** **Description:** 5% BPO **Treatment period:** minimum four weeks, maximum 14 weeks, average 6.2 weeks **Timing:** overnight or twice daily **Name of treatment group:** sulfur; **n** = **18** **Description:** 2% sulfur **Treatment period:** minimum four weeks, maximum 14 weeks, average 6.2 weeks **Timing:** overnight or twice daily **Name of treatment group:** placebo; **n** = **19** **Description:** not reported **Treatment period:** minimum four weeks, maximum 14 weeks, average 6.2 weeks **Timing:** overnight or twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Numerical point system (greatly improved +2, somewhat improved +1, no change 0, worse -1), time point unclear • Withdrawal for any reason. 18 withdrawals, time point unclear **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Scoring system (unchanged 0, decreased by less than 25% +1, 26% to 50% +2, 51% to 75% +3, 76% to 100% +4, no lesions since previous visit +5; increased by less than 25% -1, 26% to 50% -2, 51% to 75% -3, 76% to 100% -4, over 100% -5) defined by authors, time point unclear • Physicians' global evaluation of acne improvement. Numerical point system (complete improvement +3, moderate improvement +2, slight improvement +1, questionable 0, no change 0, worse -1); scoring system (unchanged or worse: -4 to 0, Minimal improvement: 0.1 to 3.99, moderate improvement: 4.00 to 5.99, good improvement: 6.00 to 8.00); time point unclear • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported number of participants who experienced minor adverse event • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Final scores calculated by using multiple numerical point system
Notes	**Funding:** supported in part by Research Grant AM-07194 and training Grant AM-05267-08 from the National Institutes of Health, U.S Public Health Service, and The Detroit General Hospital Research Corporation.

Vasarinsh 1969 *(Continued)*

In this review, two comparisons were included: sulfur + BPO versus BPO and Sulfur versus BPO.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Medications were assigned in a double-blind randomised manner with..." Comment: but the authors did not mention details on randomisation method
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Medications were assigned in a double-blind randomised manner with..." Comment: but no details on how and who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Medications were assigned in a double-blind randomised manner with..." Comment: but no details on how and who was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	72 participants were accepted for study and 54 participants completed the required observation period. No ITT analysis performed, the number of missing outcome data considered enough to introduce bias significantly
Selective reporting (reporting bias)	Unclear risk	Insufficient reporting about baseline data
Other bias	Low risk	No other potential bias identified

Weltert 2004

Study characteristics

Methods	**Aim of study:** to compare the efficacy of nicotinamide to a reference comparative product in the local treatment of moderate acne with a predominant inflammatory component, i.e. erythromycin **Design:** parallel, active control **Unit of allocation:** individuals **Allocation:** randomisation; no details **Blinding:** unclear **Duration of trial (from recruitment to last follow-up):** not described **Dropouts:** 7 in treatment; 5 in control
Participants	**Population description:** acne with inflammatory predominance **Setting:** Laboratoire Dermscan (Villeurbanne), France, all subjects were Caucasian. **Randomised number:** 158 **Age:** 19.0 +/- 2.7 in treatment; 19.3 +/- 2.9 in control

Weltert 2004 *(Continued)*

	Sex (M/F): 29/50 in treatment; 29/50 in control **Severity of illness:** moderate inflammatory acne on face (≥ 5 inflammatory elements, papules or pustules)
Interventions	**Name of treatment group:** 4% nicotinamide gel; **n** = **79** **Description:** product: Exfoliac NC Gel (Merck Medication Familiale, France) Galenic form: gel Formula: active ingredient: niacinamide 4% Excipients: aqua, alcohol denat., laureth-12, magnesium aluminium silicate, hydroxypropyl methyl cellulose, citric acid **Treatment period:** 8 weeks **Timing:** twice daily **Name of treatment group:** erythromycin; **n** = **79** **Description:** erythromycin, titre 1000 UI/mg Galenic form: liquid gel for local application Formula: active ingredient: erythromycin 4% Excipients: 96% ethyl alcohol, hydroxypropyl cellulose **Treatment period:** 8 weeks **Timing:** twice daily
Outcomes	**Primary outcomes** • Participants' global self-assessment of acne improvement (e.g. measured by a four-point scale: excellent, good, fair, and poor). Authors did not report this outcome • Withdrawal for any reason. 12 withdrawals during the 8-week treatment period **Secondary outcomes** • Change in lesion counts (total or inflamed and non-inflamed separately). Reduction of inflamed and non-inflamed lesions, week 8 • Physicians' global evaluation of acne improvement. Authors did not report this outcome • Minor adverse events (assessed as total number of participants who experienced at least one minor adverse event). Reported percentage of participants who experienced minor adverse event • Quality of life. Authors did not report this outcome **Other outcomes that were not analysed in this review** • Intensity of seborrhoea
Notes	**Funding:** not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although 'randomised' was mentioned, no details were reported for random sequence generation.

Weltert 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 and 5 dropouts in treatment and control group. No imputation method reported, but number of missing data not considered as likely to introduce bias significantly
Selective reporting (reporting bias)	Unclear risk	Insufficient data regarding "Safety" assessed through clinical scoring
Other bias	Low risk	No other potential bias identified

all-TRA: all-trans retinoic acid
AQOL: Acne quality of life
AV: acne vulgaris
AZA: azelaic acid
BPO: benzoyl peroxide
CDP: clindamycin phosphate
CLN: clindamycin
ITT: intention-to-treat
MAS: Michaelsson acne severity
RA: retinoic acid
SA: salicylic acid
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdel 2015	It was reported that "All participants underwent facial chemical peeling: 25% TCA on the right half of their face and 30% salicylic acid on the left half every 2 weeks for 2 months." The whole randomisation remains doubtful: individuals were not randomised because all persons received the same treatment. The side of the face was not randomised because all persons received the test intervention on the right side and the control intervention on the left side. Finally, there was no obvious and no described randomisation.
Anonymous 1996	This report was not a RCT (summary review).
Barak-Shinar 2017	Comparison is salicylic acid + botanicals plus soap versus soap. Botanicals are only given in the treatment group; hence, we cannot determine the efficacy of salicylic acid in the comparison.
Barkovic 2012	The study was published as an abstract. No randomisation was reported or implied. The study author could not be contacted to obtain clarification.
Bissonnette 2009	The type of intervention (lipo hydroxy acid) was ineligible for inclusion.
Breno 2002	The type of intervention (lipo hydroxy acid) was not eligible for inclusion.

Study	Reason for exclusion
Capitanio 2012	The type of interventions was not eligible for inclusion (zinc-oligosaccharide versus vehicle control).
Chantalat 2006a	No randomisation was reported or implied and the study author could not be contacted to obtain clarification.
Chassard 2006	This was a pharmacokinetic study.
Chu 1997	The type of interventions was not eligible for inclusion.
Cochran 1985	The study author could not be contacted and we were unable to obtain clarification. No wording that might connected to a RCT could be found (no randomisation, no concealment, no "accidental" assignment, no generation of randomisation numbers, no central management of allocation).
Coret 2006	The study author could not be contacted and we were unable to obtain clarification. No randomisation was reported or implied.
Cotterill 1980	This report was not a clinical trial (summary review).
Cunliffe 1992	This report was not a RCT (summary review).
Danto 1966	The type of interventions were not eligible for inclusion (5% sulfur-10% benzoyl versus 5% sulphur) and sulphur was the concomitant topical medications for acne vulgaris.
De Bersaques 1972	The type of interventions (topical vitamin A acid) was not eligible for inclusion.
Dos 2003	The study author could not be contacted and we were unable to obtain clarification. No wording that might connected to a RCT could be found (no randomisation, no concealment, no "accidental" assignment, no generation of randomisation numbers, no central management of allocation).
Draelos 2006	There were two studies in this report (Japanese and USA study) and the participants in the two studies were healthy subjects.
Elstein 1981	The type of intervention (sulfurated lime) was ineligible for inclusion.
Fang 2001	Not a RCT
Fu 2003	The type of intervention (lipohydroxyacid) was ineligible for inclusion.
Gebicki 2003	The type of intervention (1-methylnicotinamide) was ineligible for inclusion.
Gollnick 1989	This report was published as a summary review.
Gollnick 1997	This was a non-systematic review (this report was published in German and Frank Peinemann provided the information).
Green 2013	The type of interventions (MaxClarity, Proactiv, Murad) were not eligible for inclusion.
Gupta 2004	This report was published as a review.
Habbema 1989	The type of interventions was not eligible for inclusion.
Hjorth 1989	The report published two studies. The type of comparisons in the two studies were not eligible for inclusion (20% azelaic acid cream versus oral tetracycline).

Study	Reason for exclusion
Khodaeinai 2014	The type of interventions was not eligible for inclusion (10% azelaic acid gel with hydro-alcoholic base versus alcohol-free base).
Kirton 1967	The study design was not eligible for inclusion (non-randomised).
Kreysel 1967	The type of interventions (aknichthol versus aknichthol dexa) were not eligible for inclusion. (This report was published in German and Frank Peinemann provided the information).
Lee 2003	The study design was not eligible for inclusion (not RCT).
Leyden 1997	The participants were not eligible for inclusion (healthy subjects).
Linss 1981	The type of interventions (oral medications) were not eligible for inclusion. (This report was published in German and Frank Peinemann provided the information).
MacDonald 1976	The type of intervention (actinac) was not eligible for inclusion.
Miller 2005	The study was published as an abstract. No randomisation was reported or implied and the study author could not be contacted.
NCT00848744	The trial compared formulations from the same treatment.
Norris 1987	This study was published as a summary of a poster. No randomisation was reported or implied and the study author could not be contacted.
Pastuszka 2012	This paper was published as a review.
Pereira 1994	The study was not described as randomised. All included patients received the same treatment/intervention: salicylic acid and sulphur lotion for topical use. (This study was published in Portuguese and Carolina Freitas provided the information).
Pierard-Franchimont 1995	The participants were not eligible for inclusion (healthy subjects).
Plewig 1969	The type of interventions (vitamin A acid versus sulphur-resorcinol versus benzoyl peroxide) were not eligible for inclusion.
Rougier 2002	The type of intervention (lipohydroxyacid) was ineligible for inclusion.
Sardesai 2003	The study author could not be contacted and we were unable to obtain clarification. No wording that might connect to a RCT could be found (no randomisation, no concealment, no "accidental" assignment, no generation of randomisation numbers, no central management of allocation).
Schachner 1990	The type of interventions were not eligible for inclusion (erythromycin-zinc versus vehicle).
Shemer 2002	All participants received same intervention (non-randomised).
Souza 2005	The participants were not eligible for inclusion as patients with rosacea were included.
Tarimci 1997	The study design was not eligible for inclusion (non-randomised).
Thomas 1951	The study design was not eligible for inclusion (not RCT).
Touitou 2008	The type of interventions was not eligible for inclusion (clindamycin-salicylic acid versus placebo).
van Steenbergen 1968	The study author could not be contacted and we were unable to obtain clarification. There was no wording reported that might be connected to a RCT. No randomisation, no concealment, no "acci-

Study	Reason for exclusion
	dental" assignment, no generation of randomisation numbers, no central management of allocation were founded. (This study was published in German and Frank Peinemann provided the information).
Wang 1997	The study was not randomised due to the patients being divided according to the degree of greasiness of their facial skin.
Wilkinson 1966	The study design was not eligible for inclusion (not RCT).
Wilson 2007	The type of intervention was ineligible for inclusion.
Woodruff 2013	The study was published as an abstract. No randomisation was reported or implied and the study author could not be contacted.

RCT: randomised controlled trial
TCA: trichloroacetic acid

Characteristics of studies awaiting classification *[ordered by study ID]*

Bartosova 1978

Methods	Unknown
Participants	Unknown
Interventions	A: 5% benzoyl peroxide B: 3% salicylic acid C: 5% resorcin
Outcomes	• Changes in the number of comedones
Notes	We had no access to this full report.

Cavicchini 1989a

Methods	Unknown
Participants	Unknown
Interventions	A: 20% azelaic acid B: unknown
Outcomes	• Change in inflamed lesions • Rates of improvement
Notes	We had no access to this full report.

Draelos 2015

Methods	Randomised trial
Participants	80 female/male subjects 12+ years with mild to moderate acne (at least 10 inflammatory and 10 non-inflammatory lesions)
Interventions	A: unclear B: benzoyl peroxide
Outcomes	• Investigator global assessment • Investigator tolerability assessment • Acne lesion characteristics (erythema, lesion height, diameter of inflammation, and amount of pus) • Subject product assessment, and digital photos at baseline, 2, 4, and 12 weeks
Notes	We had no access to this full report.

Giannotti 1989

Methods	Unknown, this report had two studies
Participants	Participants with moderate inflammatory acne; participants with comedo acne
Interventions	A: 20% azelaic acid cream B: vehicle C: 0.05% tretinoin cream
Outcomes	• Change in inflamed and non-inflamed lesions • Clinically-relevant improvement rates • Overall response
Notes	We had no access to this full report.

IRCT201010094269N3

Methods	This is a double-blinded randomised clinical trial
Participants	**Inclusion criteria of the trial** • Gender: both • Participants with mild to moderate acne in age range 11 to 30 years old • Participants who have maximum 20 inflammatory lesions (papules and pustules) on one side of the face and have not more than three nodules or cysts on the same side of the face • Lack of other face dermatosis such as contact dermatitis, allergic or seborrhoeic dermatitis • Patient satisfaction **Exclusion criteria of the trial** • Participants using topical or systemic steroids • Participants using contraceptive pills (anti-androgen)

IRCT201010094269N3 *(Continued)*

	• Participants who used topical or oral anti-acne medications, during the previous month, including natural and UV light and herbal and traditional acne treatments • Other face dermatosis and systemic acne accelerator diseases, such as Cushing's syndrome, polycystic ovary syndrome, adrenal hyperplasia, acquired and innate immune deficiency, steroid acne and acneiform lesions • Participants with more than 20 inflammatory lesions (papules and pustules) and three nodules or cysts on one side of the face • Participants with acne excoriee • Age under 11 y/o and over 30 y/o • Participants with an inflammatory disease, except acne, on the face such as contact dermatitis, allergic or seborrhoeic dermatitis
Interventions	Intervention group: combination of erythromycin 4 g and salicylic acid in 10 cc propylene glycol and alcohol 70 degrees to an overall volume of 100 cc applied to the face with cotton applicator twice a day for 3 months. Control group: combination of erythromycin 4 g in 10 cc propylene glycol and alcohol 70 degrees to an overall volume of 100 cc applied to the face with cotton applicator twice a day for 3 months. Total number of participants enrolled: 50
Outcomes	**Primary outcome of the trial** • Acne severity index. Timepoint: every 15 days. Method of measurement: history, physical examination, counting and statistical evaluation **Secondary outcomes of the trial** • Comedon. Timepoint: every 15 days. Method of measurement: physical examination and counting • Papule. Timepoint: every 15 days. Method of measurement: physical examination and counting • Patient satisfaction. Timepoint: every 15 days. Method of measurement: history • Pustule. Timepoint: every 15 days. Method of measurement: physical examination and counting • Side effect of treatment. Timepoint: every 15 days. Method of measurement: history and physical examination • Total numbers of lesions. Timepoint: every 15 days. Method of measurement: physical examination and counting
Notes	Study completed, no results. The email we sent to the study authors had been rejected for unknown reason.

Kern 2019

Methods	Unknown, this report had two studies. First study - randomised split-face design
Participants	First study: 40 subjects, ages 16 to 25 Second study: 30 subjects, ages 18 to 45
Interventions	First study: cleansing device and salicylic acid cleaner Second study: unknown
Outcomes	• Subject's Investigator Global Acne Assessment • Skin attributes

Kern 2019 *(Continued)*

Notes	Conference abstract only with very limited information. No contact details of the author. Unable to judge whether the study meets all of our inclusion criteria, including diagnosis of acne

NCT00031096

Methods	This is a randomised, double-blind, multicentre study
Participants	**Inclusion criteria of the trial** • Predominantly facial localisation of acne • Mild to moderate acne vulgaris characterised by the presence of both inflammatory papules and/or pustules, and comedones (whiteheads/blackheads), and of a severity suitable for treatment with topical single therapy. • Minimum of 10 and a maximum of 50 inflammatory papules and/or pustules in the facial area and 10 to 100 comedones in the facial area. No more than 3 small nodules (approx. 5 mm in diameter) in the facial area • Male and female participants • Age greater or equal to 12 years • Ability and willingness to accept and comply with the administration of the investigational drugs over 12 weeks and to comply with the required medical examinations (signed informed consent) **Exclusion criteria of the trial** • Localisation of acne predominantly on the chest and/or the back or confined to the chest and/or the back • Sandpaper acne with hundreds of small facial comedones • Moderate or severe acne requiring systemic therapy • Multitude of small nodules and/or multiple large nodules, cysts, polyporous comedones, draining sinuses e.g. nodulocystic/conglobate acne • Other skin conditions that might interfere with acne diagnosis and/or evaluation (such as facial psoriasis, seborrhoeic dermatitis, perioral dermatitis and papulopustular rosacea) • Anticipated or scheduled hospitalisation, e.g. for surgery, during the study • Female participants who have not continuously used their present brand of oral contraceptive (if any) or other hormone therapy for at least 3 months • Continuous concurrent use of any topical and/or systemic treatment which affects acne • History of hypersensitivity to any ingredient of the trial drugs • Concurrent involvement in another investigational study or participation within 30 days prior to the start of this study • Must not have taken or have had the following types of treatment or therapy prior to being admitted into the study: oral isotretinoin (i.e. Accutane) for 6 months; Ortho Tri-Cyclen or Estrostep for 3 months; oral antibiotics (i.e. tetracyclines, erythromycin) for 4 weeks; systemic corticosteroids for 4 weeks; systemic non-steroidal anti-inflammatory drugs (NSAIDs) at anti-inflammatory doses for 4 weeks; topical (applied to skin) retinoid creams, ointments, gels for 2 weeks; topical antibiotics (i.e. tetracyclines, erythromycin, clindamycin) for 2 weeks; topical corticosteroids or topical non-steroidal anti-inflammatory (NSAIDs) drugs for 2 weeks; topical imidazole antimycotics for 2 weeks; topical benzoyl peroxide (BPO) for 2 weeks; topical over-the-counter remedies for acne (salicylic acid) for 2 weeks. If participants had any of the above, they may still qualify for the study following a washout period (time for the body to completely eliminate, or get rid of, the medication). The study doctor will evaluate whether there is anything else in the participants' history that may affect their safety in the study or interfere with evaluations. Participants may therefore be advised not to participate.
Interventions	A: Azelaic Acid 15% gel (SH H 655 BA) applied topically two times per day for 12 weeks (number of participants unclear)

NCT00031096 *(Continued)*

	B: Vehicle gel (SH H 655 PBA) applied topically two times per day for 12 weeks (number of participants unclear) Total estimated number of participants enrolled: 879
Outcomes	**Primary outcome of the trial** • The nominal and percentage change in lesion counts from baseline to last available visit (end of treatment) and treatment success rates based on investigator's assessment of mild to moderate acne (time frame: 12 weeks) **Secondary outcomes of the trial** • Investigator's rating of overall improvement and participant's self-assessment of overall improvement and cosmetic acceptability (time frame: 12 weeks) • Adverse event reports and participant's opinion on local tolerability of the study gels at the end of study (time frame: 12 weeks)
Notes	The study is sponsored by Bayer company. Completed, but no results posted.

NCT02755545

Methods	This is a randomised, double-blind, multicentre trial
Participants	**Inclusion criteria of the trial** • Men and women age 21 to 45 years at the time of enrolment • Individuals with mild to moderate acne (score of 2 to 3 on FDA Investigator's Global Assessment Scale 1) on the face • Individuals with at least 5 inflammatory lesions • Individuals with 10 - 100 non-inflammatory lesions • Fitzpatrick skin type I-VI • Individuals willing to provide written informed consent including photo release, Health Insurance Portability and Accountability Act (HIPAA), and are able to read, speak, write, understand English • Willing to withhold all facial treatments during the course of the study • Individuals of child-bearing potential who use an acceptable method of contraception throughout the study • Subjects must be stable on any medication they are taking for at least 30 days **Exclusion criteria of the trial** • Individuals diagnosed with allergies to topical acne products • Individuals having a condition and/or disease of the skin that the Investigator deems inappropriate for participation • Women who are nursing, pregnant, or planning to become pregnant during the study • Individuals who have pre-existing or dormant dermatologic conditions on the face which in the opinion of the investigator could interfere with the outcome of the study • Individuals using or who have used any systemic medication considered to affect the course of acne, specifically, but not exclusively antibiotics or steroids within the last 30 days prior to entry into the study • Individuals who are currently participating in another facial usage study or have participated in a clinical trial within 4 weeks prior to inclusion into the study • Individuals with any planned surgeries and/or invasive medical procedures during the course of the study

NCT02755545 *(Continued)*

	• Individuals who started hormone replacement therapy (HRT) or hormones for birth control less than 3 months prior to study entry or who plan on starting, stopping, or changing doses of HRT or hormones for birth control during the study • Individuals with facial sunburn or excessive tanned facial skin or that are not willing to avoid daily sun exposure on the face and the use of tanning beds or sunless tanning products for the duration of the study • Individuals currently taking or have taken within the last 30 days oral or topical prescription medications for acne
Interventions	A: adapalene applied topically to the entire face or other affected area of the skin once daily (number of participants unclear) B: salicylic acid applied topically to affected area of the skin one to three times daily (number of participants unclear) Total estimated number of participants enrolled: 127
Outcomes	**Primary outcome of the trial** • Percentage change in total lesions at week 12 from baseline (time frame: 12 weeks). Percentage change from baseline assessment at week 12, as assessed by investigator or designee **Secondary outcomes of the trial** • Mean change in inflammatory lesion count (time frame: week 1, week 2, week 6, week 12, week 18, week 24). Mean change from baseline assessments at week 1, week 2, week 6, week 12, week 18, and week 24 as assessed by investigator or designee. Note that papules and pustules are classified as inflammatory acne lesions. • Mean change in non-inflammatory lesion count (time frame: week 1, week 2, week 6, week 12, week 18, week 24). Mean change from baseline assessments at week 1, week 2, week 6, week 12, week 18, and week 24 as assessed by investigator or designee. Note that open and closed comedones are classified as non-inflammatory acne lesions. • Mean change in Investigator's Global Assessment (IGA) (time frame: week 1, week 2, week 6, week 12, week 18, week 24). Mean change from baseline assessments at week 1, week 2, week 6, week 12, week 18, and week 24 as assessed by investigator or designee using the IGA scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe). • Mean change in skin texture (digital images) (time frame: week 6, week 12, week 24). Mean change from baseline efficacy parameter assessment at week 6, week 12, and week 24 as assessed by trained evaluator. The efficacy parameter will be assessed globally using a modified Griffiths' 10-point scale according to the following numerical definitions (half-point scores may be used as necessary to more accurately describe the skin condition): 0 = none (best possible condition); 1 to 3 = mild; 4 to 6 = moderate; 7 to 9 = severe (worst possible condition) • Mean change in skin tone evenness (digital images) (time frame: week 6, week 12, week 24). Mean change from baseline efficacy parameter assessment at week 6, week 12, and week 24 as assessed by trained evaluator. The efficacy parameter will be assessed globally using a modified Griffiths' 10-point scale according to the following numerical definitions (half-point scores may be used as necessary to more accurately describe the skin condition): 0 = none (best possible condition); 1 to 3 = mild; 4 to 6 = moderate; 7 to 9 = severe (worst possible condition) • Mean change in skin clarity (digital images) (time frame: week 6, week 12, week 24). Mean change from baseline efficacy parameter assessment at week 6, week 12, and week 24 as assessed by trained evaluator. The efficacy parameter will be assessed globally using a modified Griffiths' 10-point scale according to the following numerical definitions (half-point scores may be used as necessary to more accurately describe the skin condition): 0 = none (best possible condition); 1 to 3 = mild; 4 to 6 = moderate; 7 to 9 = severe (worst possible condition) • Mean change in overall skin complexion (digital images) (time frame: week 6, week 12, week 24). Mean change from baseline efficacy parameter assessment at week 6, week 12, and week 24 as assessed by trained evaluator. The efficacy parameter will be assessed globally using a modified Griffiths' 10-point scale according to the following numerical definitions (half-point scores may be used as necessary to more accurately describe the skin condition): 0 = none (best possible condition); 1 to 3 = mild; 4 to 6 = moderate; 7 to 9 = severe (worst possible condition)

NCT02755545 *(Continued)*

	• Subject self-assessment questionnaire (time frame: week 1, week 2, week 6, week 12, week 24). Subjects will be asked to complete a self-assessment questionnaire at week 1, week 2, week 6, week 12, and week 24. This questionnaire has a 5-point Likert Response scale (1 = strongly agree; 5 = strongly disagree). • Incidence of adverse events (time frame: 24 weeks) • Mean change in erythema (tolerance) parameter (time frame: baseline, week 1, week 2, week 6, week 12, week 24). Investigator-reported erythema evaluations will be performed at baseline and weeks 1, 2, 6, 12, and 24 using a 4-point scale (0 = none; 3 = severe) • Mean change in dryness (tolerance) parameter (time frame: baseline, week 1, week 2, week 6, week 12, week 24). Investigator-reported dryness evaluations will be performed at baseline and weeks 1, 2, 6, 12, and 24 using a 4-point scale (0 = none; 3 = severe) • Mean change in scaling (tolerance) parameter (time frame: baseline, week 1, week 2, week 6, week 12, week 24). Investigator-reported scaling evaluations will be performed at baseline and weeks 1, 2, 6, 12, and 24 using a 4-point scale (0 = none; 3 = severe) • Mean change in stinging/burning (tolerance) parameter (time frame: baseline, week 1, week 2, week 6, week 12, week 24). Subject-reported stinging/burning evaluations will be performed at baseline and weeks 1, 2, 6, 12, and 24 using a 4-point scale (0 = none; 3 = severe)
Notes	This study is sponsored by Galderma Laboratories, LP. Completed but no results posted.

Pisani 1991

Methods	Unknown
Participants	Unknown
Interventions	Unknown
Outcomes	Unknown
Notes	We had no access to this full report.

Ponzio 1994

Methods	Randomised trial
Participants	Seventy volunteers, aged 12 to 17, with initial forms of acne
Interventions	Triclosan and salicylic acid
Outcomes	• Acne lesions • Facial seborrhoea
Notes	We had no access to this full report.

TCTR20190118001

Methods	A randomised, double-blinded, split-face, controlled trial
Participants	**Inclusion criteria of the trial**

TCTR20190118001 *(Continued)*

	Gender: both Age limit: minimum 18 Years: maximum 99 Years • Males and females with acne vulgaris aged 18 years old • Should have at least 10 inflammatory and/or non-inflammatory lesions on each side of the face • Have acne for more than 6 months **Exclusion criteria of the trial** • Other forms of acne: acne conglobata, acne excoriate, acne rosacea, acne cosmetica, acne pomade, acne fulminans, acne keloidalis, nuchae acne, chloracne acne, mechanica, and acne medicamentosa • Nodulocystic acne • On oral antibiotic for the last 1 months • On oral isotretinoin for the last 6 months • On topical antimicrobial or tretinoin for the last 2 weeks • Photosensitivity • Recent 2 to 6 months facial undermining surgery blepharoplasty rhytidectomy brow lift liposuction in the treatment area • If there is any active or past infection such as HSV herpes zoster infection • If there is any active bacterial folliculitis at this moment • History of keloid • Poor skin turgor • If patient is currently pregnant or lactating • Other comorbidities, especially immunocompromising diseases possibility of delay healing increased susceptibility to infection or excessive pigmentation after peeling • If there is any known allergy to the active ingredients in the preparation • Participants who have any other dermatoses especially facial dermatoses • Participants who like outdoor activities and could not comply with sun protection • Fitzpatrick skin type I II • Participants who had a difference of 2 grades or above comparing one side of the face to another
Interventions	A: Jessner's solution B: Salicylic acid 30% Total number of participants enrolled: 35
Outcomes	**Primary outcome of the trial** • Changes in total number of inflammatory lesions and non-inflammatory lesions. (time frame at each clinic visit lesions count) **Secondary outcomes of the trial** • Changes in post acne hyperpigmentation index (PAHPI) (time frame at each clinic visit: PAHPI) • Changes in the Michaelson Acne Score (MAS) (time frame at each clinic visit: Michaelsson Acne Score) • The frequency of overall adverse reaction towards the treatment (time frame at each clinic visit: frequency) • The participant's satisfaction towards the treatment (time frame at last clinic visit: Visual Analogue Scale)
Notes	Recruitment status: completed (no results provided) Source(s) of monetary or material support: Dermatological Society of Malaysia

Zheng 2019

Methods	A randomised, split-face, open-label, single-centre study
Participants	Subjects with mild to moderate acne
Interventions	A: 2% supramolecular salicylic acid B: 0.01% adapalene plus 5% benzoyl peroxide
Outcomes	• Acne lesions • Side effects • Skin water content • Skin lightening indexes
Notes	Cannot access full-text journal article

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR1800018343

Study name	Comparative study for salicylic acid vs glycolic acid in the treatment of mild-to-moderate acne vulgaris
Methods	Randomised parallel controlled trial
Participants	**Inclusion criteria of the trial** • Either sex aged 18 to 45 years (inclusive) • Mild to moderate facial acne vulgaris, with total lesion count less than 100, inflammatory lesion count between 5 and 40, no cyst or nodule • No treatment received in the past 3 months **Exclusion criteria of the trial** • Pregnancy or breastfeeding • Other physical or mental disease • Secondary acne and sever acne • Skin lesions (herpes, warts, wound et al) on face • Patient who has to take anti-acne medicine during the trial, e.g.: antibiotics, oral contraceptives • Patient who has received laser treatment and dermabrasion • Known allergy to glycolic acid or salicylic acid • Patient who is not able to avoid sunlight
Interventions	A: Salicylic acid peel B: Glycolic acid peel Total estimated number of participants enrolled: 60
Outcomes	**Primary outcome of the trial** • Percentage change in Inflammatory lesion count **Secondary outcomes of the trial** • Percentage change in non-Inflammatory lesion count

ChiCTR1800018343 *(Continued)*

	• Percentage change in total lesion count • Incidence of adverse events • Skin physiological function • Subject's global change assessment • Investigator's Static Global Assessment Definition: not provided. Visits: not provided.
Starting date	November 2018
Contact information	Name: Jiang Xian Address: 37 Guoxue Xiang, Wuhou District, Chengdu China, 610041 Telephone: +86 18980601693 Email: jennyxianj@163.com Affiliation: West China Hospital, Sichuan University Name: Li Xiaoxue Address: 37 Guoxue Xiang, Wuhou District, Chengdu China, 610041 Telephone: +86 15528260238 Email: li-xiaoxue@foxmail.com Affiliation: West China Hospital, Sichuan University Apps.who.int-ID: ChiCTR1800018343
Notes	Recruiting, Self-raised trial

CTRI/2018/06/014615

Study name	Comparative efficacy of glycolic acid 35% vs salicylic acid 20% peel in acne vulgaris
Methods	Randomised, parallel group trial
Participants	**Inclusion criteria of the trial** • Participants of active facial acne of grade 1 and 2, not requiring systemic therapy • Participants of either sex, age more than 18 years Mild acne (grade 1): comedones < 30; predominance of comedones papules < 10; No scarring Moderate acne (grade 2): comedones any number; predominance of papules > 10; nodules < 3; scarring +/- Severe acne (grade 3): comedones any number; many nodules; papules any number; nodules/cysts > 3; scarring + **Exclusion criteria of the trial** • Participants with active facial dermatitis or infection, polycystic ovarian disease, endocrine abnormality and tendency for keloid and hypertrophic scars • Participants who have taken oral retinoids in the last 6 months

CTRI/2018/06/014615 *(Continued)*	• Pregnant and lactating participants • Participants with known hypersensitivity to glycolic acid or salicylic acid Age minimum: not provided Age maximum: not provided Gender: not provided
Interventions	Group 1 participants will be given 35% glycolic acid (GA) peels which will be applied for a period of 3 minutes or until appearance of erythema, whichever is earlier. The applied GA shall be neutralised with 10% sodium bicarbonate solution and distilled water soaked gauze pads. Group 2 participants will be given 20% salicylic acid (SA) peels which will be applied until there is uniform light white coat of pseudo frost. After pseudo frosting, the peel will be washed away with distilled water. Total estimated number of participants enrolled: 60
Outcomes	**Primary outcome of the trial** • To study the comparative efficacy of 35% glycolic acid versus 20% salicylic acid peel in acne vulgaris. Timepoint: baseline (0 week) - 1st peel; 2nd week - 2nd peel; 4th week - 3rd peel; 6th week - 4th peel; 8th week - follow-up **Secondary outcomes of the trial** • To study the adverse effects, if any, associated with these peeling agents. (persistent erythema, burning, pain, pruritus, transient hyperpigmentation, hypopigmentation, oedema, acneiform eruption, allergic reaction, scarring, folliculitis, desquamation, post-peel cracking, any other). Timepoint: baseline (0 week) - 1st peel; 2nd week - 2nd peel; 4th week - 3rd peel; 6th week - 4th peel; 8th week - follow-up Definition: not provided Visits: see above
Starting date	July 2018
Contact information	Name: Dr Gurvinder Pal Thami Address: Department of Dermatology, Government Medical College and Hospital, Sector 32, Chandigarh 160030 Chandigarh, CHANDIGARH India Telephone: not provided Email: thamigp@gmail.com Affiliation: Government Medical College and Hospital, Chandigarh Name: Dr Purva Pande Address: Department Of Dermatology, Government Medical College and Hospital, Sector 32, Chandigarh 160030 Chandigarh, India Telephone: not provided Email: thamigp@gmail.com Affiliation: Government Medical College and Hospital, Chandigarh Apps.who.int-ID: CTRI/2018/06/014615
Notes	Not yet recruiting

NCT03832647

Study name	Anti-acne efficacy of a dermo-cosmetic product associated with the fixed combination adapalene 0.1%/benzoyl peroxide 2.5% treatment versus this treatment associated with a standard moisturizer in male and female subjects presenting with mild to moderate acne
Methods	A randomised, double-blinded trial
Participants	**Inclusion criteria of the trial** • Male and/or female subjects aged 16 to 35 years • Subjects presenting with mild to moderate acne (stage 2 or stage 3 with at least 12 inflammatory lesions on face according to the Global Acne Evaluation) • Female subjects of child-bearing potential who use the same reliable hormonal contraceptive method (oral contraceptive, implant, intrauterine device, patch, cervical cap, vaginal ring and injection) for at least 3 months prior to study inclusion and throughout the study or use a reliable non-hormonal contraceptive method (copper intrauterine device, condoms, diaphragm, cervical cap and spermicide) for at least 1 month prior to study inclusion and throughout the study or have no sexual intercourse and agreeing not to have any throughout the study or are surgically sterile (oophorectomy, hysterectomy or tubal ligation) • Subjects and/or all legal representatives (for minor subjects) who have given written informed consent • Subjects who are willing to comply with the study requirements • Subjects with social security (health insurance) coverage (according to French requirements) **Exclusion criteria of the trial** • Subjects with any systemic disorder or face dermatoses other than acne that would in any way confound interpretation of the study results (e.g. atopic dermatitis, eczema, or psoriasis) • Subjects with a condition or receiving a medication and/or with a history of medical/surgical events which, in the opinion of the investigator, could compromise the safety of the subject or affect the outcome of the study • Subjects with a history of skin cancer • Female subjects who are pregnant (positive urine pregnancy test) or lactating or who are planning to become pregnant during the study • Subjects who have started, stopped or changed of hormonal treatment (contraception, thyroid) in the 3 months prior to study inclusion • Subjects with hypersensitivity to the active substances of Epiduo (adapalene and/or benzoyl peroxide) or to one of its excipients • Subjects who are sensitive to peroxides (oxygenated water) • Subjects who have received isotretinoin treatment in the 6 months prior to study inclusion • Subjects who have been exposed to excessive UV light (natural or artificial) in the 1 month prior to the study inclusion or having planned excessive UV light exposure during the study (e.g. ski holidays, holidays in the tropic) • Subjects who have used systemic drugs for more than 3 consecutive days related to antibiotics, anti-inflammatory, corticoids, anti-acneic in the 4 weeks prior to study inclusion • Subjects who have used topical drugs for more than 3 consecutive days related to antibiotics, anti-inflammatory, corticoids, anti-acneic in the 2 weeks prior to study inclusion • Subjects who have used scrub, anti-seborrheic topical cosmetic products and/or who have applied self-tanning products on face in the 1 week prior to study inclusion • Subjects who have applied cosmetic products for more than 5 consecutive days with alpha hydroxyl-acids, vitamin C, hyaluronic acids in the 1 week prior to study inclusion • Subjects having washed the face and/or the hair on the day of study inclusion (only water is accepted the morning of the study inclusion) • Subjects having applied any topical products on face (including make-up) on the day of study inclusion

NCT03832647 *(Continued)*

- Subjects who have planned a major surgery during the study requiring hospitalisation under general anaesthesia and the use of systemic or topical drugs (e.g. antibiotics, anti-inflammatory) for more than 1 week
- Subjects who declare to be deprived of their freedom by administrative or legal decision or who are under guardianship
- Subjects who cannot be contacted by telephone in case of emergency
- Subjects belonging to the staff of the study centre
- Subjects in an exclusion period or participating in another biomedical research study

Age: 16 to 35 years

Gender: both

Interventions	Experimental group: Salicylic acid and Epiduo 0.1% to 2.5% topical gel. Salicylic acid once-a-day in the morning during 12 weeks and Epiduo gel once-a-day in the evening (before bedtime) over 12 weeks. Placebo comparator group: moisturiser and Epiduo 0.1% to 2.5% topical gel moisturiser: once-a-day, in the morning, over 12 weeks. Epiduo gel: once-a-day, in the evening (before bedtime) over 12 weeks. Total estimated number of participants enrolled: 200
Outcomes	**Primary outcome of the trial** • Evaluation of anti-acne efficacy 1 (number of retentional and inflammatory lesions) (time frame: week 0 (baseline) and week 12 (final time point)). Change in the number of retentional (open and closed comedones) and inflammatory lesions (papulae, pustule and nodules (if applicable)) on face after a 12-week application period. At week 0 (before any application) and week 12 (after a 12-week application period), a counting of the retentional (open and closed comedones) and inflammatory lesions (papulae, pustule and nodules (if applicable)) will be performed by a Dermatologist. The counting will be broken down on several parts of the face (forehead, left and right cheeks and chin). **Secondary outcomes of the trial** • Evaluation of anti-acne efficacy 2 (number of retentional and inflammatory lesions) (time frame: week 4 and week 8 (intermediary times point)). Change in the number of retentional (open and closed comedones) and inflammatory lesions (papulae, pustule and nodules (if applicable)) on face after 4- and 8-week application period. At week 4 (after 4-week application) and week 8 (after 8-week application period), counting of the retentional (open and closed comedones) and inflammatory lesions (papulae, pustule and nodules (if applicable)) will be performed by a dermatologist. Counting will be broken down on several parts of the face (forehead, left and right cheeks and chin). • Change in acne stage on face according to the Global Acne Evaluation scale after 4-, 8- and 12-week application period (time frame: week 0 (baseline), week 4 and week 8 (intermediary times point) and week 12 (final time point)). At week 0 (before any application), week 4 (after a 4-week application period), week 8 (after an 8-week application period) and week 12 (after a 12-week application period), determination of the acne stage will be performed by the dermatologist according to the Global Acne Evaluation scale (score min: 0 to score max: 5). The more the score decreased, the more efficient the treatment. • Change in visibility of residual marks after 4-, 8- and 12-week application period (time frame: week 0 (baseline), week 4 and week 8 (intermediary times point) and week 12 (final time point)). At week 0 (before any application), week 4 (after a 4-week application period), week 8 (after an 8-week application period) and week 12 (after a 12-week application period), the visibility of residual marks of acne (hyperpigmentation) will be assessed under the same conditions by the dermatologist using the scale below, which include 10 grades (0: absence to 9: numerous). The more the score decreased, the more efficient the treatment. • Change in pore visibility after 4-, 8- and 12-week application period (time frame: week 0 (baseline), week 4 and week 8 (intermediary times point) and week 12 (final time point)). At week 0 (before

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any application), week 4 (after a 4-week application period), week 8 (after an 8-week application period) and week 12 (after a 12-week application period), pore visibility will be assessed under the same conditions by the dermatologist using the scale below, which included 10 grades (0: absence to 9: numerous). The more the score decreased, the more efficient the treatment.

- Change in skin shininess after 4-, 8- and 12-week application period (time frame: week 0 (baseline), week 4 and week 8 (intermediary times point) and week 12 (final time point)). At week 0 (before any application), week 4 (after a 4-week application period), week 8 (after an 8-week application period) and week 12 (after a 12-week application period), skin shininess will be assessed under the same conditions by the dermatologist using the scale below, which included 10 grades (0: absence to 9: high). The more the score decreased, the more efficient the treatment.
- Change in skin greasiness after 4-, 8- and 12-week application period (time frame: week 0 (baseline), week 4 and week 8 (intermediary times point) and week 12 (final time point)). At week 0, week 4, week 8 and week 12, instrumental measurements will be performed by a technician/a nurse. The CL measurements (quantity of sebum (casual level)) will be taken using a SEBUMETER. The unit is in µg sebum/cm² of the skin. Only one measurement per subject will be taken in the middle of the forehead. The more the value decreased, the less greasy the skin.
- Change in skin moisturising after 4-, 8- and 12-week application period (time frame: week 0 (baseline), week 4 and week 8 (intermediary times point) and week 12 (final time point)). At week 0, week 4, week 8 and week 12, instrumental measurements will be performed by a technician/a nurse. The measurements will be taken using a CM 825 PC CORNEOMETER. Hydratation values are expressed in arbitrary units ranging from approximately 0 to 120. Three measurements per subject will be taken on the right cheekbone. The more the value increased, the more the skin is moisturised.
- Change in skin ph after 4-, 8- and 12-week application period (time frame: week 0 (baseline), week 4 and week 8 (intermediary times point) and week 12 (final time point)). At week 0, week 4, week 8 and week 12, instrumental measurements will be performed by a technician/a nurse. The measurements will be taken using a SKIN PH METER 900. The result will be expressed in pH units. Only one measurement per subject will be taken on the left cheek, near to the side of the nose. The more the value decreased, the more acidic the ph.
- Total number of hair follicles per cube at a mean depth of 38 µm after a 12-week application period (time frame: week 0 (baseline) and week 12 (final time point)). At week 0 and week 12, instrumental measurements will be performed by investigator at CHU Nantes. Confocal images are obtained by analysing the reflection of a diode laser in the skin. The lens will be directly applied to the selected skin area (on 3 non-lesional skin areas: forehead, right temple and right mandibular). Confocal images will be analysed by two confocal microscopy experts.
- Diameter of the infundibulum in µm after a 12-week application period (time frame: week 0 (baseline) and week 12 (final time point)). At week 0 and week 12, instrumental measurements will be performed by investigator at CHU Nantes. Confocal images are obtained by analysing the reflection of a diode laser in the skin. The lens will be directly applied to the selected skin area (on 3 non-lesional skin areas: forehead, right temple and right mandibular). Confocal images will be analysed by two confocal microscopy experts.
- Aspect of the border (thickness) (number and percentage) after a 12-week application period (time frame: week 0 (baseline) and week 12 (final time point)). At week 0 and week 12, instrumental measurements will be performed by investigator at CHU Nantes. Confocal images are obtained by analysing the reflection of a diode laser in the skin. The lens will be directly applied to the selected skin area (on 3 non-lesional skin areas: forehead, right temple and right mandibular). Confocal images will be analysed by two confocal microscopy experts.
- Onion-like appearance (number and percentage) after a 12-week application period (time frame: week 0 (baseline) and week 12 (final time point)). At week 0 and week 12, instrumental measurements will be performed by investigator at CHU Nantes. Confocal images are obtained by analysing the reflection of a diode laser in the skin. The lens will be directly applied to the selected skin area (on 3 non-lesional skin areas: forehead, right temple and right mandibular). Confocal images will be analysed by two confocal microscopy experts.
- Presence of amorphous material into the infundibulum (number and percentage) after a 12-week application period (time frame: week 0 (baseline) and week 12 (final time point)). At week 0 and week 12, instrumental measurements will be performed by investigator at CHU Nantes. Confocal images are obtained by analysing the reflection of a diode laser in the skin. The lens will be directly applied onto the selected skin area (on 3 non-lesional skin areas: forehead, right temple and right mandibular). Confocal images will be analysed by two confocal microscopy experts.

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- Signs of inflammation (number and percentage) after a 12-week application period (time frame: week 0 (baseline) and week 12 (final time point)). At week 0 and week 12, instrumental measurements will be performed by investigator at CHU Nantes. Confocal images are obtained by analysing the reflection of a diode laser in the skin. The lens will be directly applied onto the selected skin area (on 3 non-lesional skin areas: forehead, right temple and right mandibular). Confocal images will be analysed by two confocal microscopy experts.
- Vascularisation (number and percentage) after a 12-week application period (time frame: week 0 (baseline) and week 12 (final time point)). At week 0 and week 12, instrumental measurements will be performed by investigator at CHU Nantes. Confocal images are obtained by analysing the reflection of a diode laser in the skin. The lens will be directly applied onto the selected skin area (on 3 non-lesional skin areas: forehead, right temple and right mandibular). Confocal images will be analysed by two confocal microscopy experts.
- Presence of demodex mites (number and percentage) after a 12-week application period (time frame: week 0 (baseline) and week 12 (final time point)). At week 0 and week 12, instrumental measurements will be performed by investigator at CHU Nantes. Confocal images are obtained by analysing the reflection of a diode laser in the skin. The lens will be directly applied onto the selected skin area (on 3 non-lesional skin areas: forehead, right temple and right mandibular). Confocal images will be analysed by two confocal microscopy experts.
- Analysis of the efficacy on the skin quality using a questionnaire (time frame: week 12 (final time point)). Subjects will complete an efficacy questionnaire at the last visit (after a 12-week application period of the Investigational Product (cosmetic product and drug)). The following items will be evaluated by the subjects: a. imperfections are less visible; b. the skin is cleansed/purified; c. the complexion is homogeneous/uniform; d. the skin is comfortable; e. the skin is like hydrated; f. the skin is smoother; g. the skin is softer; h. the skin is suppler; i. the skin is less brilliant; j. the skin is matified; k. excess sebum is reduced; l. the skin has a matte touch; m. the pores of the skin are tightened; n. redness of the skin is reduced; o. the skin texture is refined; p. the marks of the skin are less visible. The following scale will be used: agree; somewhat agree; neither agree, nor disagree; somewhat disagree; disagree.
- Analysis of local tolerance using clinical assessments (time frame: week 0 (baseline), week 4 and week 8 (intermediary times point) and week 12 (final time point)). At week 0 (before any application), week 4 (after a 4-week application period), week 8 (after an 8-week application period) and week 12 (after a 12-week application period), a clinical assessment of the face skin condition will be performed by the dermatologist - physical signs: erythema, dryness and scaling; functional signs*: tightness, prickling, itching, burning sensation and others. The following scale will be used: rating 0: none, rating 1: slight, rating 2: moderate, rating 3: severe. *During the study, the subjects will have to record any skin discomfort, intensity (slight, moderate or severe) and duration in their daily log. Functional signs will be assessed by the dermatologist from a review of the daily log and interrogation of the subject.
- Overall tolerance of product assessed by the dermatologist and the subject (time frame: week 12 (final time point)). In addition, at week 12 (after a 12-week application period), the dermatologist and the subject will state the overall tolerance of the IP (cosmetic product and drug) based on rating scale: excellent tolerance, good tolerance, medium tolerance, poor tolerance.
- Analysis of cosmetic acceptability, using a questionnaire (time frame: week 12 (final time point)). Subjects will complete a cosmetic acceptability questionnaire concerning the cosmetic product at the last visit. The following items will be evaluated by the subjects: a. the product is easy to spread; b. the product is easy to apply; c. the product penetrates quickly; d. the colour of the product is pleasant; e. the scent of the product is pleasant; f. the aspect of the product is pleasant; g.the texture of the product is pleasant; h. the texture is comfortable; i. the product does not leave the skin sticky; j. the product does not leave a greasy film on the skin; k. the product leaves a silky effect. The following scale will be used: agree, somewhat agree, neither agree, nor disagree, somewhat disagree, disagree.
- Evaluation of the skin microbiota using sampling (if applicable) (time frame: week 0 (baseline) and week 12 (final time point)). At week 0 and at week 12, microbiota sampling will be performed by the same sampler (technician/nurse). Skin microbiota sample will be collected on one test site of 4 cm^2 on the middle of the left cheek and using aseptic techniques under sterile airflow generated by a portable hood. According to the results of the primary variable, the sponsor will decide to go ahead with the microbiota analysis which will be done by INRA Transfert. DNA will be extracted from the swabs. PCR amplification will be performed for each DNA sample. DNA will be PCR amplified. Cleaned pools will be sequenced on the Illumina MiSeq platform. Sequences will be then

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Starting date	February 2019
Contact information	Karine Duhamelle +33153684684 karine.duhamelle@intertek.com Caroline Derome +33153684688 caroline.derome@intertek.com
Notes	Not yet recruiting

DATA AND ANALYSES

Comparison 1. Topical azelaic acid versus other topical treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Participants' global self-assessment of acne improvement	7		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.1 azelaic acid versus adapalene - improved to very much improved (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.2 azelaic acid versus adapalene - improved to very much improved (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.3 azelaic acid versus benzoyl peroxide - good or very good improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.4 azelaic acid versus clindamycin - good or very good improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.5 azelaic acid versus clindamycin - moderately satisfied to very satisfied improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.6 azelaic acid versus erythromycin - moderately satisfied to very satisfied improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.7 azelaic acid versus tretinoin - good to excellent improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.8 azelaic acid versus benzoyl peroxide/clindamycin - much to very much improved (short term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.9 azelaic acid versus benzoyl peroxide/clindamycin - much to very much improved (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1.10 azelaic acid versus benzoyl peroxide/clindamycin - much to very much improved (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2 Withdrawal for any reason	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 azelaic acid versus adapalene (short term)	1	45	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.05, 12.01]
1.2.2 azelaic acid versus adapalene (long term)	1	55	Risk Ratio (M-H, Random, 95% CI)	2.64 [0.33, 20.99]
1.2.3 azelaic acid versus benzoyl peroxide (short term)	1	45	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.04, 4.10]
1.2.4 azelaic acid versus benzoyl peroxide (long term)	1	351	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.60, 1.29]
1.2.5 azelaic acid versus clindamycin (medium term)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2.6 azelaic acid versus clindamycin (long term)	2	329	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.48, 3.56]
1.2.7 azelaic acid versus metronidazole (long term)	1	40	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2.8 azelaic acid versus tretinoin (long term)	2	309	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.29, 1.47]
1.2.9 azelaic acid versus benzoyl peroxide/clindamycin (long term)	1	221	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.43, 3.07]
1.3 Change in lesion counts - total (percentage reduction from baseline)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.1 azelaic acid versus clindamycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.2 azelaic acid versus clindamycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.3 azelaic acid versus clindamycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.4 azelaic acid versus benzoyl peroxide/clindamycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.5 azelaic acid versus benzoyl peroxide/clindamycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3.6 azelaic acid versus benzoyl peroxide/clindamycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.4 Change in lesion counts - total	1		Other data	No numeric data
1.4.1 long term	1		Other data	No numeric data
1.5 Change in lesion counts - inflamed (percentage reduction from baseline)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.5.1 azelaic acid versus benzoyl peroxide/clindamycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.5.2 azelaic acid versus benzoyl peroxide/clindamycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.5.3 azelaic acid versus benzoyl peroxide/clindamycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.6 Change in lesion counts - inflamed (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.6.1 azelaic acid versus adapalene (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.6.2 azelaic acid versus benzoyl peroxide (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.7 Change in lesion counts - inflamed	5		Other data	No numeric data
1.8 Change in lesion counts - papules (percentage reduction from baseline)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.8.1 azelaic acid versus clindamycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.8.2 azelaic acid versus clindamycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.8.3 azelaic acid versus clindamycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.9 Change in lesion counts - papules (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.9.1 azelaic acid versus erythromycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.2 azelaic acid versus erythromycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.9.3 azelaic acid versus erythromycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10 Change in lesion counts - pustules (percentage reduction from baseline)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.1 azelaic acid versus clindamycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.2 azelaic acid versus clindamycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.10.3 azelaic acid versus clindamycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11 Change in lesion counts - pustules (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11.1 azelaic acid versus erythromycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11.2 azelaic acid versus erythromycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.11.3 azelaic acid versus erythromycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.12 Change in lesion counts - non-inflamed	6		Other data	No numeric data
1.13 Change in lesion counts - non-inflamed (percentage reduction from baseline)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.13.1 azelaic acid versus clindamycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.13.2 azelaic acid versus clindamycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.13.3 azelaic acid versus clindamycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.13.4 azelaic acid versus benzoyl peroxide/clindamycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.13.5 azelaic acid versus benzoyl peroxide/clindamycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.13.6 azelaic acid versus benzoyl peroxide/clindamycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

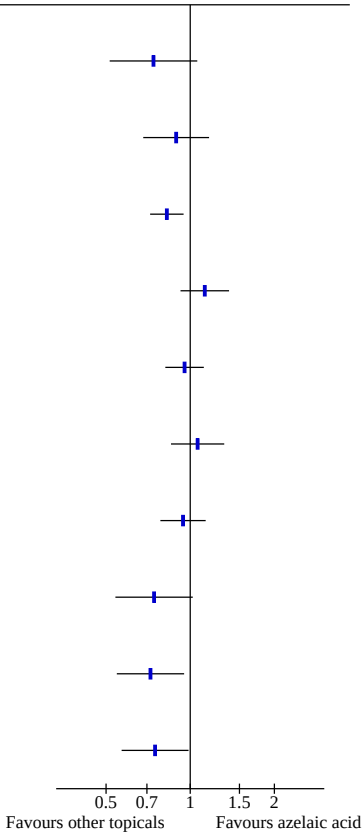
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14 Change in lesion counts - non-inflamed (number of lesions post-intervention)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.14.1 azelaic acid versus erythromycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.14.2 azelaic acid versus erythromycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.14.3 azelaic acid versus erythromycin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.14.4 azelaic acid versus adapalene (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.14.5 azelaic acid versus benzoyl peroxide (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.15 Physicians' global evaluation of acne improvement	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.15.1 azelaic acid versus benzoyl peroxide - good or very good improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.15.2 azelaic acid versus clindamycin - good or very good improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.15.3 azelaic acid versus tretinoin - good to excellent improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.15.4 azelaic acid versus benzoyl peroxide/clindamycin - clear to almost clear (short term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.15.5 azelaic acid versus benzoyl peroxide/clindamycin - clear to almost clear (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.15.6 azelaic acid versus benzoyl peroxide/clindamycin - clear to almost clear (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.16 Minor adverse events	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.16.1 total events - azelaic acid versus adapalene (medium term)	1	55	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.47, 2.85]
1.16.2 total events - azelaic acid versus benzoyl peroxide (short term)	1	30	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 4.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.3 total events - azelaic acid versus benzoyl peroxide/clindamycin (long term)	1	221	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.01, 1.52]
1.16.4 total events - azelaic acid versus clindamycin (long term)	1	100	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.67, 3.35]
1.16.5 total events - azelaic acid versus erythromycin (long term)	1	66	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.51, 1.35]
1.16.6 application site pain - azelaic acid versus benzoyl peroxide/clindamycin	1	221	Risk Ratio (M-H, Random, 95% CI)	3.17 [1.41, 7.12]
1.16.7 burning - azelaic acid versus benzoyl peroxide	1	351	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.61, 1.97]
1.16.8 burning - azelaic acid versus clindamycin	1	229	Risk Ratio (M-H, Random, 95% CI)	25.22 [1.51, 420.92]
1.16.9 burning - azelaic acid versus tretinoin	1	289	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.38, 1.71]
1.16.10 scaling - azelaic acid versus clindamycin	1	100	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.20, 2.22]
1.16.11 scaling - azelaic acid versus erythromycin	1	66	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.35, 9.01]
1.16.12 scaling - azelaic acid versus tretinoin	1	289	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.37, 0.91]
1.16.13 erythema - azelaic acid versus adapalene	1	45	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.30, 2.10]
1.16.14 erythema - azelaic acid versus benzoyl peroxide	1	45	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.21, 1.09]
1.16.15 erythema - azelaic acid versus benzoyl peroxide/clindamycin	1	221	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.41, 6.87]
1.16.16 erythema - azelaic acid versus clindamycin	1	100	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.18, 3.18]
1.16.17 erythema - azelaic acid versus erythromycin	1	66	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.16, 2.74]
1.16.18 erythema - azelaic acid versus tretinoin	1	289	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.41, 0.99]
1.16.19 dryness - azelaic acid versus adapalene	1	45	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.51, 1.26]
1.16.20 dryness - azelaic acid versus benzoyl peroxide	2	396	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.27, 1.16]

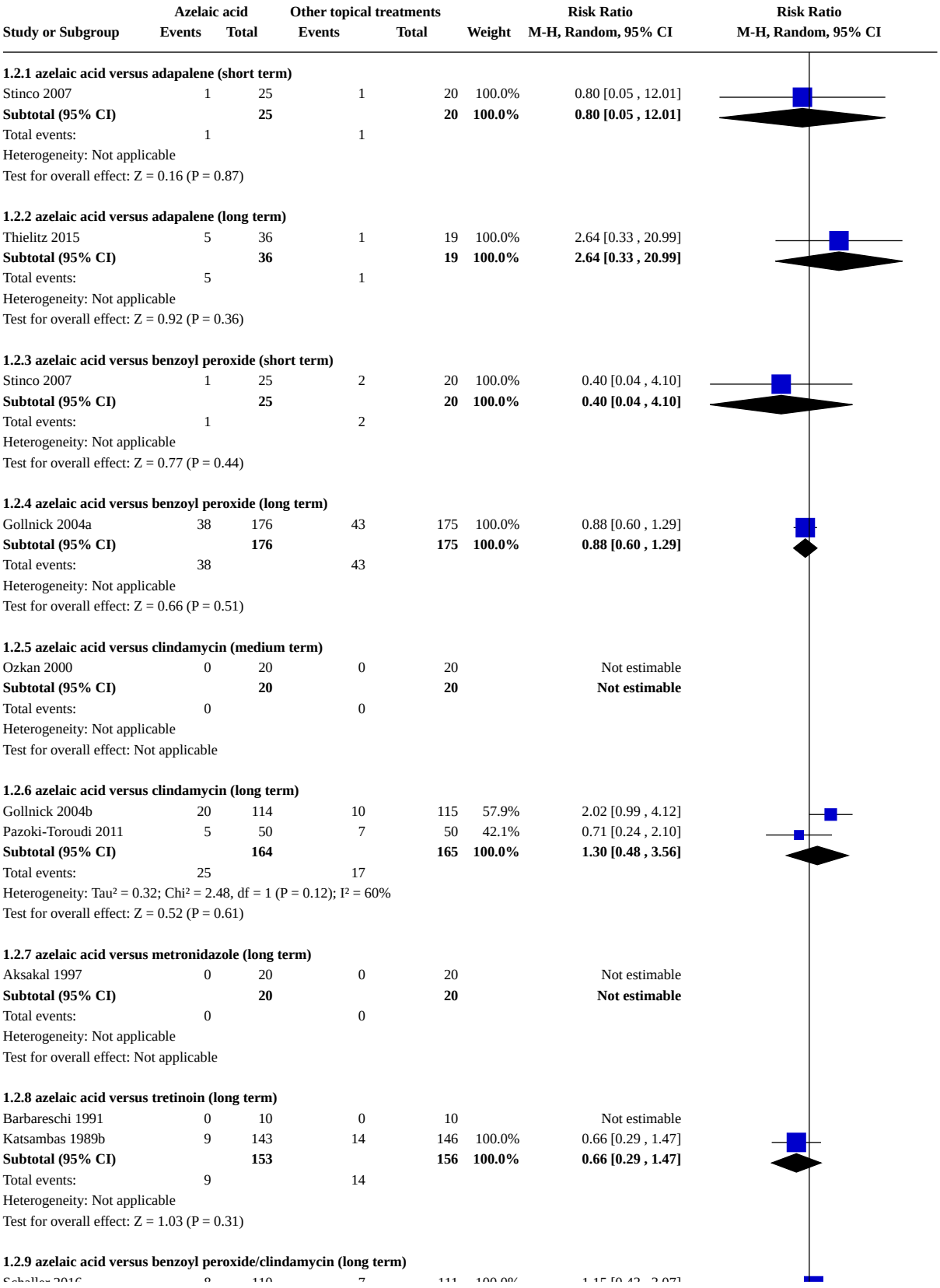
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.21 dryness - azelaic acid versus benzoyl peroxide/clindamycin	1	221	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.26, 8.88]
1.16.22 dryness - azelaic acid versus clindamycin	2	329	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.96, 6.19]
1.16.23 dryness - azelaic acid versus erythromycin	1	66	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.09, 2.25]
1.16.24 oiliness - azelaic acid versus clindamycin	1	100	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.36, 4.38]
1.16.25 oiliness - azelaic acid versus erythromycin	1	66	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.19, 4.07]
1.16.26 itching - azelaic acid versus adapalene	1	45	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.84, 1.79]
1.16.27 itching - azelaic acid versus benzoyl peroxide	2	396	Risk Ratio (M-H, Random, 95% CI)	3.29 [0.24, 45.29]
1.16.28 itching - azelaic acid versus benzoyl peroxide/clindamycin	1	221	Risk Ratio (M-H, Random, 95% CI)	3.15 [1.49, 6.68]
1.16.29 itching - azelaic acid versus clindamycin	2	329	Risk Ratio (M-H, Random, 95% CI)	2.56 [0.68, 9.57]
1.16.30 itching - azelaic acid versus erythromycin	1	66	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.29, 4.87]
1.16.31 red skin - azelaic acid versus benzoyl peroxide	1	351	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.36, 1.26]
1.16.32 red skin - azelaic acid versus clindamycin	1	229	Risk Ratio (M-H, Random, 95% CI)	6.05 [1.39, 26.44]
1.16.33 desquamation - azelaic acid versus benzoyl peroxide	1	351	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.08, 0.73]
1.16.34 eczema - azelaic acid versus clindamycin	1	229	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.06]
1.17 Quality of life	2		Other data	No numeric data

Analysis 1.1. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 1: Participants' global self-assessment of acne improvement

Study or Subgroup	Azelaic acid Events	Azelaic acid Total	Other topical treatments Events	Other topical treatments Total	Risk Ratio M-H, Random, 95% CI
1.1.1 azelaic acid versus adapalene - improved to very much improved (medium term)					
Thielitz 2015	21	36	15	19	0.74 [0.52 , 1.06]
1.1.2 azelaic acid versus adapalene - improved to very much improved (long term)					
Thielitz 2015	27	36	16	19	0.89 [0.68 , 1.17]
1.1.3 azelaic acid versus benzoyl peroxide - good or very good improvement (long term)					
Gollnick 2004a	112	176	135	175	0.82 [0.72 , 0.95]
1.1.4 azelaic acid versus clindamycin - good or very good improvement (long term)					
Gollnick 2004b	76	114	68	115	1.13 [0.92 , 1.38]
1.1.5 azelaic acid versus clindamycin - moderately satisfied to very satisfied improvement (long term)					
Pazoki-Toroudi 2011	42	50	44	50	0.95 [0.81 , 1.12]
1.1.6 azelaic acid versus erythromycin - moderately satisfied to very satisfied improvement (long term)					
Pazoki-Toroudi 2010	30	35	25	31	1.06 [0.85 , 1.32]
1.1.7 azelaic acid versus tretinoin - good to excellent improvement (long term)					
Katsambas 1989b	84	143	91	146	0.94 [0.78 , 1.14]
1.1.8 azelaic acid versus benzoyl peroxide/clindamycin - much to very much improved (short term)					
Schaller 2016	39	110	53	111	0.74 [0.54 , 1.02]
1.1.9 azelaic acid versus benzoyl peroxide/clindamycin - much to very much improved (medium term)					
Schaller 2016	45	110	63	111	0.72 [0.55 , 0.95]
1.1.10 azelaic acid versus benzoyl peroxide/clindamycin - much to very much improved (long term)					
Schaller 2016	46	110	62	111	0.75 [0.57 , 0.99]

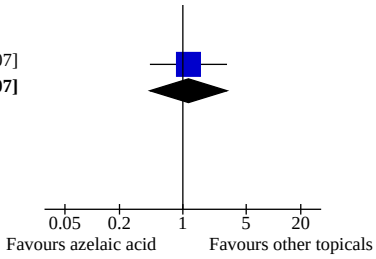


Analysis 1.2. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 2: Withdrawal for any reason



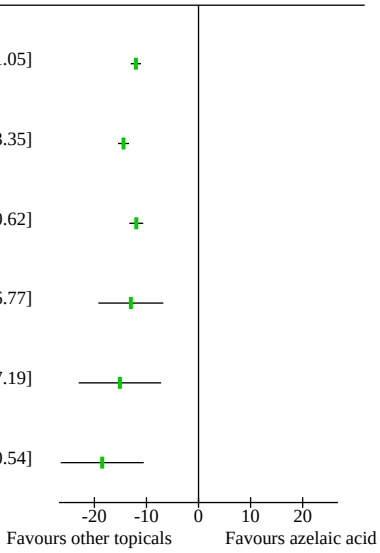
Analysis 1.2. (Continued)

1.2.9 azelaic acid versus benzoyl peroxide/clindamycin (long term)						
Schaller 2016	8	110	7	111	100.0%	1.15 [0.43 , 3.07]
Subtotal (95% CI)		**110**		**111**	**100.0%**	**1.15 [0.43 , 3.07]**
Total events:	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.78)						



Analysis 1.3. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 3: Change in lesion counts - total (percentage reduction from baseline)

	Azelaic acid			Other topical treatments			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
1.3.1 azelaic acid versus clindamycin (short term)								
Pazoki-Toroudi 2011	14.51	1.24	50	26.54	3.32	50	-12.03 [-13.01 , -11.05]	
1.3.2 azelaic acid versus clindamycin (medium term)								
Pazoki-Toroudi 2011	27.83	2.01	47	42.24	3.17	49	-14.41 [-15.47 , -13.35]	
1.3.3 azelaic acid versus clindamycin (long term)								
Pazoki-Toroudi 2011	34.94	2.67	45	46.89	3.62	43	-11.95 [-13.28 , -10.62]	
1.3.4 azelaic acid versus benzoyl peroxide/clindamycin (short term)								
Schaller 2016	30.8	23	107	43.8	23.3	105	-13.00 [-19.23 , -6.77]	
1.3.5 azelaic acid versus benzoyl peroxide/clindamycin (medium term)								
Schaller 2016	40.1	27.4	102	55.2	30.5	104	-15.10 [-23.01 , -7.19]	
1.3.6 azelaic acid versus benzoyl peroxide/clindamycin (long term)								
Schaller 2016	46.1	31.8	104	64.6	26.9	107	-18.50 [-26.46 , -10.54]	



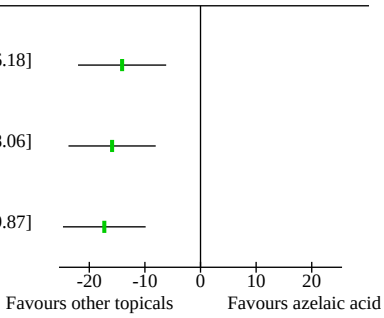
Analysis 1.4. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 4: Change in lesion counts - total

Change in lesion counts - total

Study	Time points	Azelaic acid	Other topical treatments	P value
long term				
Thielitz 2015	Long term: three months after start of treatment (percent reduction of total lesions) (n, mean ± SD)	AzA9M: n =17, 33.54 ± 39.96 AzA3M: n = 19, 38.75 ± 29.24	Adapalene: n = 19, 48.87 ± 26.39	P = 0.396 (AzA9M + AzA3M versus Adapalene)

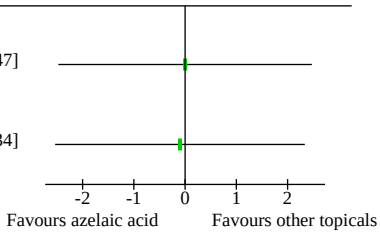
Analysis 1.5. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 5: Change in lesion counts - inflamed (percentage reduction from baseline)

Study or Subgroup	Azelaic acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.5.1 azelaic acid versus benzoyl peroxide/clindamycin (short term)							
Schaller 2016	38.1	31.1	107	52.2	27.7	105	-14.10 [-22.02 , -6.18]
1.5.2 azelaic acid versus benzoyl peroxide/clindamycin (medium term)							
Schaller 2016	49.1	30.9	102	65	26.3	104	-15.90 [-23.74 , -8.06]
1.5.3 azelaic acid versus benzoyl peroxide/clindamycin (long term)							
Schaller 2016	55	29.8	104	72.3	25	107	-17.30 [-24.73 , -9.87]



Analysis 1.6. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 6: Change in lesion counts - inflamed (number of lesions post-intervention)

Study or Subgroup	Azelaic acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.6.1 azelaic acid versus adapalene (medium term)							
Stinco 2007	10	4.73	24	10	3.54	19	0.00 [-2.47 , 2.47]
1.6.2 azelaic acid versus benzoyl peroxide (medium term)							
Stinco 2007	10	4.73	24	10.1	3.32	18	-0.10 [-2.54 , 2.34]



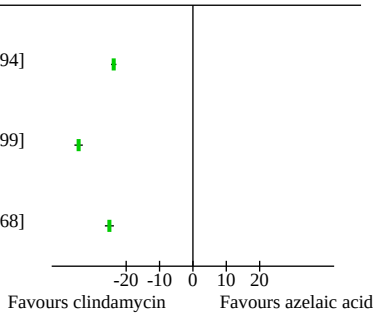
Analysis 1.7. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 7: Change in lesion counts - inflamed

Change in lesion counts - inflamed

Study	Time points	Azelaic acid	Topical treatments (Comparator)	P value
Aksakal 1997	Unclear	Unclear, not reported	Unclear, not reported (metronidazole)	P < 0.001 (statistical method not reported), Quote: "The results of this study showed that the AZA cream is more effective than the metronidazole cream in reducing counts of inflamed and non-inflamed lesions of acne"
Dunlap 1997	Medium term (number of lesion)	Unclear, not reported	Unclear, not reported (3% erythromycin/5% benzoyl peroxide)	Unclear, not reported. Quote: *"The result of the study demonstrated significant differences favoring 3% erythromycin/5% benzoyl peroxide over 20% azelaic acid for the following parameters: 1) reduction in inflammatory lesion..."*
Gollnick 2004a	Long term: four months after start of treatment (Median of percent reduction)	70%	77% (benzoyl peroxide)	P > 0.05
Gollnick 2004b	Long term: four months after start of treatment (Median of percent reduction)	71%	63% (clindamycin)	P > 0.05
Thielitz 2015	Long term: three months after start of treatment (percent change) (n, mean ± SD)	AzA3M: n = 19, -32.31 ± 38.85	n = 19, -37.99 ± 37.63 (Adapalene)	P = 0.816

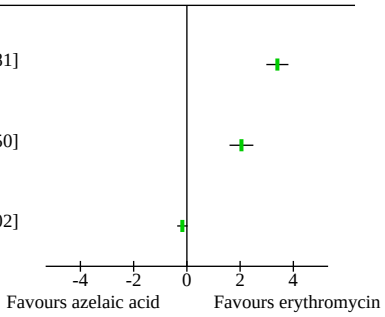
Analysis 1.8. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 8: Change in lesion counts - papules (percentage reduction from baseline)

Study or Subgroup	Azelaic acid Mean	SD	Total	Clindamycin Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.8.1 azelaic acid versus clindamycin (short term)							
Pazoki-Toroudi 2011	2.71	0.94	50	26.45	2.74	50	-23.74 [-24.54 , -22.94]
1.8.2 azelaic acid versus clindamycin (medium term)							
Pazoki-Toroudi 2011	12.98	2.74	47	47.23	3.51	49	-34.25 [-35.51 , -32.99]
1.8.3 azelaic acid versus clindamycin (long term)							
Pazoki-Toroudi 2011	28	3.21	45	53.03	3.26	43	-25.03 [-26.38 , -23.68]



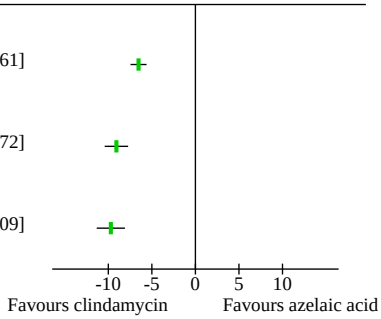
Analysis 1.9. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 9: Change in lesion counts - papules (number of lesions post-intervention)

Study or Subgroup	Azelaic acid Mean	SD	Total	Erythromycin Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.9.1 azelaic acid versus erythromycin (short term)							
Pazoki-Toroudi 2010	14.02	0.78	35	10.62	0.92	31	3.40 [2.99 , 3.81]
1.9.2 azelaic acid versus erythromycin (medium term)							
Pazoki-Toroudi 2010	10.21	1.31	35	8.16	0.31	31	2.05 [1.60 , 2.50]
1.9.3 azelaic acid versus erythromycin (long term)							
Pazoki-Toroudi 2010	10.87	0.11	35	11.04	0.54	31	-0.17 [-0.36 , 0.02]



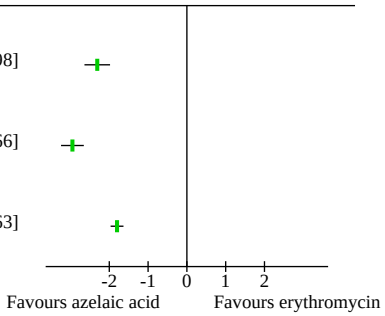
Analysis 1.10. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 10: Change in lesion counts - pustules (percentage reduction from baseline)

Study or Subgroup	Azelaic acid Mean	SD	Total	Clindamycin Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.10.1 azelaic acid versus clindamycin (short term)							
Pazoki-Toroudi 2011	23.31	2.16	50	29.84	2.52	50	-6.53 [-7.45 , -5.61]
1.10.2 azelaic acid versus clindamycin (medium term)							
Pazoki-Toroudi 2011	29.56	3.07	47	38.63	3.64	49	-9.07 [-10.42 , -7.72]
1.10.3 azelaic acid versus clindamycin (long term)							
Pazoki-Toroudi 2011	32.39	3.22	45	42.1	4.41	43	-9.71 [-11.33 , -8.09]



Analysis 1.11. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 11: Change in lesion counts - pustules (number of lesions post-intervention)

Study or Subgroup	Azelaic acid Mean	SD	Total	Erythromycin Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.11.1 azelaic acid versus erythromycin (short term)							
Pazoki-Toroudi 2010	5.9	0.61	35	8.21	0.74	31	-2.31 [-2.64 , -1.98]
1.11.2 azelaic acid versus erythromycin (medium term)							
Pazoki-Toroudi 2010	5.11	0.7	35	8.06	0.51	31	-2.95 [-3.24 , -2.66]
1.11.3 azelaic acid versus erythromycin (long term)							
Pazoki-Toroudi 2010	5.32	0.41	35	7.12	0.27	31	-1.80 [-1.97 , -1.63]



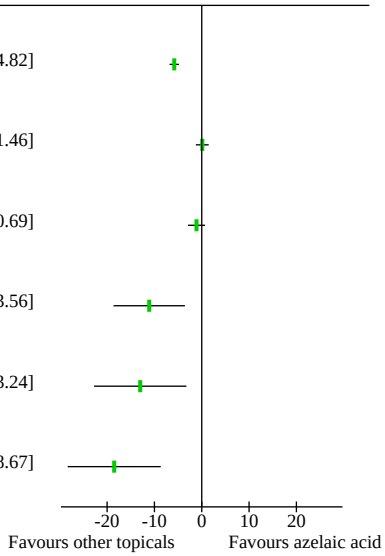
Analysis 1.12. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 12: Change in lesion counts - non-inflamed

Change in lesion counts - non-inflamed

Study	Time points	Azelaic acid	Topical treatments	P value
Aksakal 1997	Unclear (number of lesions post intervention)	Less counts	More counts (metronidazole)	P < 0.001
Barbareschi 1991	Long term: four months after start of treatment, reduction in number of lesions (mean)	23	35 (Retinoic acid)	Unclear, the author did not test the difference between groups.
Dunlap 1997	Medium term: reduction in number of comedones	Unclear, not reported	Unclear, not reported (3% erythromycin/5% benzoyl peroxide)	Unclear, not reported. Quote: " The result of the study demonstrated significant differences favoring 3% erythromycin/5% benzoyl peroxide over 20% azelaic acid for the following parameters: 2) reduction in comedones..."
Gollnick 2004a	Long term: four months after start of treatment (Median of percent reduction)	60%	71% (benzoyl peroxide)	P > 0.05
Gollnick 2004b	Long term: four months after start of treatment (Median of percent reduction)	57%	45% (clindamycin)	P < 0.05
Thielitz 2015	Long term: three months after start of treatment (percent reduction of non-inflamed lesions) (n, mean ± SD)	AzA9M: n =17, 26.36 ± 57.64 AzA3M: n = 19, 41.25 ± 32.92	Adapalene: n = 19, 55.21 ± 29.75	P = 0.063 (AzA9M + AzA3M versus Adapalene)
Thielitz 2015	Long term: three months after start of treatment, percent reduction of microcomedones (n, mean ± SD)	AzA9M: n =17, 10.61 ± 44.32 AzA3M: n = 19, 18.63 ± 54.70	Adapalene: n = 19, 27.06 ± 50.15	P = 0.25 (AzA9M + AzA3M versus Adapalene)

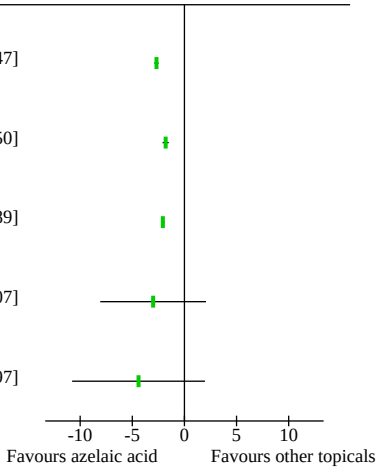
Analysis 1.13. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 13: Change in lesion counts - non-inflamed (percentage reduction from baseline)

Study or Subgroup	Azelaic acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.13.1 azelaic acid versus clindamycin (short term)							
Pazoki-Toroudi 2011	17.51	2.51	50	23.32	2.54	50	-5.81 [-6.80 , -4.82]
1.13.2 azelaic acid versus clindamycin (medium term)							
Pazoki-Toroudi 2011	40.96	3.21	47	40.85	3.56	49	0.11 [-1.24 , 1.46]
1.13.3 azelaic acid versus clindamycin (long term)							
Pazoki-Toroudi 2011	44.43	4.34	45	45.54	4.29	43	-1.11 [-2.91 , 0.69]
1.13.4 azelaic acid versus benzoyl peroxide/clindamycin (short term)							
Schaller 2016	27	28.2	107	38.1	27.8	105	-11.10 [-18.64 , -3.56]
1.13.5 azelaic acid versus benzoyl peroxide/clindamycin (medium term)							
Schaller 2016	35.5	31.2	102	48.5	39.8	104	-13.00 [-22.76 , -3.24]
1.13.6 azelaic acid versus benzoyl peroxide/clindamycin (long term)							
Schaller 2016	42.1	37.5	104	60.6	35.3	107	-18.50 [-28.33 , -8.67]



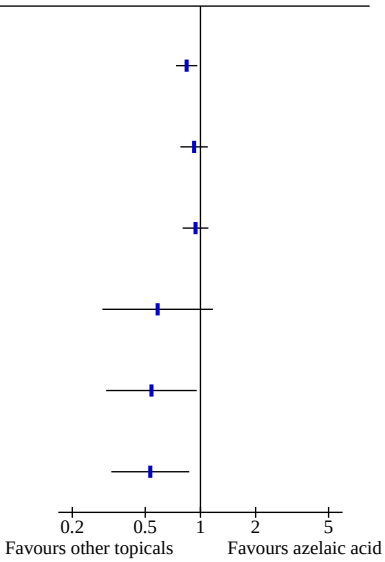
Analysis 1.14. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 14: Change in lesion counts - non-inflamed (number of lesions post-intervention)

Study or Subgroup	Azelaic acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.14.1 azelaic acid versus erythromycin (short term)							
Pazoki-Toroudi 2010	6.12	0.39	35	8.8	0.46	31	-2.68 [-2.89 , -2.47]
1.14.2 azelaic acid versus erythromycin (medium term)							
Pazoki-Toroudi 2010	5.52	0.71	35	7.32	0.51	31	-1.80 [-2.10 , -1.50]
1.14.3 azelaic acid versus erythromycin (long term)							
Pazoki-Toroudi 2010	3.29	0.43	35	5.36	0.31	31	-2.07 [-2.25 , -1.89]
1.14.4 azelaic acid versus adapalene (medium term)							
Stinco 2007	22.9	8.77	24	25.9	8.14	19	-3.00 [-8.07 , 2.07]
1.14.5 azelaic acid versus benzoyl peroxide (medium term)							
Stinco 2007	22.9	8.77	24	27.3	11.51	18	-4.40 [-10.77 , 1.97]

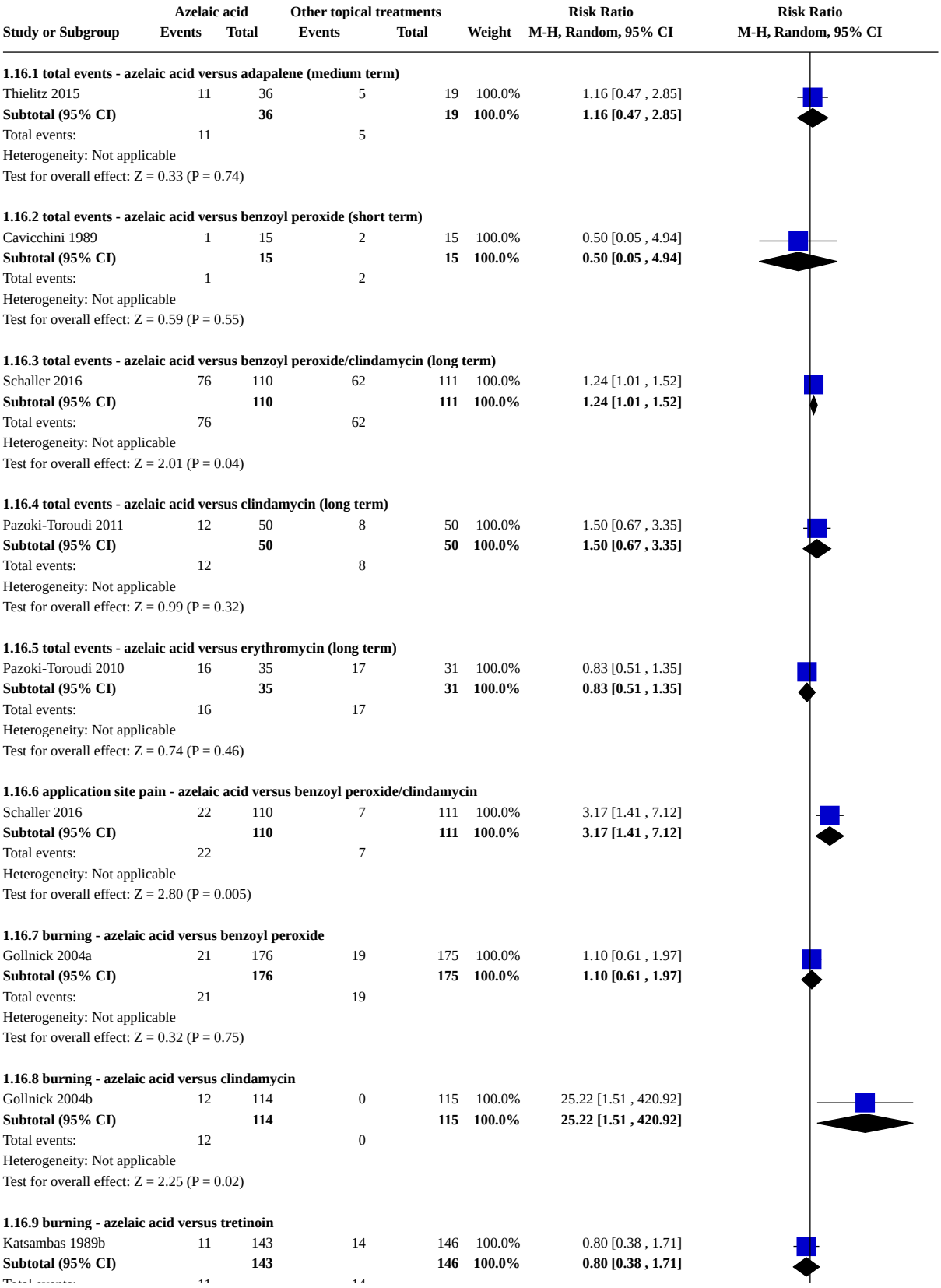


Analysis 1.15. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 15: Physicians' global evaluation of acne improvement

Study or Subgroup	Azelaic acid Events	Azelaic acid Total	Other topical treatments Events	Other topical treatments Total	Risk Ratio M-H, Random, 95% CI
1.15.1 azelaic acid versus benzoyl peroxide - good or very good improvement (long term)					
Gollnick 2004a	115	176	136	175	0.84 [0.74 , 0.96]
1.15.2 azelaic acid versus clindamycin - good or very good improvement (long term)					
Gollnick 2004b	76	114	83	115	0.92 [0.78 , 1.10]
1.15.3 azelaic acid versus tretinoin - good to excellent improvement (long term)					
Katsambas 1989b	93	143	101	146	0.94 [0.80 , 1.11]
1.15.4 azelaic acid versus benzoyl peroxide/clindamycin - clear to almost clear (short term)					
Schaller 2016	11	110	19	111	0.58 [0.29 , 1.17]
1.15.5 azelaic acid versus benzoyl peroxide/clindamycin - clear to almost clear (medium term)					
Schaller 2016	15	110	28	111	0.54 [0.31 , 0.95]
1.15.6 azelaic acid versus benzoyl peroxide/clindamycin - clear to almost clear (long term)					
Schaller 2016	19	110	36	111	0.53 [0.33 , 0.87]

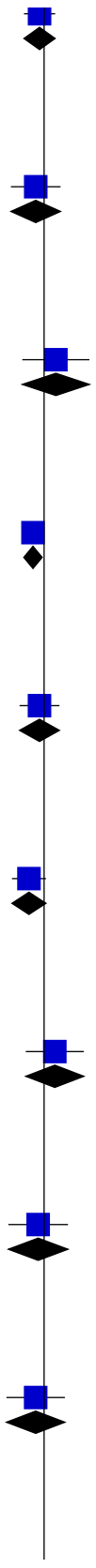


Analysis 1.16. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 16: Minor adverse events



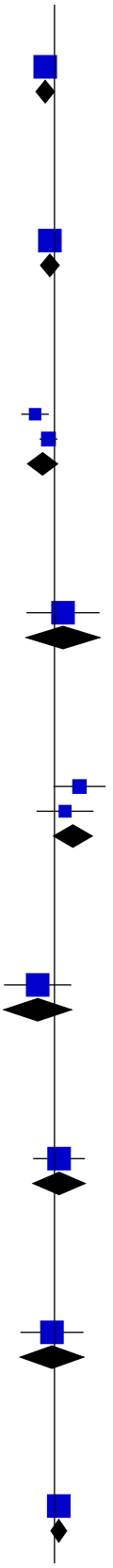
Analysis 1.16. (Continued)

Katsambas 1989b	11	143	14	146	100.0%	0.80 [0.38 , 1.71]
Subtotal (95% CI)		**143**		**146**	**100.0%**	**0.80 [0.38 , 1.71]**
Total events:	11		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
1.16.10 scaling - azelaic acid versus clindamycin						
Pazoki-Toroudi 2011	4	50	6	50	100.0%	0.67 [0.20 , 2.22]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.67 [0.20 , 2.22]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.16.11 scaling - azelaic acid versus erythromycin						
Pazoki-Toroudi 2010	4	35	2	31	100.0%	1.77 [0.35 , 9.01]
Subtotal (95% CI)		**35**		**31**	**100.0%**	**1.77 [0.35 , 9.01]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.16.12 scaling - azelaic acid versus tretinoin						
Katsambas 1989b	24	143	42	146	100.0%	0.58 [0.37 , 0.91]
Subtotal (95% CI)		**143**		**146**	**100.0%**	**0.58 [0.37 , 0.91]**
Total events:	24		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.37 (P = 0.02)						
1.16.13 erythema - azelaic acid versus adapalene						
Stinco 2007	6	25	6	20	100.0%	0.80 [0.30 , 2.10]
Subtotal (95% CI)		**25**		**20**	**100.0%**	**0.80 [0.30 , 2.10]**
Total events:	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.16.14 erythema - azelaic acid versus benzoyl peroxide						
Stinco 2007	6	25	10	20	100.0%	0.48 [0.21 , 1.09]
Subtotal (95% CI)		**25**		**20**	**100.0%**	**0.48 [0.21 , 1.09]**
Total events:	6		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
1.16.15 erythema - azelaic acid versus benzoyl peroxide/clindamycin						
Schaller 2016	5	110	3	111	100.0%	1.68 [0.41 , 6.87]
Subtotal (95% CI)		**110**		**111**	**100.0%**	**1.68 [0.41 , 6.87]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.16.16 erythema - azelaic acid versus clindamycin						
Pazoki-Toroudi 2011	3	50	4	50	100.0%	0.75 [0.18 , 3.18]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.75 [0.18 , 3.18]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
1.16.17 erythema - azelaic acid versus erythromycin						
Pazoki-Toroudi 2010	3	35	4	31	100.0%	0.66 [0.16 , 2.74]
Subtotal (95% CI)		**35**		**31**	**100.0%**	**0.66 [0.16 , 2.74]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
1.16.18 erythema - azelaic acid versus tretinoin						



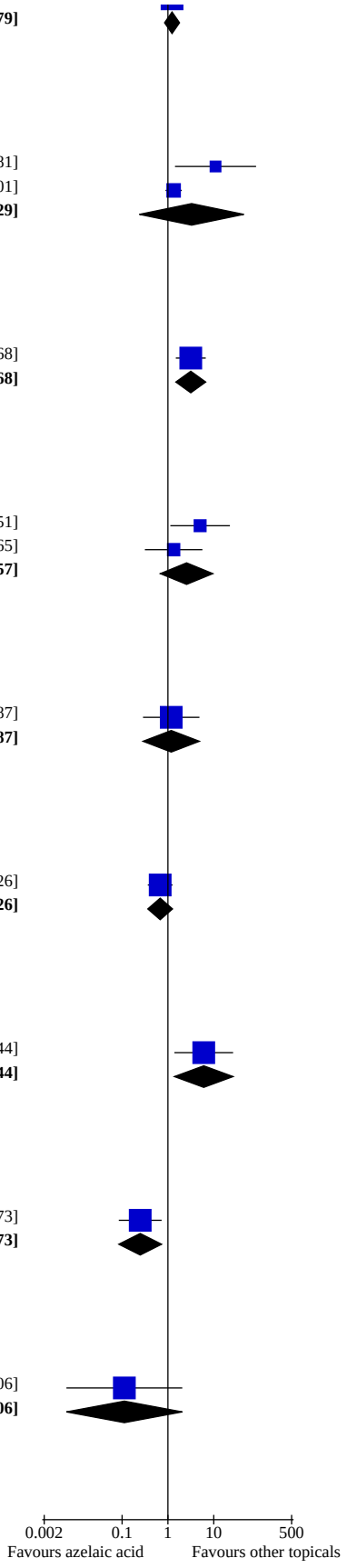
Analysis 1.16. (Continued)

1.16.18 erythema - azelaic acid versus tretinoin						
Katsambas 1989b	25	143	40	146	100.0%	0.64 [0.41 , 0.99]
Subtotal (95% CI)		**143**		**146**	**100.0%**	**0.64 [0.41 , 0.99]**
Total events:	25		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.16.19 dryness - azelaic acid versus adapalene						
Stinco 2007	14	25	14	20	100.0%	0.80 [0.51 , 1.26]
Subtotal (95% CI)		**25**		**20**	**100.0%**	**0.80 [0.51 , 1.26]**
Total events:	14		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
1.16.20 dryness - azelaic acid versus benzoyl peroxide						
Gollnick 2004a	11	176	28	175	43.9%	0.39 [0.20 , 0.76]
Stinco 2007	14	25	15	20	56.1%	0.75 [0.49 , 1.15]
Subtotal (95% CI)		**201**		**195**	**100.0%**	**0.56 [0.27 , 1.16]**
Total events:	25		43			
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 3.37$, df = 1 (P = 0.07); $I^2 = 70\%$						
Test for overall effect: Z = 1.57 (P = 0.12)						
1.16.21 dryness - azelaic acid versus benzoyl peroxide/clindamycin						
Schaller 2016	3	110	2	111	100.0%	1.51 [0.26 , 8.88]
Subtotal (95% CI)		**110**		**111**	**100.0%**	**1.51 [0.26 , 8.88]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
1.16.22 dryness - azelaic acid versus clindamycin						
Gollnick 2004b	10	114	3	115	54.3%	3.36 [0.95 , 11.90]
Pazoki-Toroudi 2011	5	50	3	50	45.7%	1.67 [0.42 , 6.60]
Subtotal (95% CI)		**164**		**165**	**100.0%**	**2.44 [0.96 , 6.19]**
Total events:	15		6			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.55$, df = 1 (P = 0.46); $I^2 = 0\%$						
Test for overall effect: Z = 1.88 (P = 0.06)						
1.16.23 dryness - azelaic acid versus erythromycin						
Pazoki-Toroudi 2010	2	35	4	31	100.0%	0.44 [0.09 , 2.25]
Subtotal (95% CI)		**35**		**31**	**100.0%**	**0.44 [0.09 , 2.25]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.16.24 oiliness - azelaic acid versus clindamycin						
Pazoki-Toroudi 2011	5	50	4	50	100.0%	1.25 [0.36 , 4.38]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**1.25 [0.36 , 4.38]**
Total events:	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
1.16.25 oiliness - azelaic acid versus erythromycin						
Pazoki-Toroudi 2010	3	35	3	31	100.0%	0.89 [0.19 , 4.07]
Subtotal (95% CI)		**35**		**31**	**100.0%**	**0.89 [0.19 , 4.07]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.88)						
1.16.26 itching - azelaic acid versus adapalene						
Stinco 2007	20	25	13	20	100.0%	1.23 [0.84 , 1.79]
Subtotal (95% CI)		**25**		**20**	**100.0%**	**1.23 [0.84 , 1.79]**
Total events:	20		13			



Analysis 1.16. (Continued)

Subtotal (95% CI)		**25**		**20**	**100.0%**	**1.23 [0.84 , 1.79]**	
Total events:	20		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.08 (P = 0.28)							
1.16.27 itching - azelaic acid versus benzoyl peroxide							
Gollnick 2004a	11	176	1	175	42.9%	10.94 [1.43 , 83.81]	
Stinco 2007	20	25	12	20	57.1%	1.33 [0.89 , 2.01]	
Subtotal (95% CI)		**201**		**195**	**100.0%**	**3.29 [0.24 , 45.29]**	
Total events:	31		13				
Heterogeneity: Tau² = 3.09; Chi² = 6.51, df = 1 (P = 0.01); I² = 85%							
Test for overall effect: Z = 0.89 (P = 0.37)							
1.16.28 itching - azelaic acid versus benzoyl peroxide/clindamycin							
Schaller 2016	25	110	8	111	100.0%	3.15 [1.49 , 6.68]	
Subtotal (95% CI)		**110**		**111**	**100.0%**	**3.15 [1.49 , 6.68]**	
Total events:	25		8				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.00 (P = 0.003)							
1.16.29 itching - azelaic acid versus clindamycin							
Gollnick 2004b	10	114	2	115	48.9%	5.04 [1.13 , 22.51]	
Pazoki-Toroudi 2011	4	50	3	50	51.1%	1.33 [0.31 , 5.65]	
Subtotal (95% CI)		**164**		**165**	**100.0%**	**2.56 [0.68 , 9.57]**	
Total events:	14		5				
Heterogeneity: Tau² = 0.34; Chi² = 1.61, df = 1 (P = 0.20); I² = 38%							
Test for overall effect: Z = 1.39 (P = 0.16)							
1.16.30 itching - azelaic acid versus erythromycin							
Pazoki-Toroudi 2010	4	35	3	31	100.0%	1.18 [0.29 , 4.87]	
Subtotal (95% CI)		**35**		**31**	**100.0%**	**1.18 [0.29 , 4.87]**	
Total events:	4		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.23 (P = 0.82)							
1.16.31 red skin - azelaic acid versus benzoyl peroxide							
Gollnick 2004a	15	176	22	175	100.0%	0.68 [0.36 , 1.26]	
Subtotal (95% CI)		**176**		**175**	**100.0%**	**0.68 [0.36 , 1.26]**	
Total events:	15		22				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.22 (P = 0.22)							
1.16.32 red skin - azelaic acid versus clindamycin							
Gollnick 2004b	12	114	2	115	100.0%	6.05 [1.39 , 26.44]	
Subtotal (95% CI)		**114**		**115**	**100.0%**	**6.05 [1.39 , 26.44]**	
Total events:	12		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.39 (P = 0.02)							
1.16.33 desquamation - azelaic acid versus benzoyl peroxide							
Gollnick 2004a	4	176	16	175	100.0%	0.25 [0.08 , 0.73]	
Subtotal (95% CI)		**176**		**175**	**100.0%**	**0.25 [0.08 , 0.73]**	
Total events:	4		16				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.54 (P = 0.01)							
1.16.34 eczema - azelaic acid versus clindamycin							
Gollnick 2004b	0	114	4	115	100.0%	0.11 [0.01 , 2.06]	
Subtotal (95% CI)		**114**		**115**	**100.0%**	**0.11 [0.01 , 2.06]**	
Total events:	0		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.47 (P = 0.14)							



Analysis 1.17. Comparison 1: Topical azelaic acid versus other topical treatments, Outcome 17: Quality of life

Quality of life

Study	Time points	Azelaic acid	Topical treatments	P value
Schaller 2016	Long term: 12 weeks after start of treatment - Children's Dermatology Life Quality Index (percent change, mean ± SD)	-36.8% ± 74.8, n = 108	-60.5% ± 70.6, n = 107	unclear
Thielitz 2015	Long term: three months after start of treatment - Dermatology Life Quality Index questionnaire (absolute change, n mean ± SD)	AzA9M: n =17, -1.88 ± 3.35 AzA3M: n = 19, -2.74 ± 2.90	Adapalene: n = 19, -2.58 ± 4.68	P = 0.549 (adapalene vs AzA9M + 3M)

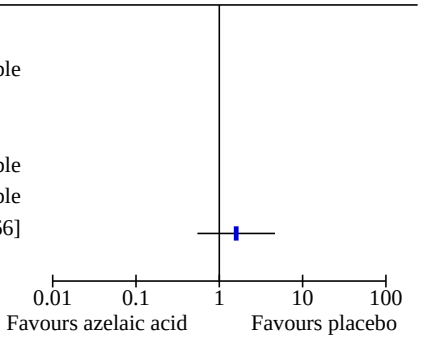
Comparison 2. Topical azelaic acid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Withdrawal for any reason	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1.1 medium term	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1.2 long term	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.2 Change in lesion counts - > 50% inflamed reduction	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.2.1 long term	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.3 Change in lesion counts - inflamed (percentage reduction from baseline)	3		Other data	No numeric data
2.3.1 short term	1		Other data	No numeric data
2.3.2 medium term	2		Other data	No numeric data
2.3.3 long term	2		Other data	No numeric data
2.3.4 long term (split-face trials)	1		Other data	No numeric data
2.4 Change in lesion counts - > 50% non-inflamed reduction	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.4.1 long term	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.5 Change in lesion counts - non-inflamed (percentage reduction from baseline)	2		Other data	No numeric data
2.5.1 medium term	1		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5.2 long term	1		Other data	No numeric data
2.5.3 long term (split-face trials)	1		Other data	No numeric data
2.6 Change in lesion counts (percentage reduction from baseline)	3		Other data	No numeric data
2.6.1 medium term	1		Other data	No numeric data
2.6.2 long term	1		Other data	No numeric data
2.6.3 long term (split-face trials)	1		Other data	No numeric data
2.7 Change in lesion counts (number of lesions post-intervention)	1		Other data	No numeric data
2.7.1 short term	1		Other data	No numeric data
2.8 Change in lesion counts - comedones (reduction in number of lesions post-intervention)	1		Other data	No numeric data
2.8.1 long term	1		Other data	No numeric data
2.9 Physicians' global evaluation of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.9.1 Good to excellent improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.10 Minor adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.10.1 burning	1	92	Risk Ratio (M-H, Random, 95% CI)	4.56 [0.53, 39.24]
2.10.2 scaling	2	147	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.16, 13.48]
2.10.3 erythema	2	147	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.39, 9.78]
2.10.4 dryness	1	55	Risk Ratio (M-H, Random, 95% CI)	2.92 [0.15, 57.90]
2.10.5 oiliness	1	55	Risk Ratio (M-H, Random, 95% CI)	4.08 [0.22, 75.25]
2.10.6 itching	2	147	Risk Ratio (M-H, Random, 95% CI)	5.45 [0.68, 43.53]
2.10.7 total events (medium term)	1	60	Risk Ratio (M-H, Random, 95% CI)	19.00 [1.16, 312.42]

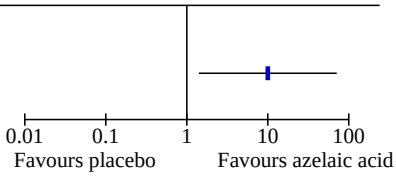
Analysis 2.1. Comparison 2: Topical azelaic acid versus placebo, Outcome 1: Withdrawal for any reason

Study or Subgroup	Azelaic acid Events	Azelaic acid Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
2.1.1 medium term					
Iraji 2007	0	30	0	30	Not estimable
2.1.2 long term					
Barbareschi 1991	0	10	0	10	Not estimable
Cunliffe 1989	0	20	0	20	Not estimable
Katsambas 1989a	7	43	5	49	1.60 [0.55 , 4.66]



Analysis 2.2. Comparison 2: Topical azelaic acid versus placebo, Outcome 2: Change in lesion counts - > 50% inflamed reduction

Study or Subgroup	Azelaic acid Events	Azelaic acid Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
2.2.1 long term					
Cunliffe 1989	10	20	1	20	10.00 [1.41 , 70.99]



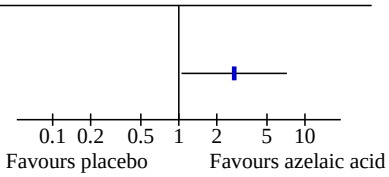
Analysis 2.3. Comparison 2: Topical azelaic acid versus placebo, Outcome 3: Change in lesion counts - inflamed (percentage reduction from baseline)

Change in lesion counts - inflamed (percentage reduction from baseline)

Study	Azelaic acid (mean)	Placebo (mean)	P value
short term			
Cunliffe 1989	Unclear, not reported	Unclear, not reported	P < 0.001, the results demonstrated significant difference favouring azelaic acid over placebo cream.
medium term			
Cunliffe 1989	Unclear, not reported	Unclear, not reported	P < 0.0025, the results demonstrated significant difference favouring azelaic acid over placebo cream.
Katsambas 1989a	Unclear, not reported	Unclear, not reported	P < 0.05, the results demonstrated significant difference favouring azelaic acid over placebo cream.
long term			
Cunliffe 1989	Long term: three months after start of treatment, unclear, not reported	Unclear, not reported	P < 0.001, the results demonstrated significant difference favouring azelaic acid over placebo cream.
Katsambas 1989a	Long term: three months after start of treatment, 72%	47%	P < 0.05, the results demonstrated significant difference favouring azelaic acid over placebo cream.
long term (split-face trials)			
Hayashi 2012	Long term: 12 weeks after start of treatment, 68.7%	54.5%	unclear, not reported

Analysis 2.4. Comparison 2: Topical azelaic acid versus placebo, Outcome 4: Change in lesion counts - > 50% non-inflamed reduction

Study or Subgroup	Azelaic acid Events	Azelaic acid Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
2.4.1 long term					
Cunliffe 1989	11	20	4	20	2.75 [1.05 , 7.20]



Analysis 2.5. Comparison 2: Topical azelaic acid versus placebo, Outcome 5: Change in lesion counts - non-inflamed (percentage reduction from baseline)

Change in lesion counts - non-inflamed (percentage reduction from baseline)

Study	Azelaic acid (mean)	Placebo (mean)	P value
medium term			
Cunliffe 1989	Unclear, not reported	Unclear, not reported	P < 0.027, the results demonstrated significant difference favouring azelaic acid over placebo cream.
long term			
Cunliffe 1989	Long term: three months after start of treatment, unclear, not reported	Unclear, not reported	P < 0.027, the results demonstrated significant difference favouring azelaic acid over placebo cream.
long term (split-face trials)			
Hayashi 2012	Long term: 12 weeks after start of treatment, 59.0%	46.5%	Unclear, not reported

Analysis 2.6. Comparison 2: Topical azelaic acid versus placebo, Outcome 6: Change in lesion counts (percentage reduction from baseline)

Change in lesion counts (percentage reduction from baseline)

Study	Subgroup	Topical azelaic acid	Placebo	P value
medium term				
Iraji 2007	Papules number	51.2%	19.3%	0.003
Iraji 2007	Total lesion counts	60.6%	19.9%	0.002
Iraji 2007	Acne severity index	65.2%	21.3%	0.001
Iraji 2007	Comedones numbers	87.3%	23.2%	0.001
Iraji 2007	Pustules number	42.1%	17.8%	0.08
long term				
Katsambas 1989a	Long term: three months after start of treatment, comedones numbers	55.6%	0%	significant difference
long term (split-face trials)				
Hayashi 2012	Long term: 12 weeks after start of treatment, total lesion counts	59.6%	45.6%	<0.001

Analysis 2.7. Comparison 2: Topical azelaic acid versus placebo, Outcome 7: Change in lesion counts (number of lesions post-intervention)

Change in lesion counts (number of lesions post-intervention)

Study	Subgroup	Topical azelaic acid	Placebo	P value

short term				
Pazoki-Toroudi 2010	comedones	mean ± SD: 6.12 ± 0.39	mean ± SD: 30.02 ± 3.0, n = 20	< 0.001
Pazoki-Toroudi 2010	papules	mean ± SD: 14.02 ± 0.78	mean ± SD: 22.22 ± 1.64, n = 20	< 0.001
Pazoki-Toroudi 2010	pustules	mean ± SD: 5.9 ± 0.61	mean ± SD: 12.22 ± 1.04, n = 20	< 0.001

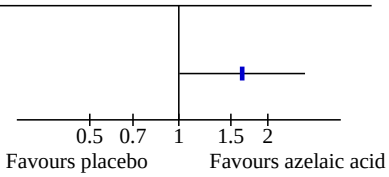
Analysis 2.8. Comparison 2: Topical azelaic acid versus placebo, Outcome 8: Change in lesion counts - comedones (reduction in number of lesions post-intervention)

Change in lesion counts - comedones (reduction in number of lesions post-intervention)

Study	Azelaic acid	Placebo	P value
long term			
Barbareschi 1991	Long term: four months after start of treatment, 23	3	Unclear, the author did not test the difference between groups.
Barbareschi 1991	Four months after start of treatment, number of lesions reduction post intervention, scanning electron microscopy measured comedones: 9.4±6.93	0.1±3.14	0.05

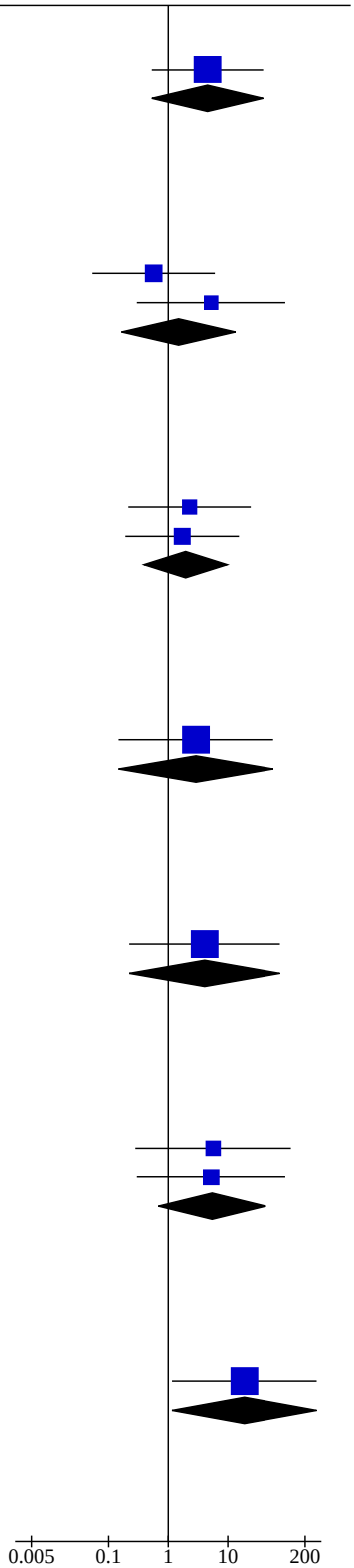
Analysis 2.9. Comparison 2: Topical azelaic acid versus placebo, Outcome 9: Physicians' global evaluation of acne improvement

Study or Subgroup	Azelaic acid Events	Azelaic acid Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
2.9.1 Good to excellent improvement (long term)					
Katsambas 1989a	23	43	16	49	1.64 [1.00 , 2.67]

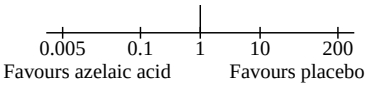


Analysis 2.10. Comparison 2: Topical azelaic acid versus placebo, Outcome 10: Minor adverse events

Study or Subgroup	Azelaic acid Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 burning						
Katsambas 1989a	4	43	1	49	100.0%	4.56 [0.53 , 39.24]
Subtotal (95% CI)		**43**		**49**	**100.0%**	**4.56 [0.53 , 39.24]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						
2.10.2 scaling						
Katsambas 1989a	1	43	2	49	56.7%	0.57 [0.05 , 6.07]
Pazoki-Toroudi 2010	4	35	0	20	43.3%	5.25 [0.30 , 92.76]
Subtotal (95% CI)		**78**		**69**	**100.0%**	**1.49 [0.16 , 13.48]**
Total events:	5		2			
Heterogeneity: Tau² = 0.77; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.35 (P = 0.72)						
2.10.3 erythema						
Katsambas 1989a	2	43	1	49	46.3%	2.28 [0.21 , 24.26]
Pazoki-Toroudi 2010	3	35	1	20	53.7%	1.71 [0.19 , 15.40]
Subtotal (95% CI)		**78**		**69**	**100.0%**	**1.96 [0.39 , 9.78]**
Total events:	5		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						
2.10.4 dryness						
Pazoki-Toroudi 2010	2	35	0	20	100.0%	2.92 [0.15 , 57.90]
Subtotal (95% CI)		**35**		**20**	**100.0%**	**2.92 [0.15 , 57.90]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
2.10.5 oiliness						
Pazoki-Toroudi 2010	3	35	0	20	100.0%	4.08 [0.22 , 75.25]
Subtotal (95% CI)		**35**		**20**	**100.0%**	**4.08 [0.22 , 75.25]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
2.10.6 itching						
Katsambas 1989a	2	43	0	49	47.7%	5.68 [0.28 , 115.18]
Pazoki-Toroudi 2010	4	35	0	20	52.3%	5.25 [0.30 , 92.76]
Subtotal (95% CI)		**78**		**69**	**100.0%**	**5.45 [0.68 , 43.53]**
Total events:	6		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.60 (P = 0.11)						
2.10.7 total events (medium term)						
Iraji 2007	9	30	0	30	100.0%	19.00 [1.16 , 312.42]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**19.00 [1.16 , 312.42]**
Total events:	9		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						



Analysis 2.10. (Continued)



Comparison 3. Topical azelaic acid versus no treatment

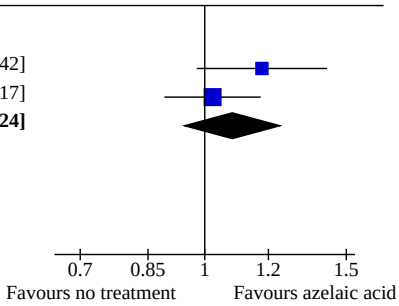
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Participants' global self-assessment of acne improvement	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1.1 moderately satisfied to very satisfied improvement (long term)	2	171	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.94, 1.24]
3.2 Withdrawal for any reason	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 long term	2	150	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.37, 1.22]
3.3 Change in lesion counts - total (percentage reduction from baseline)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.3.1 short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.3.2 medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.3.3 long term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.4 Change in lesion counts - non-inflamed (percentage reduction from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.1 short term	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.2 medium term	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4.3 long term	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.5 Change in lesion counts - papules (percentage reduction from baseline)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.5.1 short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5.2 medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.5.3 long term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.6 Change in lesion counts - pustules (percentage reduction from baseline)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.6.1 short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.6.2 medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.6.3 long term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.7 Change in lesion counts - inflamed (number of lesions post-intervention)	1		Other data	No numeric data
3.7.1 short term	1		Other data	No numeric data
3.7.2 medium term	1		Other data	No numeric data
3.7.3 long term	1		Other data	No numeric data
3.8 Change in lesion counts - comedones (number of lesions post-intervention)	1		Other data	No numeric data
3.8.1 short term	1		Other data	No numeric data
3.8.2 medium term	1		Other data	No numeric data
3.8.3 long term	1		Other data	No numeric data
3.9 Minor adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.9.1 scaling	2	171	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.15, 1.50]
3.9.2 erythema	2	171	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.12, 1.21]
3.9.3 dryness	2	171	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.20, 1.85]
3.9.4 oiliness	2	171	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.27, 2.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9.5 itching	2	171	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.23, 2.29]
3.9.6 total events (long term)	2	171	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.36, 0.97]

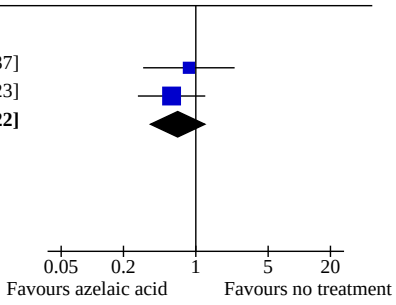
Analysis 3.1. Comparison 3: Topical azelaic acid versus no treatment, Outcome 1: Participants' global self-assessment of acne improvement

Study or Subgroup	Azelaic acid Events	Azelaic acid Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 moderately satisfied to very satisfied improvement (long term)						
Pazoki-Toroudi 2010	38	40	25	31	39.8%	1.18 [0.98 , 1.42]
Pazoki-Toroudi 2011	45	50	44	50	60.2%	1.02 [0.89 , 1.17]
Subtotal (95% CI)		**90**		**81**	**100.0%**	**1.08 [0.94 , 1.24]**
Total events:	83		69			
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 1 (P = 0.23); I² = 31%						
Test for overall effect: Z = 1.13 (P = 0.26)						



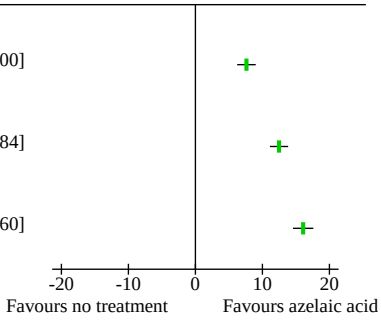
Analysis 3.2. Comparison 3: Topical azelaic acid versus no treatment, Outcome 2: Withdrawal for any reason

Study or Subgroup	Azelaic acid Events	Azelaic acid Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 long term						
Pazoki-Toroudi 2011	6	50	7	50	35.2%	0.86 [0.31 , 2.37]
Picosse 2015	7	25	12	25	64.8%	0.58 [0.28 , 1.23]
Subtotal (95% CI)		**75**		**75**	**100.0%**	**0.67 [0.37 , 1.22]**
Total events:	13		19			
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Not applicable						



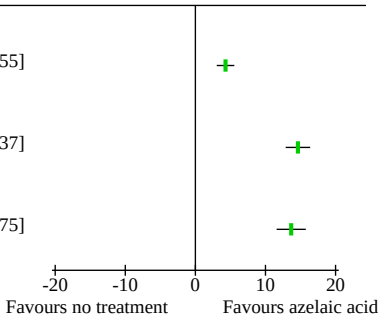
Analysis 3.3. Comparison 3: Topical azelaic acid versus no treatment, Outcome 3: Change in lesion counts - total (percentage reduction from baseline)

Study or Subgroup	Azelaic acid Mean	SD	Total	No treatment Mean	SD	Total	Mean Difference IV, Random, 95% CI
3.3.1 short term							
Pazoki-Toroudi 2011	34.16	3.72	50	26.54	3.32	50	7.62 [6.24 , 9.00]
3.3.2 medium term							
Pazoki-Toroudi 2011	54.72	3.64	48	42.24	3.17	49	12.48 [11.12 , 13.84]
3.3.3 long term							
Pazoki-Toroudi 2011	62.97	3.62	44	46.89	3.62	43	16.08 [14.56 , 17.60]



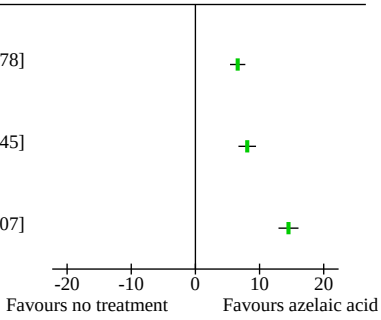
Analysis 3.4. Comparison 3: Topical azelaic acid versus no treatment, Outcome 4: Change in lesion counts - non-inflamed (percentage reduction from baseline)

Study or Subgroup	Azelaic acid Mean	SD	Total	No treatment Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.4.1 short term							
Pazoki-Toroudi 2011	27.62	3.73	50	23.32	2.54	50	4.30 [3.05 , 5.55]
3.4.2 medium term							
Pazoki-Toroudi 2011	55.48	5.06	48	40.85	3.56	49	14.63 [12.89 , 16.37]
3.4.3 long term							
Pazoki-Toroudi 2011	59.21	5.54	44	45.54	4.29	43	13.67 [11.59 , 15.75]



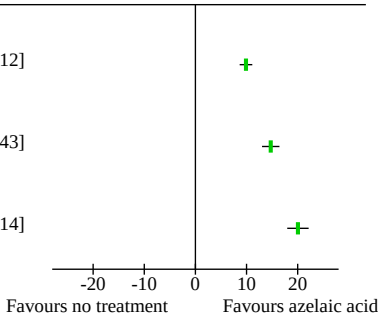
Analysis 3.5. Comparison 3: Topical azelaic acid versus no treatment, Outcome 5: Change in lesion counts - papules (percentage reduction from baseline)

Study or Subgroup	Azelaic acid Mean	SD	Total	No treatment Mean	SD	Total	Mean Difference IV, Random, 95% CI
3.5.1 short term							
Pazoki-Toroudi 2011	33.13	3.32	50	26.54	2.74	50	6.59 [5.40 , 7.78]
3.5.2 medium term							
Pazoki-Toroudi 2011	55.31	3.37	48	47.23	3.51	49	8.08 [6.71 , 9.45]
3.5.3 long term							
Pazoki-Toroudi 2011	67.54	4.11	44	53.03	3.26	43	14.51 [12.95 , 16.07]



Analysis 3.6. Comparison 3: Topical azelaic acid versus no treatment, Outcome 6: Change in lesion counts - pustules (percentage reduction from baseline)

Study or Subgroup	Azelaic acid Mean	SD	Total	No treatment Mean	SD	Total	Mean Difference IV, Random, 95% CI
3.6.1 short term							
Pazoki-Toroudi 2011	39.73	3.67	50	29.84	2.52	50	9.89 [8.66 , 11.12]
3.6.2 medium term							
Pazoki-Toroudi 2011	53.36	4.81	48	38.63	3.64	49	14.73 [13.03 , 16.43]
3.6.3 long term							
Pazoki-Toroudi 2011	62.15	5.49	44	42.1	4.41	43	20.05 [17.96 , 22.14]



Analysis 3.7. Comparison 3: Topical azelaic acid versus no treatment, Outcome 7: Change in lesion counts - inflamed (number of lesions post-intervention)

Change in lesion counts - inflamed (number of lesions post-intervention)

Study	Subgroup	Topical azelaic acid	No treatment	P value
short term				
Pazoki-Toroudi 2010	pustules	mean ± SD: 5.72 ± 0.66	mean ± SD: 8.21 ± 0.74	< 0.01
Pazoki-Toroudi 2010	papules	mean ± SD: 8.53 ± 0.62	mean ± SD: 10.62 ± 0.92	< 0.01
medium term				
Pazoki-Toroudi 2010	pustules	mean ± SD: 4.2 ± 0.39	mean ± SD: 8.06 ± 0.51	< 0.01
Pazoki-Toroudi 2010	papules	mean ± SD: 6.01 ± 0.23	mean ± SD: 8.16 ± 0.31	< 0.01
long term				
Pazoki-Toroudi 2010	pustules	mean ± SD: 4.22 ± 0.3	mean ± SD: 7.12 ± 0.27	< 0.01
Pazoki-Toroudi 2010	papules	mean ± SD: 6.27 ± 0.41	mean ± SD: 11.04 ± 0.54	< 0.01

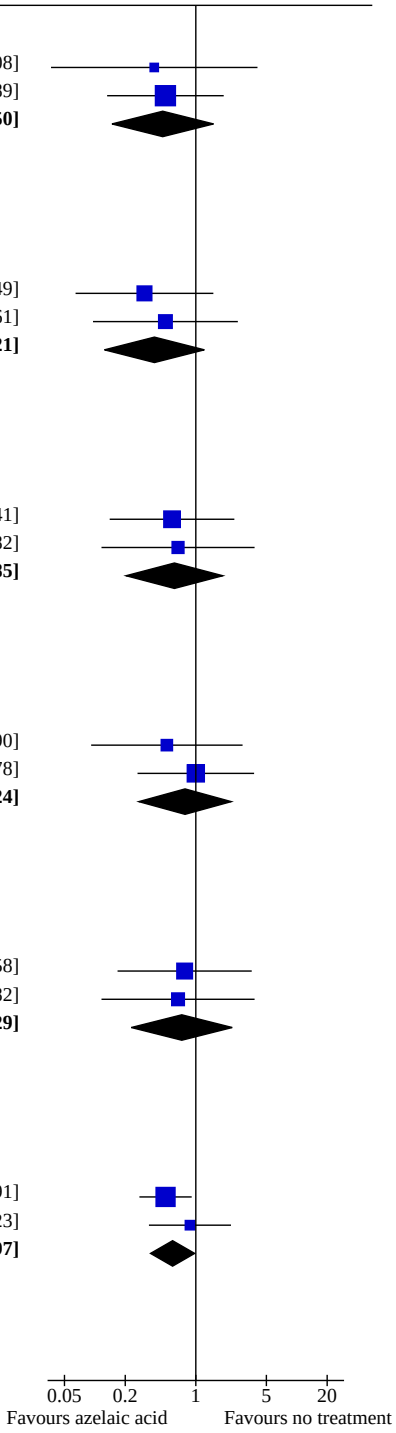
Analysis 3.8. Comparison 3: Topical azelaic acid versus no treatment, Outcome 8: Change in lesion counts - comedones (number of lesions post-intervention)

Change in lesion counts - comedones (number of lesions post-intervention)

Study	Subgroup	Topical azelaic acid	No treatment	P value
short term				
Pazoki-Toroudi 2010	comedones	mean ± SD: 5.24 ± 0.61	mean ± SD: 8.8 ± 0.46	< 0.01
medium term				
Pazoki-Toroudi 2010	comedones	mean ± SD: 2.22 ± 0.21	mean ± SD: 7.32 ± 0.51	< 0.01
long term				
Pazoki-Toroudi 2010	comedones	mean ± SD: 2.28 ± 0.09	mean ± SD: 5.36 ± 0.31	< 0.01

Analysis 3.9. Comparison 3: Topical azelaic acid versus no treatment, Outcome 9: Minor adverse events

Study or Subgroup	Azelaic acid Events	Total	No treatment Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 scaling						
Pazoki-Toroudi 2010	1	40	2	31	24.2%	0.39 [0.04 , 4.08]
Pazoki-Toroudi 2011	3	50	6	50	75.8%	0.50 [0.13 , 1.89]
Subtotal (95% CI)		**90**		**81**	**100.0%**	**0.47 [0.15 , 1.50]**
Total events:	4		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
3.9.2 erythema						
Pazoki-Toroudi 2010	2	40	5	31	52.5%	0.31 [0.06 , 1.49]
Pazoki-Toroudi 2011	2	50	4	50	47.5%	0.50 [0.10 , 2.61]
Subtotal (95% CI)		**90**		**81**	**100.0%**	**0.39 [0.12 , 1.21]**
Total events:	4		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
3.9.3 dryness						
Pazoki-Toroudi 2010	3	40	4	31	60.1%	0.58 [0.14 , 2.41]
Pazoki-Toroudi 2011	2	50	3	50	39.9%	0.67 [0.12 , 3.82]
Subtotal (95% CI)		**90**		**81**	**100.0%**	**0.61 [0.20 , 1.85]**
Total events:	5		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.39)						
3.9.4 oiliness						
Pazoki-Toroudi 2010	2	40	3	31	37.2%	0.52 [0.09 , 2.90]
Pazoki-Toroudi 2011	4	50	4	50	62.8%	1.00 [0.26 , 3.78]
Subtotal (95% CI)		**90**		**81**	**100.0%**	**0.78 [0.27 , 2.24]**
Total events:	6		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.65)						
3.9.5 itching						
Pazoki-Toroudi 2010	3	40	3	31	56.6%	0.78 [0.17 , 3.58]
Pazoki-Toroudi 2011	2	50	3	50	43.4%	0.67 [0.12 , 3.82]
Subtotal (95% CI)		**90**		**81**	**100.0%**	**0.73 [0.23 , 2.29]**
Total events:	5		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.59)						
3.9.6 total events (long term)						
Pazoki-Toroudi 2010	11	40	17	31	71.1%	0.50 [0.28 , 0.91]
Pazoki-Toroudi 2011	7	50	8	50	28.9%	0.88 [0.34 , 2.23]
Subtotal (95% CI)		**90**		**81**	**100.0%**	**0.59 [0.36 , 0.97]**
Total events:	18		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						



Comparison 4. Topical salicylic acid versus other topical treatments

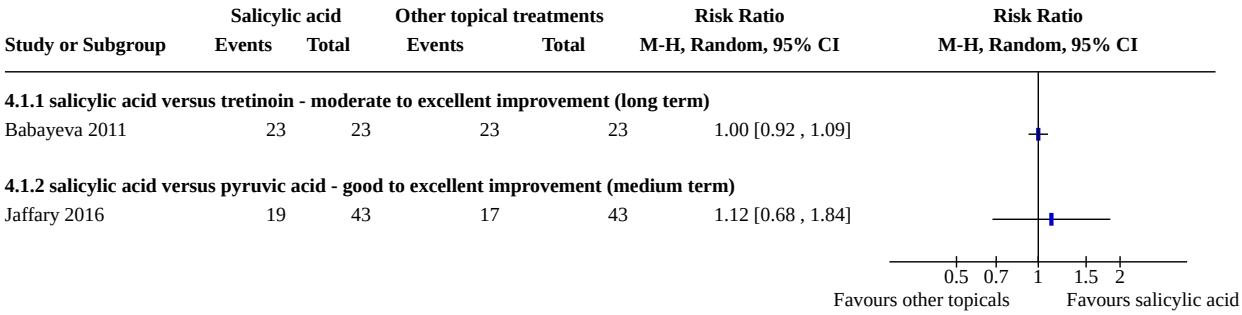
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Participants' global self-assessment of acne improvement	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.1 salicylic acid versus tretinoin - moderate to excellent improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1.2 salicylic acid versus pyruvic acid - good to excellent improvement (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.2 Participants' global self-assessment of acne improvement	3		Other data	No numeric data
4.2.1 split-face trials	2		Other data	No numeric data
4.2.2 parallel trial	1		Other data	No numeric data
4.3 Withdrawal for any reason	7		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.1 salicylic acid versus pyruvic acid (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.2 salicylic acid versus benzoyl peroxide (short term)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.3 salicylic acid versus benzoyl peroxide (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.4 salicylic acid versus tretinoin (long term)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3.5 salicylic acid versus Jessner's solution (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.4 Change in lesion counts - total (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.4.1 salicylic acid versus tretinoin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.4.2 salicylic acid versus tretinoin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.4.3 salicylic acid versus tretinoin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.5 Change in lesion counts - inflamed (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.5.1 salicylic acid versus tretinoin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5.2 salicylic acid versus tretinoin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.5.3 salicylic acid versus tretinoin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.6 Change in lesion counts - inflamed (mean counts or %)	3		Other data	No numeric data
4.6.1 parallel trials	1		Other data	No numeric data
4.6.2 split-face trials	2		Other data	No numeric data
4.7 Change in lesion counts - papules (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.7.1 salicylic acid versus pyruvic acid (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.7.2 salicylic acid versus pyruvic acid (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.8 Change in lesion count - pustules (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.8.1 salicylic acid versus pyruvic acid (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.8.2 salicylic acid versus pyruvic acid (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.9 Change in lesion counts - non-inflamed (number of lesions post-intervention)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.9.1 salicylic acid versus tretinoin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.9.2 salicylic acid versus tretinoin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.9.3 salicylic acid versus tretinoin (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.9.4 salicylic acid versus pyruvic acid (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.9.5 salicylic acid versus pyruvic acid (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.10 Change in lesion counts - non-inflamed (counts or %)	3		Other data	No numeric data
4.10.1 parallel trials	1		Other data	No numeric data
4.10.2 split-face trials	2		Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.11 Change in lesion counts - various types of acne lesions (counts or %)	4		Other data	No numeric data
4.11.1 parallel trials	2		Other data	No numeric data
4.11.2 split-face trials	1		Other data	No numeric data
4.11.3 cross-over trials	1		Other data	No numeric data
4.12 Physicians' global evaluation of acne improvement	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.12.1 salicylic acid versus tretinoin - moderate to excellent improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.12.2 salicylic acid versus Jessner's solution - fair to good improvement (long term))	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.12.3 salicylic acid versus pyruvic acid - good to excellent improvement (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.13 Physicians' global evaluation of acne improvement (%)	1		Other data	No numeric data
4.13.1 split-face trials	1		Other data	No numeric data
4.14 Physicians' global evaluation of acne improvement	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.14.1 salicylic acid versus lipohydroxy acid - 3-point scale defined by investigator, high = well (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.14.2 salicylic acid versus lipohydroxy acid - 3-point scale defined by investigator, high = well (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.14.3 salicylic acid versus lipohydroxy acid - 3-point scale defined by investigator, high = well (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.15 Minor adverse events	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.15.1 dryness - salicylic acid versus tretinoin	1	46	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.70, 1.94]
4.15.2 peeling - salicylic acid versus tretinoin	1	46	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.40, 1.26]
4.15.3 erythema - salicylic acid versus tretinoin	1	46	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.38, 2.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.15.4 burning - salicylic acid versus tretinoin	1	46	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.50, 2.63]
4.15.5 itching - salicylic acid versus tretinoin	1	46	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.16, 2.22]
4.15.6 postpeel burning and stinging - salicylic acid versus Jessner's solution	1	40	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.81, 2.58]
4.15.7 postpeel erythema - salicylic acid versus Jessner's solution	1	40	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.50, 4.52]
4.15.8 postpeel hyperpigmentation - salicylic acid versus Jessner's solution	1	40	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 2.94]
4.15.9 total events - salicylic acid versus benzoyl peroxide (short term)	1	60	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.15.10 total events - salicylic acid versus benzoyl peroxide (medium term)	1	41	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.01, 4.11]
4.15.11 total events - salicylic acid versus tretinoin (long term)	2	74	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.66, 2.87]
4.16 Quality of life (QoL) - AQOL (score, post-intervention)	2		Other data	No numeric data

Analysis 4.1. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 1: Participants' global self-assessment of acne improvement



Analysis 4.2. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 2: Participants' global self-assessment of acne improvement

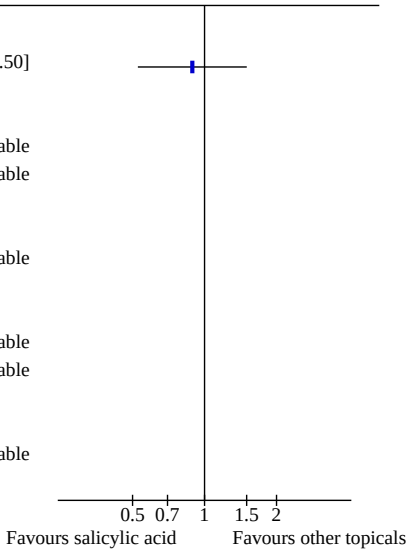
Participants' global self-assessment of acne improvement

Study	Duration	Items	Salicylic acid	Topical treatments (comparator)	P value
split-face trials					
Bae 2013	short term	mild to good improvement	12 (92.3%)	11 (84.6%) (Jessner's Solution)	P value was not reported; Quote" "In terms of subject global assessment...there is no sig-

					nificant differences between the groups..."
Kessler 2008	treatment duration of 10 weeks, measured at two months post-treatment	patient self-assessment questionnaire	35%	41%(glycolic acid peel)	P value was not reported.
parallel trial					
Chantalat 2006	medium term	acne parameters and broad skin benefits	Unclear, not reported	Unclear, not reported (10% benzoyl peroxide, BPO)	Unclear, not reported. Quote: "Subject self assessment results show that subjects treated with the microgel complex reported a greater improvement...compared to 10% BPO."

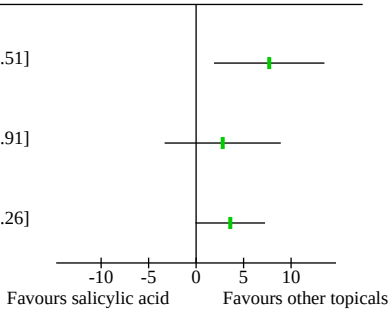
Analysis 4.3. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 3: Withdrawal for any reason

Study or Subgroup	Salicylic acid Events	Salicylic acid Total	Other topical treatments Events	Other topical treatments Total	Risk Ratio M-H, Random, 95% CI
4.3.1 salicylic acid versus pyruvic acid (medium term)					
Jaffary 2016	16	43	18	43	0.89 [0.53 , 1.50]
4.3.2 salicylic acid versus benzoyl peroxide (short term)					
Draelos 2016	0	30	0	30	Not estimable
Shalita 1989	0	15	0	15	Not estimable
4.3.3 salicylic acid versus benzoyl peroxide (medium term)					
Chantalat 2006	0	20	0	21	Not estimable
4.3.4 salicylic acid versus tretinoin (long term)					
Babayeva 2011	0	23	0	23	Not estimable
NilFroushzadeh 2009	0	14	0	14	Not estimable
4.3.5 salicylic acid versus Jessner's solution (long term)					
Dayal 2017	0	20	0	20	Not estimable



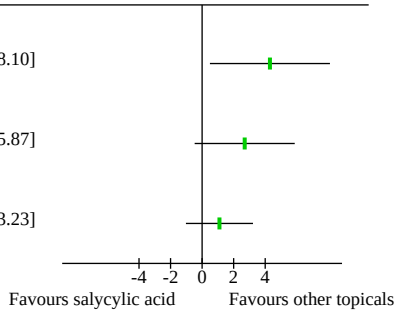
Analysis 4.4. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 4: Change in lesion counts - total (number of lesions post-intervention)

Study or Subgroup	Salicylic acid Mean	Salicylic acid SD	Salicylic acid Total	Other topical treatments Mean	Other topical treatments SD	Other topical treatments Total	Mean Difference IV, Random, 95% CI
4.4.1 salicylic acid versus tretinoin (short term)							
Babayeva 2011	37.3	10.4	23	29.6	9.7	23	7.70 [1.89 , 13.51]
4.4.2 salicylic acid versus tretinoin (medium term)							
Babayeva 2011	23.2	11.8	23	20.4	9.2	23	2.80 [-3.31 , 8.91]
4.4.3 salicylic acid versus tretinoin (long term)							
Babayeva 2011	13.2	6.9	23	9.6	5.7	23	3.60 [-0.06 , 7.26]



Analysis 4.5. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 5: Change in lesion counts - inflamed (number of lesions post-intervention)

Study or Subgroup	Salicylic acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
4.5.1 salicylic acid versus tretinoin (short term)							
Babayeva 2011	15.8	7.2	23	11.5	5.9	23	4.30 [0.50 , 8.10]
4.5.2 salicylic acid versus tretinoin (medium term)							
Babayeva 2011	10.7	6.1	23	8	4.8	23	2.70 [-0.47 , 5.87]
4.5.3 salicylic acid versus tretinoin (long term)							
Babayeva 2011	4.9	4.1	23	3.8	3.2	23	1.10 [-1.03 , 3.23]



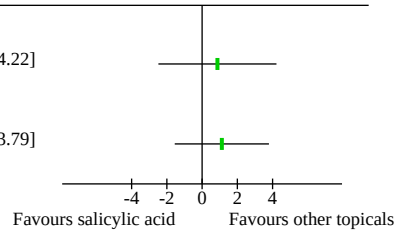
Analysis 4.6. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 6: Change in lesion counts - inflamed (mean counts or %)

Change in lesion counts - inflamed (mean counts or %)

Study	Outcome	Salicylic acid	Topical treatments (comparator)	P value
parallel trials				
Babayeva 2011	Percent reduction -inflamed (long term)	77.6%	81.5%	P value was not reported. Quote: "...these differences were not statistically significant..."
split-face trials				
Bae 2013	Average reduction of inflamed lesion (medium term)	4.4	5.7 (Jessner's solution peels)	P value was not reported; Quote" Inflammatory acne lesion counts did not differ significantly between salicylic acid and Jessner's solution peels"
Levesque 2011	Mean inflamed lesion counts post intervention (long term: 12 weeks after start of treatment)	3.9	3.7 (lipohydroxyacid peels)	P = 0.111. Quote:"The mean number of inflammatory lesions was 6.1 and 6.6 at Day 14 (baseline) and 3.7 and 3.9 at Day 98 on the sides that received the LHA and salicylic acid peels..."

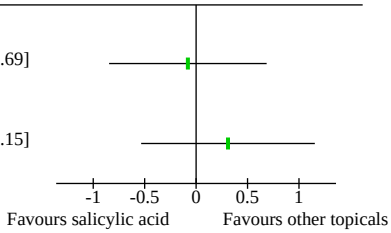
Analysis 4.7. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 7: Change in lesion counts - papules (number of lesions post-intervention)

Study or Subgroup	Salicylic acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
4.7.1 salicylic acid versus pyruvic acid (short term)							
Jaffary 2016	6.28	6	27	5.41	6.3	25	0.87 [-2.48 , 4.22]
4.7.2 salicylic acid versus pyruvic acid (medium term)							
Jaffary 2016	4.16	5.5	27	3.04	4.3	25	1.12 [-1.55 , 3.79]



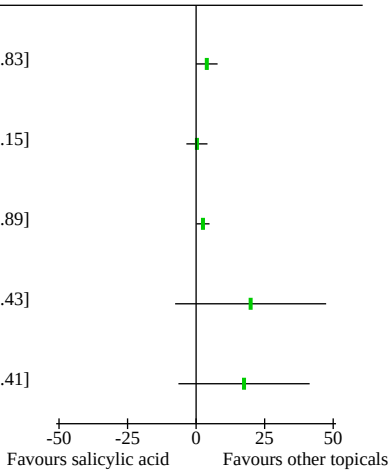
Analysis 4.8. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 8: Change in lesion count - pustules (number of lesions post-intervention)

Study or Subgroup	Salicylic acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
4.8.1 salicylic acid versus pyruvic acid (short term)							
Jaffary 2016	0.96	1.3	27	1.04	1.5	25	-0.08 [-0.85 , 0.69]
4.8.2 salicylic acid versus pyruvic acid (medium term)							
Jaffary 2016	1.2	1.7	27	0.89	1.4	25	0.31 [-0.53 , 1.15]



Analysis 4.9. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 9: Change in lesion counts - non-inflamed (number of lesions post-intervention)

Study or Subgroup	Salicylic acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
4.9.1 salicylic acid versus tretinoin (short term)							
Babayeva 2011	21.5	7.1	23	17.6	6.5	23	3.90 [-0.03 , 7.83]
4.9.2 salicylic acid versus tretinoin (medium term)							
Babayeva 2011	13	6.9	23	12.7	6.4	23	0.30 [-3.55 , 4.15]
4.9.3 salicylic acid versus tretinoin (long term)							
Babayeva 2011	8.3	4.7	23	5.8	3.5	23	2.50 [0.11 , 4.89]
4.9.4 salicylic acid versus pyruvic acid (short term)							
Jaffary 2016	59.48	67.1	27	39.59	27.7	25	19.89 [-7.65 , 47.43]
4.9.5 salicylic acid versus pyruvic acid (medium term)							
Jaffary 2016	50.04	55.6	27	32.56	29.4	25	17.48 [-6.45 , 41.41]



Analysis 4.10. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 10: Change in lesion counts - non-inflamed (counts or %)

Change in lesion counts - non-inflamed (counts or %)

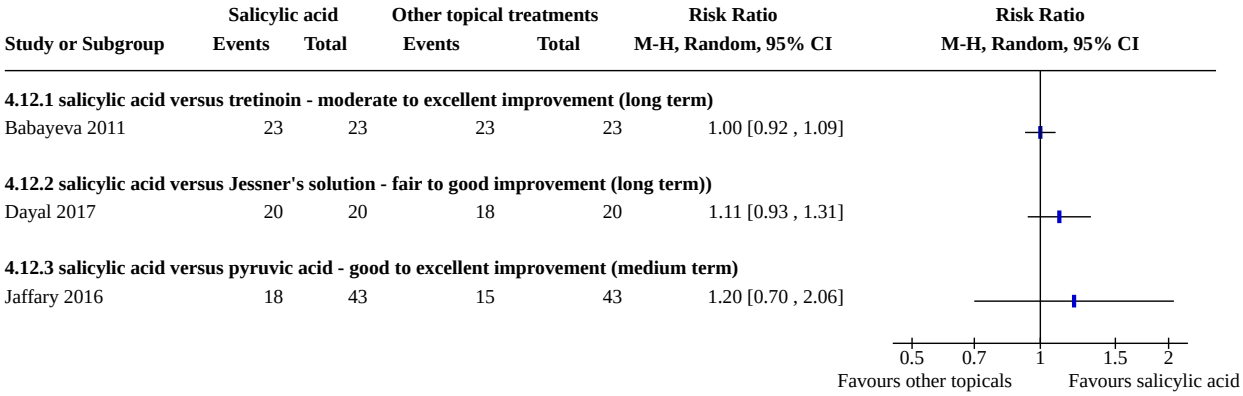
Study	Time points	Salicylic acid	Topical treatments (comparator)	P value
parallel trials				
Babayeva 2011	Percent reduction - long term	81.5%	87.2%	P value was not reported. Quote: "...these differences were not statistically significant..."
split-face trials				
Bae 2013	Average number reduction of non-inflamed - medium term	8	4.3	0.04
Levesque 2011	Percent reduction - long term: 12 weeks after start of treatment	48.5%	55.6% (lipohydroxyacid peels)	0.878

Analysis 4.11. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 11: Change in lesion counts - various types of acne lesions (counts or %)

Change in lesion counts - various types of acne lesions (counts or %)

Study	Time points	Salicylic acid	Topical treatments (comparator)	P value
parallel trials				
Babayeva 2011	Percent reduction - total lesions (long term: 12 weeks after start of treatment)	80.2%	85.6% (Tretinoin)	P value was not reported. Quote: "...these differences were not statistically significant..."
NilFroushzadeh 2009	Percent reduction - open comedones (long term: 12 weeks after start of treatment)	64.26%	67% (Tretinoin)	>0.05
NilFroushzadeh 2009	Percent reduction - papule (long term: 12 weeks after start of treatment)	84.5%	71.67% (Tretinoin)	0.031
NilFroushzadeh 2009	Percent reduction - total lesions (long term: 12 weeks after start of treatment)	77.91%	72.20% (Tretinoin)	0.039
NilFroushzadeh 2009	Percent reduction - pustules (long term: 12 weeks after start of treatment)	90%	76.19% (Tretinoin)	>0.05
NilFroushzadeh 2009	Percent reduction - closed comedones (long term: 12 weeks after start of treatment)	87.05%	60.94% (Tretinoin)	0.011
split-face trials				
Kessler 2008	Percent reduction - total lesion(treatment duration of 10 weeks, measured at one month post-treatment)	47%	43% (30% glycolic acid peel)	> 0.05
cross-over trials				
Shalita 1989	number of lesions post intervention - comedo counts (short term)	10.9	14.9 (10% benzoyl peroxide wash)	No difference

Analysis 4.12. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 12: Physicians' global evaluation of acne improvement



Analysis 4.13. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 13: Physicians' global evaluation of acne improvement (%)

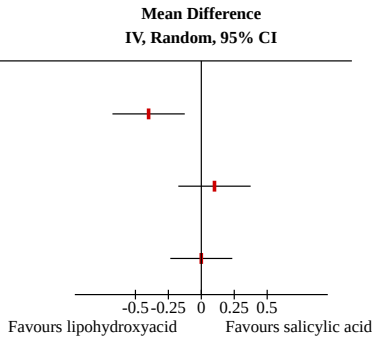
Physicians' global evaluation of acne improvement (%)

Study	Time points	Salicylic acid	Topical treatments (comparator)	P value
split-face trials				

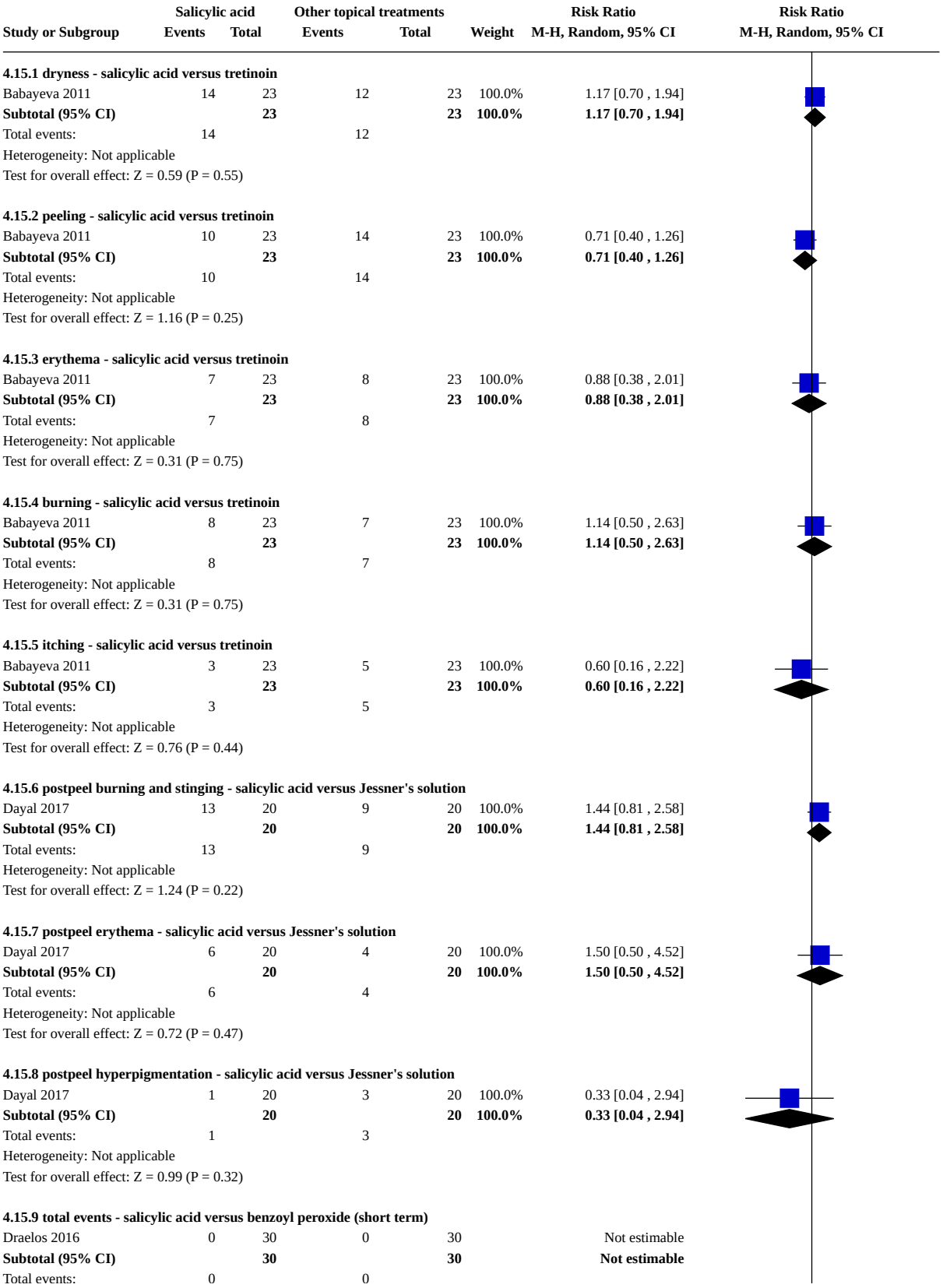
Kessler 2008	Good to fair improvement (treatment duration of 10 weeks, measured at two months post-treatment)	81%	75% (30% glycolic acid)	Unclear, not reported. The author did not report whether there is any statistical difference between groups.

Analysis 4.14. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 14: Physicians' global evaluation of acne improvement

Study or Subgroup	MD	SE	Mean Difference IV, Random, 95% CI
4.14.1 salicylic acid versus lipohydroxy acid - 3-point scale defined by investigator, high = well (short term)			
Levesque 2011	-0.4	0.14	-0.40 [-0.67 , -0.13]
4.14.2 salicylic acid versus lipohydroxy acid - 3-point scale defined by investigator, high = well (medium term)			
Levesque 2011	0.1	0.14	0.10 [-0.17 , 0.37]
4.14.3 salicylic acid versus lipohydroxy acid - 3-point scale defined by investigator, high = well (long term)			
Levesque 2011	0	0.12	0.00 [-0.24 , 0.24]

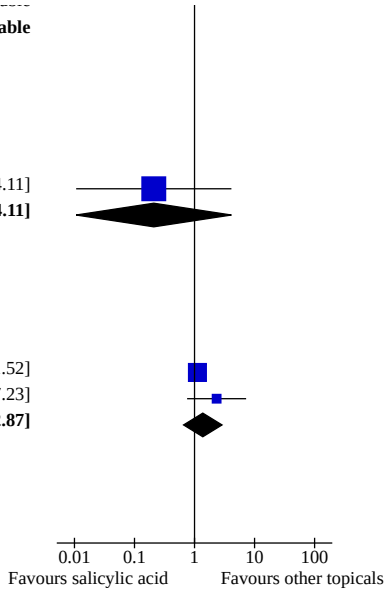


Analysis 4.15. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 15: Minor adverse events



Analysis 4.15. (Continued)

Subtotal (95% CI)		**30**		**30**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.15.10 total events - salicylic acid versus benzoyl peroxide (medium term)						
Chantalat 2006	0	20	2	21	100.0%	0.21 [0.01 , 4.11]
Subtotal (95% CI)		**20**		**21**	**100.0%**	**0.21 [0.01 , 4.11]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
4.15.11 total events - salicylic acid versus tretinoin (long term)						
Babayeva 2011	19	23	17	23	72.0%	1.12 [0.82 , 1.52]
NilFroushzadeh 2009	7	14	3	14	28.0%	2.33 [0.75 , 7.23]
Subtotal (95% CI)		**37**		**37**	**100.0%**	**1.37 [0.66 , 2.87]**
Total events:	26		20			
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 1.96$, df = 1 (P = 0.16); $I^2 = 49\%$						
Test for overall effect: Z = 0.84 (P = 0.40)						



Analysis 4.16. Comparison 4: Topical salicylic acid versus other topical treatments, Outcome 16: Quality of life (QoL) - AQOL (score, post-intervention)

Quality of life (QoL) - AQOL (score, post-intervention)

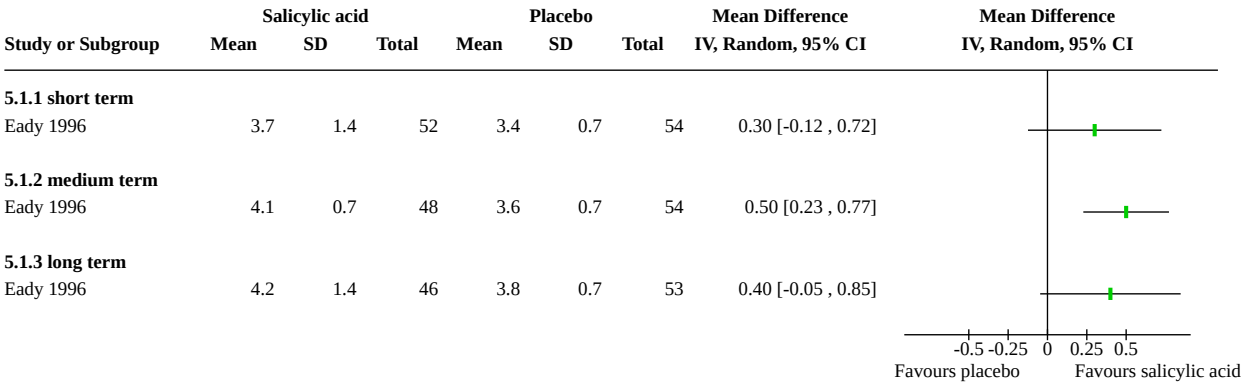
Study	Time points	Salicylic acid: mean ± sd	Topical treatments: mean ± sd (comparator)	P value
Babayeva 2011	Long term: 12 weeks after start of treatment	0.95 ± 1.9	0.91 ± 1.64 (tretinoin)	P value was not reported. Quote: "there were no significant differences in AQOL between treatment groups at baseline and at the end of the study"
Chantalat 2006	Short term and medium term	Unclear, not reported	Unclear, not reported	P value was not reported. Quote: "ARQL results show that subjects treated with novel microgel complex experienced a significant improvement in ARQL starting 2 weeks after baseline and continuing through the 6-week study."

Comparison 5. Topical salicylic acid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Participants' global self-assessment of acne improvement (score, high=well)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1.1 short term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1.2 medium term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

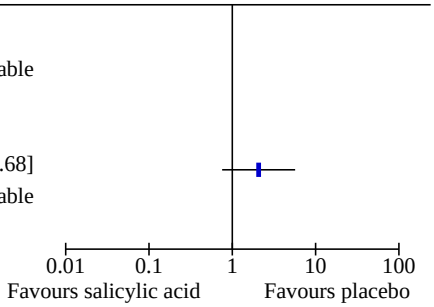
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1.3 long term	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.2 Withdrawal for any reason	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.2.1 short term	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.2.2 long term	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.3 Change in lesion counts (counts or %)	3		Other data	No numeric data
5.4 Change in lesion counts - inflamed (counts or %)	2		Other data	No numeric data
5.5 Change in lesion counts - non-inflamed (counts or %)	2		Other data	No numeric data
5.6 Physicians' global evaluation of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.6.1 good or excellent improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.7 Minor adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.7.1 total events (short term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.7.2 total events (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Topical salicylic acid versus placebo, Outcome 1: Participants' global self-assessment of acne improvement (score, high=well)



Analysis 5.2. Comparison 5: Topical salicylic acid versus placebo, Outcome 2: Withdrawal for any reason

Study or Subgroup	Salicylic acid Events	Salicylic acid Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
5.2.1 short term					
Draelos 2016	0	30	0	30	Not estimable
5.2.2 long term					
Eady 1996	10	56	5	58	2.07 [0.76 , 5.68]
Shalita 1981	0	25	0	24	Not estimable



Analysis 5.3. Comparison 5: Topical salicylic acid versus placebo, Outcome 3: Change in lesion counts (counts or %)

Change in lesion counts (counts or %)

Study	Subgroup	Salicylic acid	Placebo	P value
Eady 1996	Number of whitehead reduction (short, medium and long term)	Unclear, not reported	Unclear, not reported	no difference; no difference; < 0.002
Eady 1996	Number of total counts reduction (short, medium and long term)	Unclear, not reported	Unclear, not reported	no difference; < 0.043; < 0.001
Eady 1996	Number of papules reduction (short, medium and long term)	Unclear, not reported	Unclear, not reported	no difference; no difference; 0.022
Shalita 1981	Percent reduction -total (long term: 12 weeks after start of treatment)	38.4%	24.6%	not report and the author did not state whether this difference is significant
Techapichetvanich 2011	Percent reduction - noninflamed (long term: 10 weeks after start of treatment)	83.77%	25.83%	0.001
Techapichetvanich 2011	Percent reduction - total counts (long term: 10 weeks after start of treatment)	83.97%	35.94%	0.001

Analysis 5.4. Comparison 5: Topical salicylic acid versus placebo, Outcome 4: Change in lesion counts - inflamed (counts or %)

Change in lesion counts - inflamed (counts or %)

Study	Subgroup	Salicylic acid	Placebo	P value
Eady 1996	Number reduction - short, medium and long term (12 weeks after start of treatment)	Unclear, not reported	Unclear, not reported	no difference; no difference; < 0.022
Shalita 1981	percent reduction - short term	29.5%	20%	not report and the author did not state whether this difference is significant
Shalita 1981	percent reduction - medium term	44.6%	23%	not report and the author did not state whether this difference is significant
Shalita 1981	percent reduction - long term: 12 weeks after start of treatment	54%	29%	not report and the author did not state whether this difference is significant

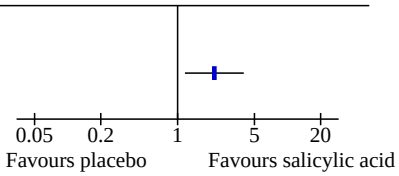
Analysis 5.5. Comparison 5: Topical salicylic acid versus placebo, Outcome 5: Change in lesion counts - non-inflamed (counts or %)

Change in lesion counts - non-inflamed (counts or %)

Study	Subgroup	Salicylic acid	Placebo	P value
Eady 1996	Number reduction - short, medium and long term (12 weeks after start of treatment)	Unclear, not reported	Unclear, not reported	no difference; 0.047; < 0.001
Shalita 1981	Percent reduction - open comedones (long term: 12 weeks after start of treatment)	39%	28%	not reported, but the author stated the difference is significant.
Shalita 1981	Percent reduction - closed comedones (long term: 12 weeks after start of treatment)	21%	21%	No difference

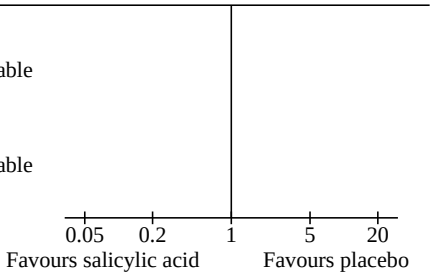
Analysis 5.6. Comparison 5: Topical salicylic acid versus placebo, Outcome 6: Physicians' global evaluation of acne improvement

Study or Subgroup	Salicylic acid Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.6.1 good or excellent improvement						
Shalita 1981	18	25	8	24	2.16 [1.17 , 4.00]	



Analysis 5.7. Comparison 5: Topical salicylic acid versus placebo, Outcome 7: Minor adverse events

Study or Subgroup	Salicylic acid Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.7.1 total events (short term)						
Draelos 2016	0	30	0	30	Not estimable	
5.7.2 total events (long term)						
Shalita 1981	0	25	0	24	Not estimable	



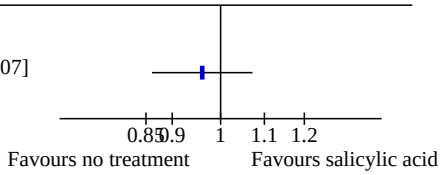
Comparison 6. Topical salicylic acid versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Participants' global self-assessment of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1.1 moderate to excellent improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Withdrawal for any reason	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.2.1 long term	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3 Change in lesion counts - total (percentage reduction from baseline)	3		Other data	No numeric data
6.4 Change in lesion counts - inflamed (percentage reduction from baseline)	2		Other data	No numeric data
6.5 Change in lesion counts - non-inflamed (percentage reduction from baseline)	2		Other data	No numeric data
6.6 Physicians' global evaluation of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.6.1 moderate to excellent improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.7 Minor adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.7.1 dryness	1	50	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.25, 5.68]
6.7.2 peeling	1	50	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.74, 3.03]
6.7.3 erythema	1	50	Risk Ratio (M-H, Random, 95% CI)	4.00 [0.94, 17.00]
6.7.4 burning	1	50	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.71, 3.89]
6.7.5 itching	1	50	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.45, 6.24]
6.7.6 total events (long term)	2	78	Risk Ratio (M-H, Random, 95% CI)	3.43 [0.14, 82.00]
6.8 Quality of life (QoL) - AQOL (score, post-intervention)	1		Other data	No numeric data

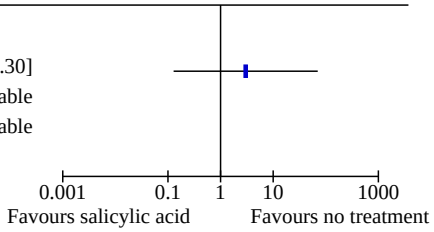
Analysis 6.1. Comparison 6: Topical salicylic acid versus no treatment, Outcome 1: Participants' global self-assessment of acne improvement

Study or Subgroup	Salicylic acid Events	Salicylic acid Total	No treatment Events	No treatment Total	Risk Ratio M-H, Random, 95% CI
6.1.1 moderate to excellent improvement (long term)					
Akarsu 2012	24	25	25	25	0.96 [0.86 , 1.07]



Analysis 6.2. Comparison 6: Topical salicylic acid versus no treatment, Outcome 2: Withdrawal for any reason

Study or Subgroup	Salicylic acid Events	Salicylic acid Total	No treatment Events	No treatment Total	Risk Ratio M-H, Random, 95% CI
6.2.1 long term					
Akarsu 2012	1	25	0	25	3.00 [0.13 , 70.30]
Kar 2013	0	30	0	30	Not estimable
NilFroushzadeh 2009	0	14	0	14	Not estimable



Analysis 6.3. Comparison 6: Topical salicylic acid versus no treatment, Outcome 3: Change in lesion counts - total (percentage reduction from baseline)

Change in lesion counts - total (percentage reduction from baseline)

Study	Subgroup	Salicylic acid	No treatment	P value
Akarsu 2012	Percent reduction - total (long term: 12 weeks after start of treatment)	94.3%	79.2%	Quote:"The mean percent reductions in NIL, IL and TL counts were significantly higher for patients in group 1 as opposed to the patients in group 2 at week 12".
Kar 2013	Percent reduction - total (long term: 16 weeks after start of treatment)	92.5%	73.4%	not report and the author did not state whether this difference is significant
NilFroushzadeh 2009	Percent reduction - total lesions (long term: 12 weeks after start of treatment)	77.91%	55.95%	0.039

Analysis 6.4. Comparison 6: Topical salicylic acid versus no treatment, Outcome 4: Change in lesion counts - inflamed (percentage reduction from baseline)

Change in lesion counts - inflamed (percentage reduction from baseline)

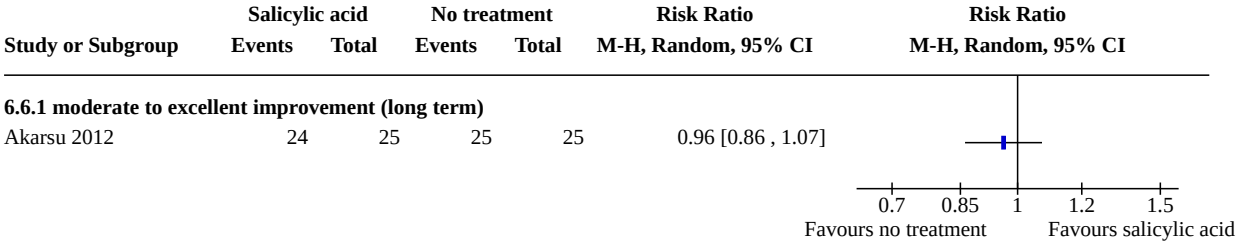
Study	Subgroup	Salicylic acid	No treatment	P value
Akarsu 2012	long term: 12 weeks after start of treatment	98.2%	73.8%	Quote:"The mean percent reductions in NIL, IL and TL counts were significantly higher for patients in group 1 as opposed to the patients in group 2 at week 12".
NilFroushzadeh 2009	long term: 12 weeks after start of treatment	papules: 84.5% pustules: 90%	papules: 26.63% pustules: 80%	papules: P = 0.031; pustules: P > 0.05

Analysis 6.5. Comparison 6: Topical salicylic acid versus no treatment, Outcome 5: Change in lesion counts - non-inflamed (percentage reduction from baseline)

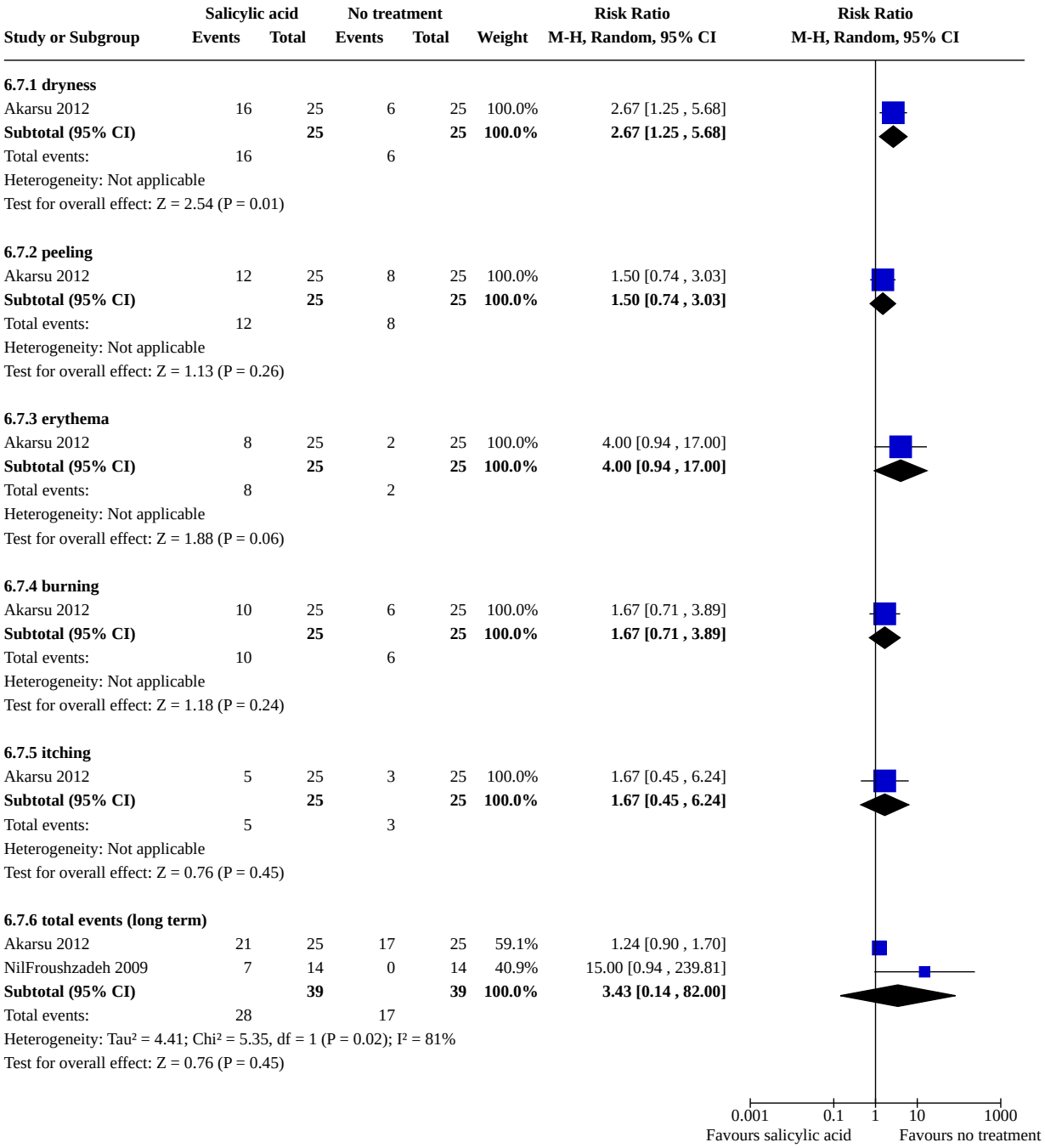
Change in lesion counts - non-inflamed (percentage reduction from baseline)

Study	Subgroup	Salicylic acid	No treatment	P value
Akarsu 2012	long term: 12 weeks after start of treatment	94.7%	81.1%	Quote:"The mean percent reductions in NIL, IL and TL counts were significantly higher for patients in group 1 as opposed to the patients in group 2 at week 12".
NilFroushzadeh 2009	long term: 12 weeks after start of treatment	open comedones:64.26% closed comedones:87.05%	open comedones:58.33% closed comedones:31.28%	open comedones: P > 0.05 closed comedones: P = 0.011

Analysis 6.6. Comparison 6: Topical salicylic acid versus no treatment, Outcome 6: Physicians' global evaluation of acne improvement



Analysis 6.7. Comparison 6: Topical salicylic acid versus no treatment, Outcome 7: Minor adverse events



Analysis 6.8. Comparison 6: Topical salicylic acid versus no treatment, Outcome 8: Quality of life (QoL) - AQOL (score, post-intervention)

Quality of life (QoL) - AQOL (score, post-intervention)

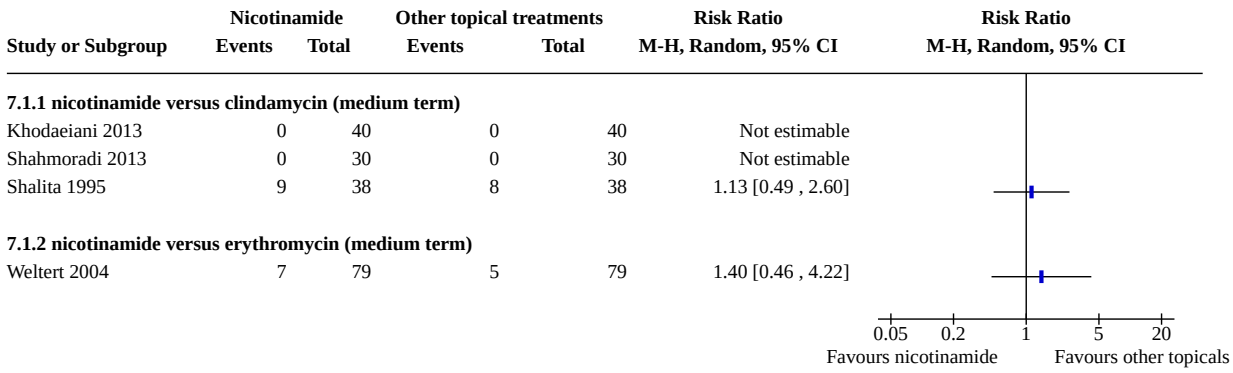
Study	Time points	Salicylic acid (median, 95%CI)	No treatment (median, 95%CI)	P value
Akarsu 2012	Long term: 12 weeks after start of treatment	0.5 (0.6-2.1)	1 (1.5-4.3)	Quote: "there were no significant differences in AQOL between treatment groups at baseline and at the end of the study".

Comparison 7. Topical nicotinamide versus other topical treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Withdrawal for any reason	4		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1.1 nicotinamide versus clindamycin (medium term)	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1.2 nicotinamide versus erythromycin (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.2 Change in lesion counts - inflamed (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.2.1 nicotinamide versus clindamycin (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.2.2 nicotinamide versus clindamycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.3 Change in lesion counts - inflamed counts (counts or %)	2		Other data	No numeric data
7.3.1 short term	1		Other data	No numeric data
7.3.2 medium term	2		Other data	No numeric data
7.4 Change in lesion counts - comedones (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.4.1 nicotinamide versus erythromycin (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.5 Physicians' global evaluation of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.5.1 nicotinamide versus clindamycin - moderately or much better improvement (short term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.5.2 nicotinamide versus clindamycin - moderately or much better improvement (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.6 Physicians' global evaluation of acne improvement	1		Other data	No numeric data
7.6.1 short term	1		Other data	No numeric data
7.6.2 medium term	1		Other data	No numeric data
7.7 Minor adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

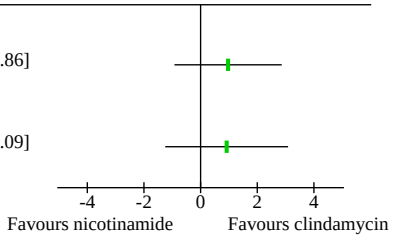
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.7.1 itching - nicotinamide versus clindamycin	1	80	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.32, 5.58]
7.7.2 burning - nicotinamide versus clindamycin	1	80	Risk Ratio (M-H, Random, 95% CI)	3.50 [0.77, 15.83]
7.7.3 crusting - nicotinamide versus clindamycin	1	80	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.78]
7.7.4 greasy skin - nicotinamide versus clindamycin	1	80	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.68]
7.7.5 dermatitis - nicotinamide versus clindamycin	1	80	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 71.51]
7.7.6 total events - nicotinamide versus clindamycin (medium term)	3	216	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.73, 1.99]
7.7.7 pertinent clinical signs - nicotinamide versus erythromycin (short term)	1	158	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.60, 2.99]
7.7.8 pertinent clinical signs - nicotinamide versus erythromycin (medium term)	1	158	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.50, 2.44]
7.7.9 functional or physical signs - nicotinamide versus erythromycin (short term)	1	158	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.61, 1.82]
7.7.10 functional or physical signs - nicotinamide versus erythromycin (medium term)	1	158	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.38, 1.48]

Analysis 7.1. Comparison 7: Topical nicotinamide versus other topical treatments, Outcome 1: Withdrawal for any reason



Analysis 7.2. Comparison 7: Topical nicotinamide versus other topical treatments, Outcome 2: Change in lesion counts - inflamed (number of lesions post-intervention)

Study or Subgroup	Nicotinamide Mean	SD	Total	Clindamycin Mean	SD	Total	Mean Difference IV, Random, 95% CI
7.2.1 nicotinamide versus clindamycin (short term)							
Khodaeiani 2013	49.6	3.74	40	48.63	4.83	40	0.97 [-0.92 , 2.86]
7.2.2 nicotinamide versus clindamycin (medium term)							
Khodaeiani 2013	24.45	5.39	40	23.53	4.46	40	0.92 [-1.25 , 3.09]



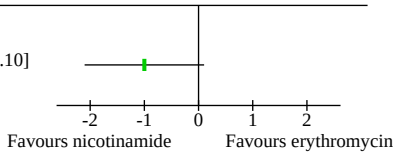
Analysis 7.3. Comparison 7: Topical nicotinamide versus other topical treatments, Outcome 3: Change in lesion counts - inflamed counts (counts or %)

Change in lesion counts - inflamed counts (counts or %)

Study	Subgroup	Nicotinamide (mean, sd)	Topical treatments (mean, sd)	P value
short term				
Shalita 1995	Percent reduction - inflamed	Unclear	Unclear	0.06
medium term				
Shalita 1995	Percent reduction - inflamed	59.5±41.2	42.7±41.3	0.17
Weltert 2004	Number of lesions post intervention - inflamed lesion counts	4±8	5±5	not report, the author did not state whether the difference is statistical significant.

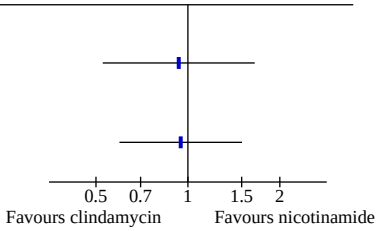
Analysis 7.4. Comparison 7: Topical nicotinamide versus other topical treatments, Outcome 4: Change in lesion counts - comedones (number of lesions post-intervention)

Study or Subgroup	Nicotinamide Mean	SD	Total	Erythromycin Mean	SD	Total	Mean Difference IV, Random, 95% CI
7.4.1 nicotinamide versus erythromycin (medium term)							
Weltert 2004	12	4	79	13	3	79	-1.00 [-2.10 , 0.10]



Analysis 7.5. Comparison 7: Topical nicotinamide versus other topical treatments, Outcome 5: Physicians' global evaluation of acne improvement

Study or Subgroup	Nicotinamide Events	Total	Clindamycin Events	Total	Risk Ratio M-H, Random, 95% CI
7.5.1 nicotinamide versus clindamycin - moderately or much better improvement (short term)					
Shalita 1995	14	38	15	38	0.93 [0.53 , 1.66]
7.5.2 nicotinamide versus clindamycin - moderately or much better improvement (medium term)					
Shalita 1995	18	38	19	38	0.95 [0.60 , 1.50]

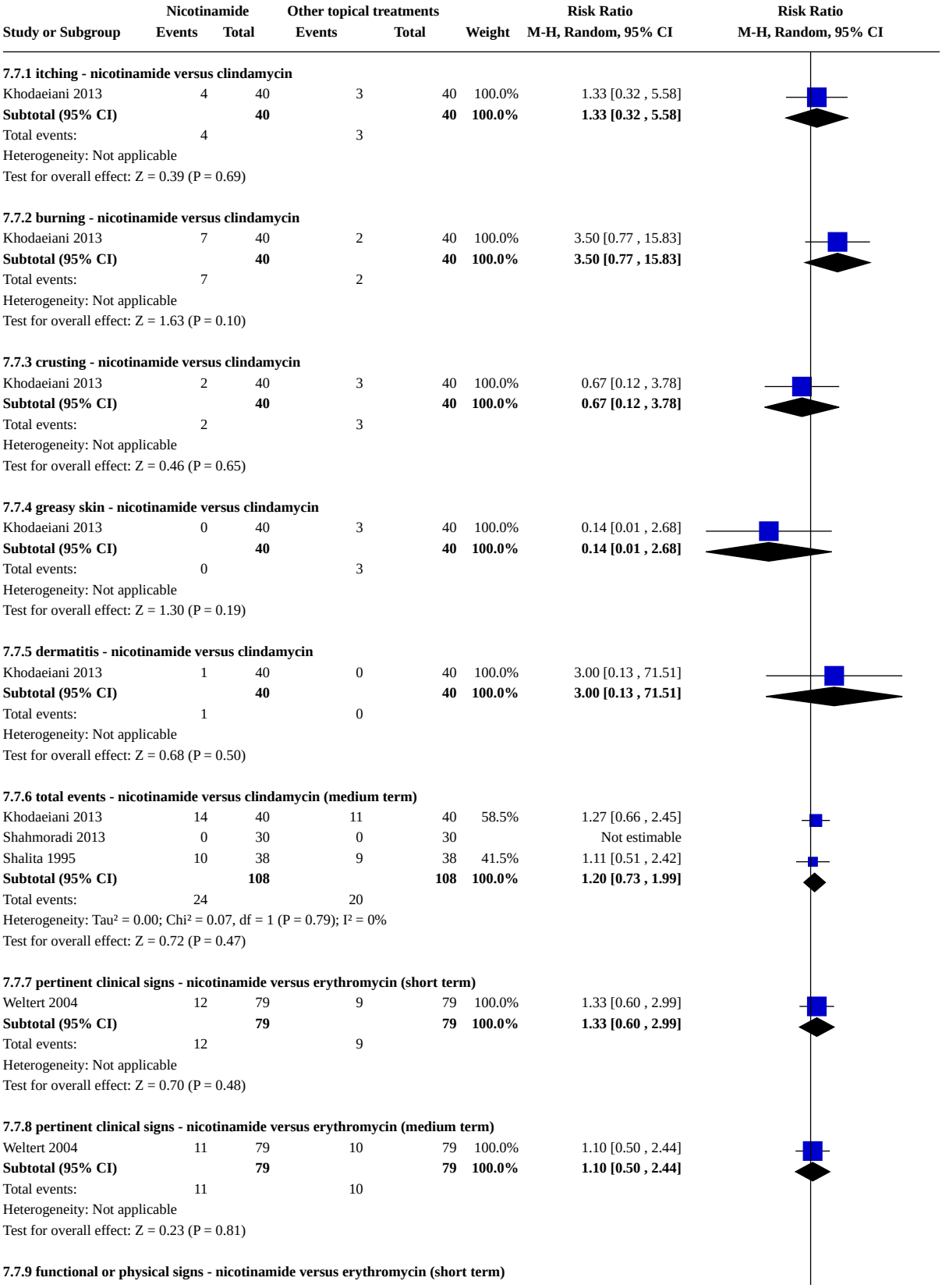


Analysis 7.6. Comparison 7: Topical nicotinamide versus other topical treatments, Outcome 6: Physicians' global evaluation of acne improvement

Physicians' global evaluation of acne improvement

Study	Items	Nicotinamide (%)	Clindamycin (%)	P value
short term				
Shalita 1995	moderately or much better improvement	36%	40%	0.36
medium term				
Shalita 1995	moderately or much better improvement	86%	68%	0.19

Analysis 7.7. Comparison 7: Topical nicotinamide versus other topical treatments, Outcome 7: Minor adverse events



Analysis 7.7. (Continued)

7.7.9 functional or physical signs - nicotinamide versus erythromycin (short term)

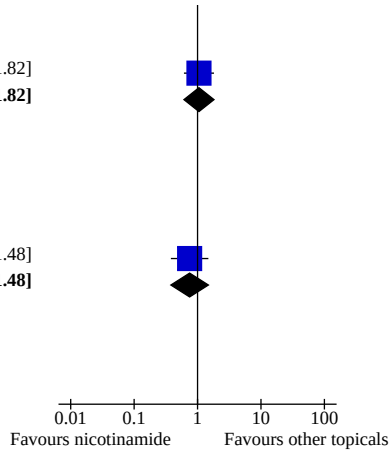
Weltert 2004	20	79	19	79	100.0%	1.05 [0.61 , 1.82]
Subtotal (95% CI)		**79**		**79**	**100.0%**	**1.05 [0.61 , 1.82]**
Total events:	20		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.85)

7.7.10 functional or physical signs - nicotinamide versus erythromycin (medium term)

Weltert 2004	12	79	16	79	100.0%	0.75 [0.38 , 1.48]
Subtotal (95% CI)		**79**		**79**	**100.0%**	**0.75 [0.38 , 1.48]**
Total events:	12		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)



Comparison 8. Topical sulphur versus other topical treatments

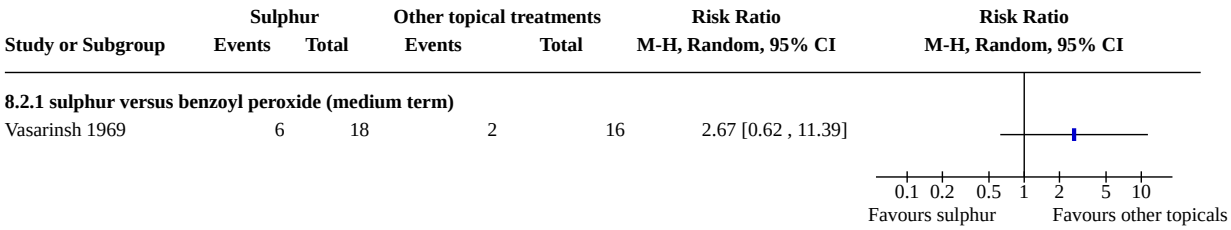
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Participants' global self assessment of acne improvement (numerical point system defined by investigator, high = well)	1		Other data	No numeric data
8.1.1 medium term	1		Other data	No numeric data
8.2 Withdrawal for any reason	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.2.1 sulphur versus benzoyl peroxide (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.3 Change in lesion counts (scores, high = well)	1		Other data	No numeric data
8.4 Physicians' global evaluation of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.4.1 sulphur versus benzoyl peroxide - moderate to good improvement (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.5 Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high = well)	1		Other data	No numeric data
8.5.1 medium term	1		Other data	No numeric data
8.6 Minor adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.6.1 erythema and drying - sulphur versus benzoyl peroxide	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Topical sulphur versus other topical treatments, Outcome 1: Participants' global self assessment of acne improvement (numerical point system defined by investigator, high = well)

Participants' global self assessment of acne improvement (numerical point system defined by investigator, high = well)

Study	Sulfur-benzoyl peroxide	Benzoyl peroxide	Sulfur	Placebo	P value
medium term					
Vasarinsh 1969	1.15	0.66	0.75	0.53	not report, the author did not state whether the difference is statistical significant.

Analysis 8.2. Comparison 8: Topical sulphur versus other topical treatments, Outcome 2: Withdrawal for any reason

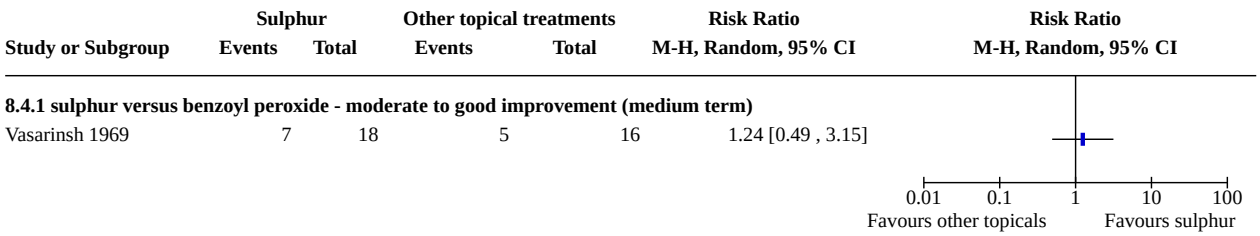


Analysis 8.3. Comparison 8: Topical sulphur versus other topical treatments, Outcome 3: Change in lesion counts (scores, high = well)

Change in lesion counts (scores, high = well)

Study	Time points	Sulphur-benzoyl peroxide	Benzoyl peroxide	Sulphur	Placebo	P value
Vasarinsh 1969	Numerical point system defined by investigator (high=well): comedone-pustule (medium term)	0.81	0.55	-0.70	0.00	not reported, the author did not state whether the difference is statistical significant.
	Numerical point system defined by investigator (high=well): papule-cyst (medium term)	0.91	0.69	0.30	0.53	not reported, the author did not state whether the difference is statistical significant.

Analysis 8.4. Comparison 8: Topical sulphur versus other topical treatments, Outcome 4: Physicians' global evaluation of acne improvement

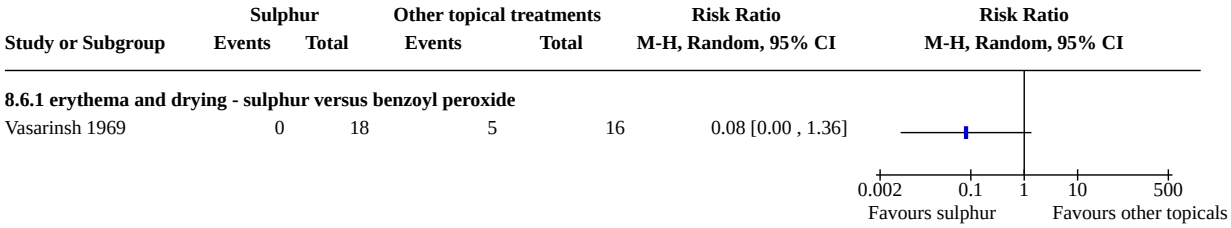


Analysis 8.5. Comparison 8: Topical sulphur versus other topical treatments, Outcome 5: Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high = well)

Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high = well)

Study	Sulfur-benzoyl peroxide	Benzoyl peroxide	Sulfur	Placebo	P value
medium term					
Vasarinsh 1969	1.53	1.07	0.50	0.94	not report, the author did not state whether the difference is statistical significant.

Analysis 8.6. Comparison 8: Topical sulphur versus other topical treatments, Outcome 6: Minor adverse events



Comparison 9. Topical sulphur versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Participants' global self-assessment of acne improvement (numerical point system defined by investigator, high=well)	1		Other data	No numeric data
9.1.1 medium term	1		Other data	No numeric data
9.2 Withdrawal for any reason	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2.1 medium term	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.3 Change in lesion counts (scores, high = well)	1		Other data	No numeric data
9.4 Physicians' global evaluation of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.4.1 moderate to good improvement (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.5 Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high = well)	1		Other data	No numeric data
9.5.1 medium term	1		Other data	No numeric data

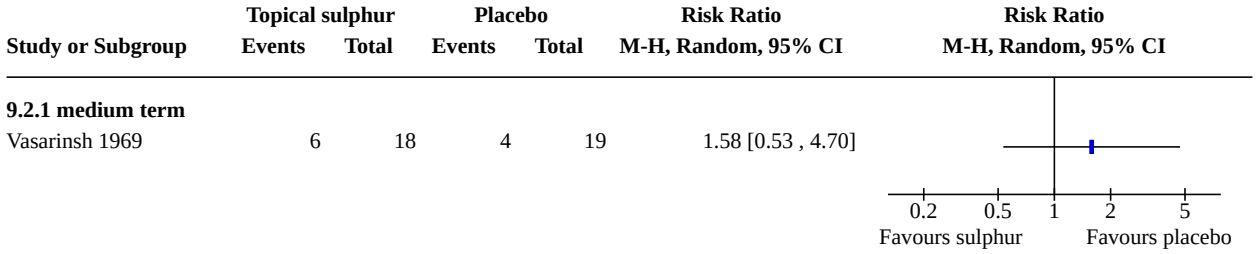
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.6 Minor adverse events - erythema and drying	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Topical sulphur versus placebo, Outcome 1: Participants' global self-assessment of acne improvement (numerical point system defined by investigator, high=well)

Participants' global self-assessment of acne improvement (numerical point system defined by investigator, high=well)

Study	Sulfur-benzoyl peroxide	Benzoyl peroxide	Sulfur	Placebo	P value
medium term					
Vasarinsh 1969	1.15	0.66	0.75	0.53	not report, the author did not state whether the difference is statistical significant.

Analysis 9.2. Comparison 9: Topical sulphur versus placebo, Outcome 2: Withdrawal for any reason



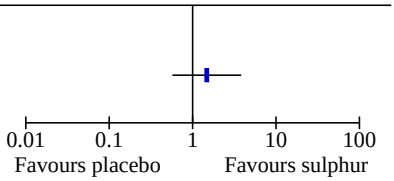
Analysis 9.3. Comparison 9: Topical sulphur versus placebo, Outcome 3: Change in lesion counts (scores, high = well)

Change in lesion counts (scores, high = well)

Study	Time points	Sulphur-benzoyl peroxide	Benzoyl peroxide	Sulphur	Placebo	P value
Vasarinsh 1969	Numerical point system defined by investigator (high=well): comedone-pustule (medium term)	0.81	0.55	-0.70	0.00	not reported, the author did not state whether the difference is statistical significant.
	Numerical point system defined by investigator (high=well): papule-cyst (medium term)	0.91	0.69	0.30	0.53	not reported, the author did not state whether the difference is statistical significant.

Analysis 9.4. Comparison 9: Topical sulphur versus placebo, Outcome 4: Physicians' global evaluation of acne improvement

Study or Subgroup	Sulphur Events	Sulphur Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
9.4.1 moderate to good improvement (medium term)					
Vasarinsh 1969	7	18	5	19	1.48 [0.57 , 3.82]



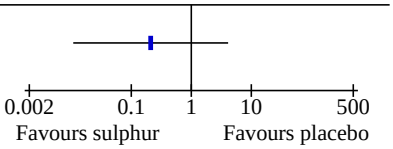
Analysis 9.5. Comparison 9: Topical sulphur versus placebo, Outcome 5: Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high = well)

Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high = well)

Study	Sulfur-benzoyl peroxide	Benzoyl peroxide	Sulfur	Placebo	P value
medium term					
Vasarinsh 1969	1.53	1.07	0.50	0.94	not report, the author did not state whether the difference is statistical significant.

Analysis 9.6. Comparison 9: Topical sulphur versus placebo, Outcome 6: Minor adverse events - erythema and drying

Study or Subgroup	Sulphur Events	Sulphur Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Vasarinsh 1969	0	18	2	19	0.21 [0.01 , 4.11]



Comparison 10. Topical sulphur versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Participants' global self-assessment of acne improvement (numerical point system defined by investigator, high = well)	1		Other data	No numeric data
10.1.1 medium term	1		Other data	No numeric data
10.2 Withdrawal for any reason	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.2.1 medium term	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

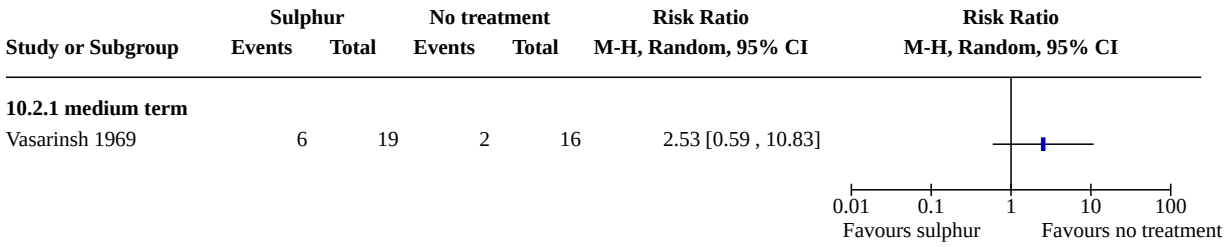
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Change in lesion counts (scores, high = well)	1		Other data	No numeric data
10.4 Physicians' global evaluation of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.4.1 moderate to good improvement (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.5 Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high=well)	1		Other data	No numeric data
10.5.1 medium term	1		Other data	No numeric data
10.6 Minor adverse events - erythema and drying	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10: Topical sulphur versus no treatment, Outcome 1: Participants' global self-assessment of acne improvement (numerical point system defined by investigator, high = well)

Participants' global self-assessment of acne improvement (numerical point system defined by investigator, high = well)

Study	Sulfur-benzoyl peroxide	Benzoyl peroxide	Sulfur	Placebo	P value
medium term					
Vasarinsh 1969	1.15	0.66	0.75	0.53	not report, the author did not state whether the difference is statistical significant.

Analysis 10.2. Comparison 10: Topical sulphur versus no treatment, Outcome 2: Withdrawal for any reason



Analysis 10.3. Comparison 10: Topical sulphur versus no treatment, Outcome 3: Change in lesion counts (scores, high = well)

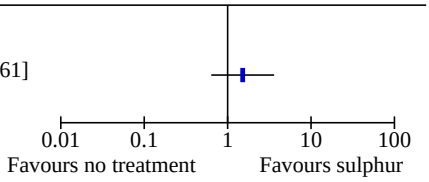
Change in lesion counts (scores, high = well)

Study	Time points	Sulphur-benzoyl peroxide	Benzoyl peroxide	Sulphur	Placebo	P value
Vasarinsh 1969	Numerical point system defined by investigator (high=well): come-	0.81	0.55	-0.70	0.00	not reported, the author did not state whether the differ-

done-pustule (medium term)					ence is statistical significant.
Numerical point system defined by investigator (high=well): papule-cyst (medium term)	0.91	0.69	0.30	0.53	not reported, the author did not state whether the difference is statistical significant.

Analysis 10.4. Comparison 10: Topical sulphur versus no treatment, Outcome 4: Physicians' global evaluation of acne improvement

Study or Subgroup	Sulphur Events	Sulphur Total	No treatment Events	No treatment Total	Risk Ratio M-H, Random, 95% CI
10.4.1 moderate to good improvement (medium term)					
Vasarinsh 1969	9	19	5	16	1.52 [0.64 , 3.61]



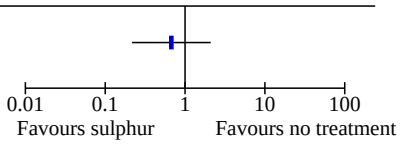
Analysis 10.5. Comparison 10: Topical sulphur versus no treatment, Outcome 5: Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high=well)

Physicians' global evaluation of acne improvement (numerical point system defined by investigator, high=well)

Study	Sulfur-benzoyl peroxide	Benzoyl peroxide	Sulfur	Placebo	P value
medium term					
Vasarinsh 1969	1.53	1.07	0.50	0.94	not report, the author did not state whether the difference is statistical significant.

Analysis 10.6. Comparison 10: Topical sulphur versus no treatment, Outcome 6: Minor adverse events - erythema and drying

Study or Subgroup	Sulphur Events	Sulphur Total	No treatment Events	No treatment Total	Risk Ratio M-H, Random, 95% CI
Vasarinsh 1969	4	19	5	16	0.67 [0.22 , 2.09]



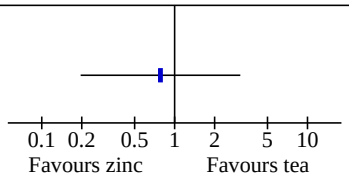
Comparison 11. Topical zinc versus other topical treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Withdrawal for any reason	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1.1 zinc versus tea (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.2 Change in lesion counts - papules (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.2.1 zinc versus tea (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.3 Change in lesion counts - pustules (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.3.1 zinc versus tea (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.4 Physicians' global evaluation of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.4.1 zinc versus tea - moderate or good response (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.5 Minor adverse events - total events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.5.1 zinc versus tea (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

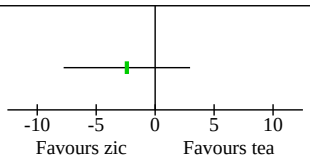
Analysis 11.1. Comparison 11: Topical zinc versus other topical treatments, Outcome 1: Withdrawal for any reason

	Topical zinc		Tea lotion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
11.1.1 zinc versus tea (medium term)						
Sharquie 2008	3	23	4	24	0.78 [0.20 , 3.12]	



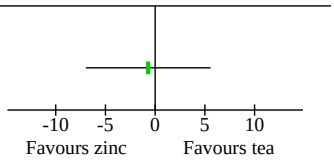
Analysis 11.2. Comparison 11: Topical zinc versus other topical treatments, Outcome 2: Change in lesion counts - papules (number of lesions post-intervention)

	Topical zinc			Tea lotion			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
11.2.1 zinc versus tea (medium term)								
Sharquie 2008	12	8.7	20	14.4	8.6	20	-2.40 [-7.76 , 2.96]	



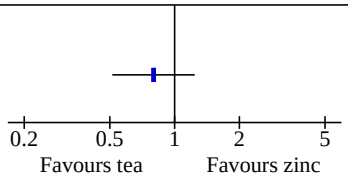
Analysis 11.3. Comparison 11: Topical zinc versus other topical treatments, Outcome 3: Change in lesion counts - pustules (number of lesions post-intervention)

Study or Subgroup	Topical zinc Mean	SD	Total	Tea lotion Mean	SD	Total	Mean Difference IV, Random, 95% CI
11.3.1 zinc versus tea (medium term)							
Sharquie 2008	14.5	10.7	20	15.2	9.5	20	-0.70 [-6.97 , 5.57]



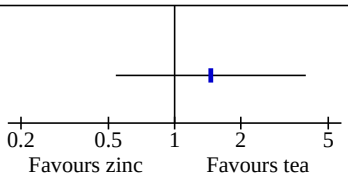
Analysis 11.4. Comparison 11: Topical zinc versus other topical treatments, Outcome 4: Physicians' global evaluation of acne improvement

Study or Subgroup	Topical zinc Events	Total	Tea lotion Events	Total	Risk Ratio M-H, Random, 95% CI
11.4.1 zinc versus tea - moderate or good response (medium term)					
Sharquie 2008	13	23	17	24	0.80 [0.51 , 1.24]



Analysis 11.5. Comparison 11: Topical zinc versus other topical treatments, Outcome 5: Minor adverse events - total events

Study or Subgroup	Topical zinc Events	Total	Tea lotion Events	Total	Risk Ratio M-H, Random, 95% CI
11.5.1 zinc versus tea (medium term)					
Sharquie 2008	7	23	5	24	1.46 [0.54 , 3.95]



Comparison 12. Topical zinc versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Participants' global self-assessment of acne improvement (visual analogue scale)	1		Other data	No numeric data
12.1.1 long term	1		Other data	No numeric data
12.2 Withdrawal for any reason	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.2.1 long term	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3 Change in lesion counts - total (lesion counts reduction)	1		Other data	No numeric data
12.3.1 medium term	1		Other data	No numeric data
12.3.2 long term	1		Other data	No numeric data
12.4 Change in lesion counts - inflamed (lesion counts reduction)	2		Other data	No numeric data
12.4.1 short term	1		Other data	No numeric data
12.4.2 medium term	1		Other data	No numeric data
12.4.3 long term	2		Other data	No numeric data
12.5 Change in lesion counts - non-inflamed (lesion counts reduction)	2		Other data	No numeric data
12.5.1 short term	1		Other data	No numeric data
12.5.2 medium term	2		Other data	No numeric data
12.5.3 long term	2		Other data	No numeric data
12.6 Physicians' global evaluation of acne improvement (visual analogue scale)	1		Other data	No numeric data
12.6.1 long term	1		Other data	No numeric data
12.7 Minor adverse events	1		Other data	No numeric data

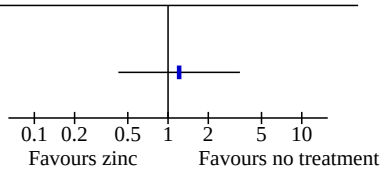
Analysis 12.1. Comparison 12: Topical zinc versus no treatment, Outcome 1: Participants' global self-assessment of acne improvement (visual analogue scale)

Participants' global self-assessment of acne improvement (visual analogue scale)

Study	Topical zinc (mean, SD)	No treatment (mean, SD)	P value
long term			
Cunliffe 2005	Long term: 16 weeks after start of treatment, unclear, not reported	Unclear, not reported	P value was not reported. Quote:" There were no significant difference."

Analysis 12.2. Comparison 12: Topical zinc versus no treatment, Outcome 2: Withdrawal for any reason

Study or Subgroup	Topical zinc Events	Topical zinc Total	No treatment Events	No treatment Total	Risk Ratio M-H, Random, 95% CI
12.2.1 long term					
Cunliffe 2005	7	80	6	83	1.21 [0.43 , 3.45]



Analysis 12.3. Comparison 12: Topical zinc versus no treatment, Outcome 3: Change in lesion counts - total (lesion counts reduction)

Change in lesion counts - total (lesion counts reduction)

Study	Topical zinc (mean, SD)	No treatment (mean, SD)	P value
medium term			
Cunliffe 2005	Unclear, not reported	Unclear, not reported	0.707
long term			
Cunliffe 2005	Long term: 16 weeks after start of treatment, unclear, not reported	Unclear, not reported	0.707

Analysis 12.4. Comparison 12: Topical zinc versus no treatment, Outcome 4: Change in lesion counts - inflamed (lesion counts reduction)

Change in lesion counts - inflamed (lesion counts reduction)

Study	Topical zinc (mean, SD)	No treatment (mean, SD)	P value
short term			
Bojar 1994	Unclear	Unclear	Unclear
medium term			
Bojar 1994	Unclear	Unclear	Unclear
long term			
Bojar 1994	12 weeks after start of treatment, Unclear	Unclear	Unclear
Cunliffe 2005	16 weeks after start of treatment, Unclear, not reported	Unclear, not reported	0.626

Analysis 12.5. Comparison 12: Topical zinc versus no treatment, Outcome 5: Change in lesion counts - non-inflamed (lesion counts reduction)

Change in lesion counts - non-inflamed (lesion counts reduction)

Study	Topical zinc (mean, SD)	No treatment (mean, SD)	P value
short term			
Bojar 1994	Unclear	Unclear	Unclear
medium term			
Bojar 1994	Unclear	Unclear	Unclear
Cunliffe 2005	Unclear	Unclear	0.769
long term			
Bojar 1994	12 weeks after start of treatment, Unclear	Unclear	Unclear
Cunliffe 2005	16 weeks after start of treatment, Unclear	Unclear	0.769

Analysis 12.6. Comparison 12: Topical zinc versus no treatment, Outcome 6: Physicians' global evaluation of acne improvement (visual analogue scale)

Physicians' global evaluation of acne improvement (visual analogue scale)

Study	Topical zinc (mean, SD)	No treatment (mean, SD)	P value
long term			
Cunliffe 2005	16 weeks after start of treatment, Unclear	Unclear	No difference, no exact P value reported

Analysis 12.7. Comparison 12: Topical zinc versus no treatment, Outcome 7: Minor adverse events

Minor adverse events

Study	Time points	Topical zinc (counts/n)	No treatment (counts/n)	P value
Cunliffe 2005	long term (12 weeks after start of treatment)	91/80	117/83	Unclear

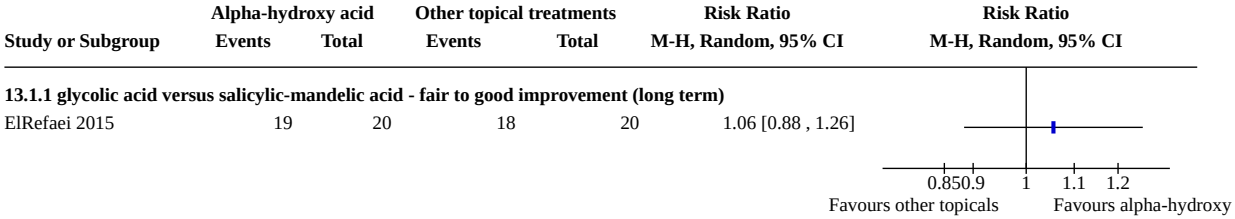
Comparison 13. Topical alpha-hydroxy acid versus other topical treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Participants' global self-assessment of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.1.1 glycolic acid versus salicylic-mandelic acid - fair to good improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2 Withdrawal for any reason	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2.1 gluconolactone versus benzoyl peroxide (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.2.2 glycolic acid versus salicylic-mandelic acid (long term)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.3 Change in lesion counts - non-inflamed (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.3.1 glycolic acid versus salicylic-mandelic acid (short term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.3.2 glycolic acid versus salicylic-mandelic acid (medium term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.4 Change in lesion counts - papules (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.4.1 glycolic acid versus salicylic-mandelic acid (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.5 Change in lesion counts - pustules (number of lesions post-intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

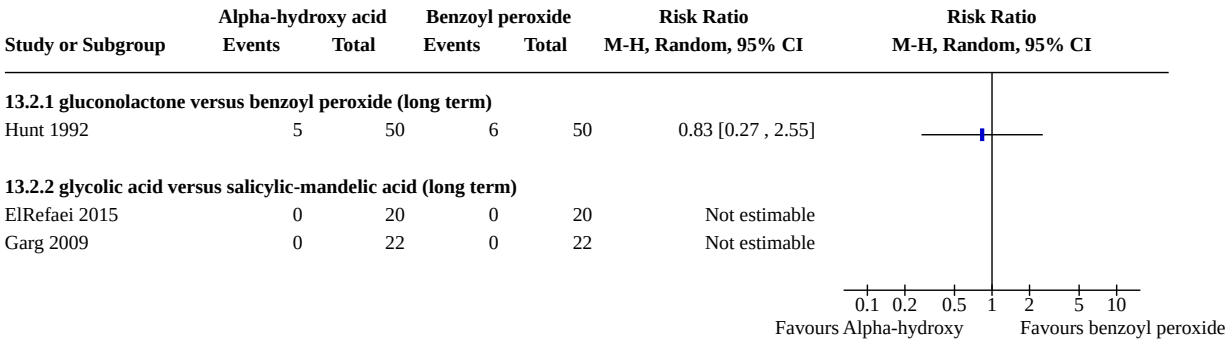
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.5.1 glycolic acid versus salicylic-mandelic acid (long term)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.6 Change in lesion counts - total (counts or %)	2		Other data	No numeric data
13.6.1 parallel trials	1		Other data	No numeric data
13.6.2 split-face trials	1		Other data	No numeric data
13.7 Change in lesion counts - inflamed (counts)	2		Other data	No numeric data
13.7.1 parallel trials	1		Other data	No numeric data
13.7.2 split-face trials	1		Other data	No numeric data
13.8 Change in lesion counts - non-inflamed (counts)	2		Other data	No numeric data
13.8.1 parallel trials	1		Other data	No numeric data
13.8.2 split-face trials	1		Other data	No numeric data
13.9 Physicians' global evaluation of acne improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.9.1 glycolic acid versus salicylic-mandelic acid - fair to good improvement (short term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.9.2 glycolic acid versus salicylic-mandelic acid - fair to good improvement (medium term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.9.3 glycolic acid versus salicylic-mandelic acid - fair to good improvement (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13.10 Physicians' global evaluation of acne improvement (%)	1		Other data	No numeric data
13.10.1 split-face trials	1		Other data	No numeric data
13.11 Minor adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.11.1 total events - gluconolactone versus benzoyl peroxide (long term)	1	100	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.27, 0.85]
13.11.2 total events - glycolic acid versus salicylic - mandelic acid (long term)	1	44	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.72, 4.52]
13.11.3 burning or sensation - glycolic acid versus salicylic - mandelic acid	1	40	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.10, 2.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.11.4 desquamation - glycolic acid versus salicylic - mandelic acid	2	84	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.11, 9.60]
13.11.5 dryness - glycolic acid versus salicylic - mandelic acid	1	40	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.57]
13.11.6 acne flare - glycolic acid versus salicylic - mandelic acid	2	84	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.22, 4.63]

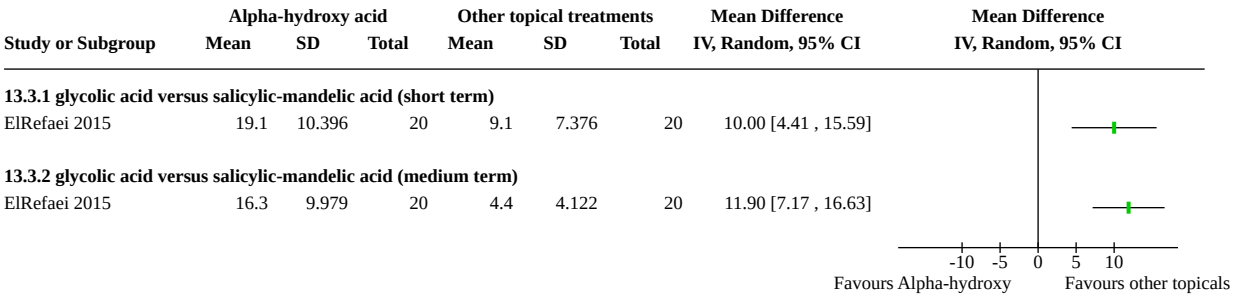
Analysis 13.1. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 1: Participants' global self-assessment of acne improvement



Analysis 13.2. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 2: Withdrawal for any reason

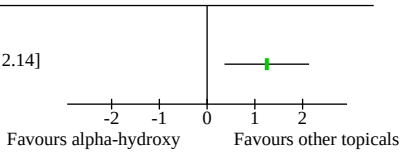


Analysis 13.3. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 3: Change in lesion counts - non-inflamed (number of lesions post-intervention)



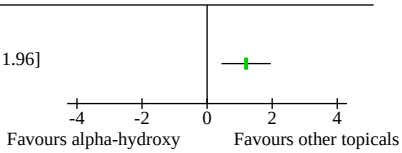
Analysis 13.4. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 4: Change in lesion counts - papules (number of lesions post-intervention)

Study or Subgroup	Alpha-hydroxy acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
13.4.1 glycolic acid versus salicylic-mandelic acid (long term)							
ElRefaei 2015	3.25	1.41	20	2	1.45	20	1.25 [0.36 , 2.14]



Analysis 13.5. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 5: Change in lesion counts - pustules (number of lesions post-intervention)

Study or Subgroup	Alpha-hydroxy acid Mean	SD	Total	Other topical treatments Mean	SD	Total	Mean Difference IV, Random, 95% CI
13.5.1 glycolic acid versus salicylic-mandelic acid (long term)							
ElRefaei 2015	2.95	1.468	20	1.75	0.91	20	1.20 [0.44 , 1.96]



Analysis 13.6. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 6: Change in lesion counts - total (counts or %)

Change in lesion counts - total (counts or %)

Study	Time points	Alpha-hydroxy acid, mean ± SD or %	Topical treatments, mean ± SD or %	P vaule
parallel trials				
Hunt 1992	Short term - lesion counts reduction	gluconolactone 14% in solution, not reported	benzoyl peroxide 5% lotion, not reported	No difference
Hunt 1992	Long term: 12 weeks after start of treatment - lesion counts reduction	gluconolactone 14% in solution, not reported	benzoyl peroxide 5% lotion, not reported	No difference
Hunt 1992	Medium term - lesion counts reduction	gluconolactone 14% in solution, not reported	benzoyl peroxide 5% lotion, not reported	No difference
split-face trials				
Kessler 2008	Percent reduction - total lesion(treatment duration of 10 weeks, measured at one month post-treatment)	30% glycolic acid peel, 43%	30% salicylic acid peel, 47%	> 0.05

Analysis 13.7. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 7: Change in lesion counts - inflamed (counts)

Change in lesion counts - inflamed (counts)

Study	Time points	Alpha-hydroxy acid (mean, SD)	Benzoyl peroxide (mean, SD)	P value
parallel trials				
Hunt 1992	Short term - lesion counts reduction	Unclear, not reported	Unclear, not reported	No difference
Hunt 1992	Medium term - lesion counts reduction	Unclear, not reported	Unclear, not reported	Benzoyl peroxide was significantly better than gluconolactone at eight and twelve weeks ($P < 0.05$)

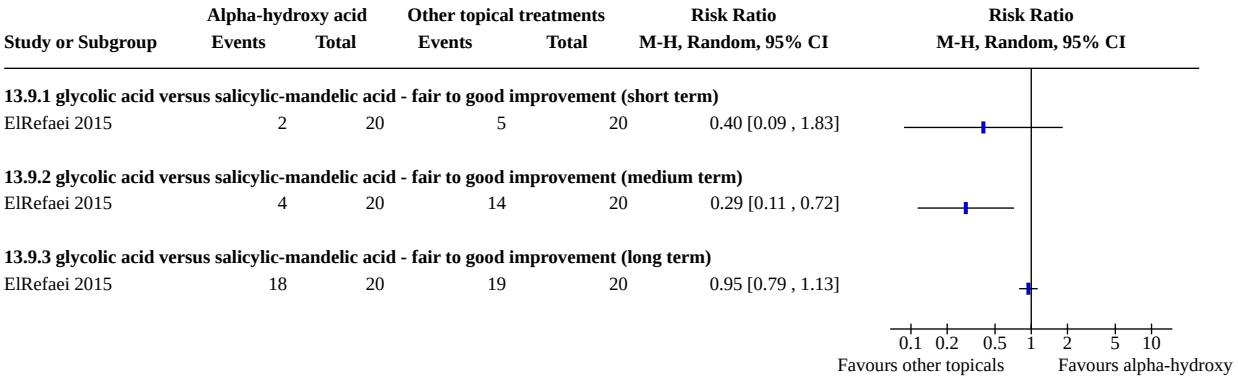
Hunt 1992	Long term: 12 weeks after start of treatment - lesion counts reduction	Unclear, not reported	Unclear, not reported	Benzoyl peroxide was significantly better than gluconolactone at eight and twelve weeks (P< 0.05)
split-face trials				
Ilknur 2010	Long term: six months after start of treatment (number of lesions post intervention)	6.88±5.18	7.00±7.26	>0.05
Ilknur 2010	Short term (number of lesions post intervention)	10.08±5.72	8.67±4.48	>0.05
Ilknur 2010	Medium term (number of lesions post intervention)	8.29±4.50	8.88±4.81	>0.05

Analysis 13.8. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 8: Change in lesion counts - non-inflamed (counts)

Change in lesion counts - non-inflamed (counts)

Study	Time points	Alpha-hydroxy acid (mean, SD)	Benzoyl peroxide (mean, SD)	P value
parallel trials				
Hunt 1992	Medium term - lesion counts reduction	Unclear, not reported	Unclear, not reported	No difference
Hunt 1992	Long term: 12 weeks after start of treatment - lesion counts reduction	Unclear, not reported	Unclear, not reported	No difference
Hunt 1992	Short term - lesion counts reduction	Unclear, not reported	Unclear, not reported	No difference
split-face trials				
Ilknur 2010	Long term: six months after start of treatment (number of lesions post intervention)	18.29±12.93	17.13±14.22	>0.05
Ilknur 2010	Medium term (number of lesions post intervention)	36.29±37.37	36.00±40.42	>0.05
Ilknur 2010	Short term (number of lesions post intervention)	42.67±50.36	43.17±50.38	>0.05

Analysis 13.9. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 9: Physicians' global evaluation of acne improvement



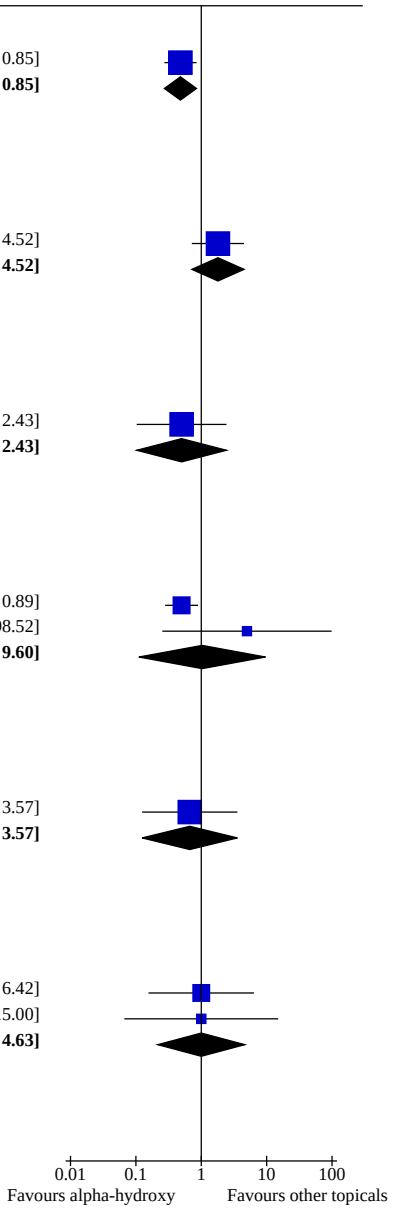
Analysis 13.10. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 10: Physicians' global evaluation of acne improvement (%)

Physicians' global evaluation of acne improvement (%)

Study	Time points	Alpha-hydroxy acid, %	Comparator, %	P value
split-face trials				
Kessler 2008	Good to fair improvement (treatment duration of 10 weeks, measured at two months post-treatment)	30% glycolic acid peels, 75%	30% salicylic acid peels, 81%	Unclear, not reported. The author did not report whether there is any statistical difference between groups.

Analysis 13.11. Comparison 13: Topical alpha-hydroxy acid versus other topical treatments, Outcome 11: Minor adverse events

Study or Subgroup	Alpha-hydroxy acid Events	Alpha-hydroxy acid Total	Other topical treatments Events	Other topical treatments Total	Weight	Risk Ratio M-H, Random, 95% CI
13.11.1 total events - gluconolactone versus benzoyl peroxide (long term)						
Hunt 1992	12	50	25	50	100.0%	0.48 [0.27 , 0.85]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.48 [0.27 , 0.85]**
Total events:	12		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.54 (P = 0.01)						
13.11.2 total events - glycolic acid versus salicylic - mandelic acid (long term)						
Garg 2009	9	22	5	22	100.0%	1.80 [0.72 , 4.52]
Subtotal (95% CI)		**22**		**22**	**100.0%**	**1.80 [0.72 , 4.52]**
Total events:	9		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
13.11.3 burning or sensation - glycolic acid versus salicylic - mandelic acid						
ElRefaei 2015	2	20	4	20	100.0%	0.50 [0.10 , 2.43]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.50 [0.10 , 2.43]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
13.11.4 desquamation - glycolic acid versus salicylic - mandelic acid						
ElRefaei 2015	8	20	16	20	68.5%	0.50 [0.28 , 0.89]
Garg 2009	2	22	0	22	31.5%	5.00 [0.25 , 98.52]
Subtotal (95% CI)		**42**		**42**	**100.0%**	**1.03 [0.11 , 9.60]**
Total events:	10		16			
Heterogeneity: $Tau^2 = 1.80$; $Chi^2 = 2.50$, df = 1 (P = 0.11); $I^2 = 60\%$						
Test for overall effect: Z = 0.03 (P = 0.98)						
13.11.5 dryness - glycolic acid versus salicylic - mandelic acid						
ElRefaei 2015	2	20	3	20	100.0%	0.67 [0.12 , 3.57]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**0.67 [0.12 , 3.57]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
13.11.6 acne flare - glycolic acid versus salicylic - mandelic acid						
ElRefaei 2015	2	20	2	20	68.0%	1.00 [0.16 , 6.42]
Garg 2009	1	22	1	22	32.0%	1.00 [0.07 , 15.00]
Subtotal (95% CI)		**42**		**42**	**100.0%**	**1.00 [0.22 , 4.63]**
Total events:	3		3			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0\%$						
Test for overall effect: Z = 0.00 (P = 1.00)						

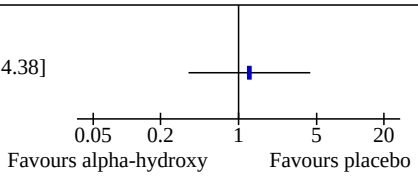


Comparison 14. Topical alpha-hydroxy acid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Withdrawal for any reason	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1.1 gluconolactone versus placebo (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.2 Minor adverse events - total events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.2.1 gluconolactone versus placebo (long term)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

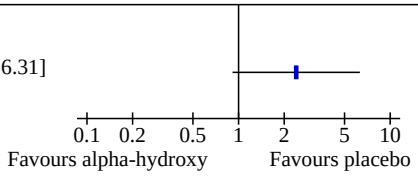
Analysis 14.1. Comparison 14: Topical alpha-hydroxy acid versus placebo, Outcome 1: Withdrawal for any reason

Study or Subgroup	Alpha-hydroxy acid Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
14.1.1 gluconolactone versus placebo (long term)					
Hunt 1992	5	50	4	50	1.25 [0.36 , 4.38]



Analysis 14.2. Comparison 14: Topical alpha-hydroxy acid versus placebo, Outcome 2: Minor adverse events - total events

Study or Subgroup	Alpha-hydroxy acid Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
14.2.1 gluconolactone versus placebo (long term)					
Hunt 1992	12	50	5	50	2.40 [0.91 , 6.31]



ADDITIONAL TABLES

Table 1. Glossary of medical terms

Medical term	Explanation
Acne vulgaris	A common chronic skin disorder of sebaceous follicles, mainly affecting the face, chest, and back[a]
Chemokine	A group of small cytokines that act as chemical messengers to induce chemotaxis in leukocytes[c]
Comedone	A clogged hair follicle in the skin. It can present as a blackhead or whitehead[a]

Table 1. Glossary of medical terms *(Continued)*

Cytokine	A small protein released by cells that function as molecular messengers between cells[c]
Erythema	Redness of the skin, caused by vascular congestion or increased perfusion[b]
Hyperkeratosis	Thickening of the outer layer of skin often associated with a quantitative abnormality of keratin[b]
Keratinocytes	The predominant cell type in the epidermis, forming a touch protective layer[a]
Microcomedones	Early and small plugging of the follicle with excess keratin and sebum[b]
Nodule	A solid mass in the skin, more than 0.5 cm in diameter[b]
Papule	A circumscribed palpable elevation, less than 0.5 cm in diameter[b]
Pilosebaceous unit	A structure consisting of a hair follicle, sebaceous gland, and an arrector pili muscle[b]
Propionibacterium acnes (Cutibacterium acnes)	Gram-positive bacterium related to acne development[b]
Pustule	A visible accumulation of free pus[b]
Scar	Skin areas of fibrous tissue replacing normal skin after injury[b]
Sebum	The oily, waxy substance produced by sebaceous glands[b]
Stratum corneum	The outermost layer of the epidermis, where cells have lost nuclei and cytoplasmic organelles[b]
Toll-like receptor	A class of proteins that recognise conserved products unique to microbial metabolism in immune response[c]

[a] *Andrews' Diseases of the Skin: Clinical Dermatology*, 11th Edition, 2011, Elsevier Inc.
[b] *Rook's Textbook of Dermatology*, Eighth Edition, 2010, Blackwell Publishing Ltd.
[c] *Immunology*, Sixth Edition, 2001, Harcourt Asia Pte Ltd.

Table 2. Clinical classification of acne[a]

Acne vulgaris	
Acne variants	Neonatal acne
	Infantile acne
	Acne conglobata
	Acne fulminans
	SAPHO syndrome
	PAPA syndrome
	Acne excoriee des jeunes filles
	Acne mechanica

Table 2. Clinical classification of acne[a] *(Continued)*

	Acne with solid facial oedema
	Acne with associated endocrinology abnormalities
Acneiform eruptions	Steroid folliculitis
	Drug-induced acne
	Epidermal growth factor receptor inhibitor associated eruption
	Occupational acne and chloracne
	Gram-negative folliculitis
	Radiation acne
	Tropical acne
	Acne aestivalis
	Pseudoacne of the nasal crease
	Apert syndrome

[a] *Fitzpatrick's Dermatology in General Medicine*, Eighth edition, 2012, The McGraw-Hill Companies, Inc.

Table 3. Acne severity for all studies

Studies	Acne severity	Notes
Akarsu 2012	Mild to moderate	Defined as "10-50 inflamed lesions and 10-100 non-inflamed lesions above the mandibular line, no cystic or nodular lesions."
Aksakal 1997	Moderate to severe	Graded by using the Allen-Smith Scale (grades of 4 to 8)
Babayeva 2011	Mild to moderate	Defined as "10-50 inflamed lesions and 10-100 non-inflamed lesions above the mandibular line, no cystic or nodular lesions."
Bae 2013	Mild to moderate	Graded using the Burke and Cunliffe Scale (Leeds technique) (grades of 0.25 to 3.0)
Barbareschi 1991	Probably mild to moderate[a]	Participants with comedonic acne included, no further details
Bojar 1994	Mild to moderate	Graded using the Burke and Cunliffe Scale (Leeds technique) (grades of 0.5 to 3.0)
Cavicchini 1989	Probably mild to moderate[a]	Participants with papulopustular acne included, median number of inflamed lesions was less than 20
Chantalat 2005	Mild to moderate	Acne severity grading method not reported, this study was published as an abstract
Chantalat 2006	Mild to moderate	Acne severity grading method not reported, this study was published as an abstract

Table 3. Acne severity for all studies *(Continued)*

Chantalat 2007	Not reported	Acne severity grading method not reported, this study was published as an abstract
Chen 2007	Mild to moderate	Acne severity grading method not reported, this study was published as an abstract
Cunliffe 1989	Mild to moderate	Acne severity grading method not reported, only mentioned "the trial was for the treatment of mild to moderate acne" in the Discussion section, no details
Cunliffe 2005	Mild to moderate	Graded using the Leeds Revised Acne Grading Scale (grades of 2 to 7)
Dayal 2017	Mild to moderate	Graded using a simple system (based on the predominant lesions present: mild, moderate, severe, cystic)
Draelos 2016	Mild to moderate	Acne severity grading method not reported, a minimum of 10 non-inflamed lesions and a minimum of 10 inflamed lesions
Dunlap 1997	Probably moderate to severe[a]	Grade Ⅱ or Ⅲ, Pillsbury classification system
Eady 1996	Mild to moderate	Graded using the Leeds technique, no details
ElRefaei 2015	Moderate to severe	Graded according to the Hayashi classification system (mild, moderate, severe, or very severe)
Garg 2009	Probably moderate to severe/cystic[a]	Mean baseline Michaelsson acne severity index score > 80, the improvement of comedones, papules, pustules, nodules and cysts was assessed
Gollnick 2004a	Mild to moderate	Acne severity grading method not reported
Gollnick 2004b	Mild to moderate	Acne severity grading method not reported
Hayashi 2012	Not reported	Total lesion counts > 30, no further details, this study was published as an abstract
Hunt 1992	Mild to moderate	Graded using the Burke and Cunliffe Scale (Leeds technique), no further details
Ilknur 2010	Probably mild to moderate[a]	Graded using the Burke and Cunliffe Scale (Leeds technique), grades of 0.25 to 2.0, participants with non-inflamed lesions and superficial inflamed lesions
Iraji 2007	Mild to moderate	Graded using the Burke and Cunliffe Scale (Leeds technique), no further details
Jaffary 2016	Mild to moderate	Defined as "no more than five pustules forms and no cysts, nodules, and colloidal deep scar"
Kar 2013	Moderate to severe	Average baseline Michaelsson acne severity index in the two treatment arms was 64.1 ± 4.4 and 63.0 ± 5.1
Katsambas 1989a	Moderate inflammatory acne	Degree Ⅱ or Ⅲ, Plewig-Kligmann classification system, participants with papulopustular acne were included
Katsambas 1989b	Probably mild to moderate[a]	Participants with comedonal acne, no further details

Table 3. Acne severity for all studies *(Continued)*

Kessler 2008	Mild to moderately severe	Acne severity grading method not reported, a minimum of 10 papules and/or pustules
Khodaeiani 2013	Moderate inflammatory acne	Grade Ⅲ, the Leeds technique
Kim 1999	Mild to moderate	Graded using the Leeds technique, grades of 0.25 to 2.0
Levesque 2011	Probably mild to moderate[a]	Subjects with comedonal acne (at least 5 non-inflamed lesions on each side of the face and < 30 inflamed lesions on entire face)
NilFroushzadeh 2009	Mild to moderate	Acne severity grading method not reported
Ozkan 2000	Mild to moderate	Graded using the Leeds technique, ≤ 3.0
Pazoki-Toroudi 2010	Mild to moderate	Defined as "at least 10 inflammatory lesions on the face and with a maximum of three nodules"
Pazoki-Toroudi 2011	Mild to moderate	A clinical diagnosis of mild to moderate acne, ≥ 10 facial lesions
Picosse 2015	Not reported	No details, this study was published as an abstract
Schaller 2016	Mild to moderate	Investigators' static global assessment score of mild or moderate
Shahmoradi 2013	Mild to moderate	Self-defined grading system (mild acne: the presence of non-inflammatory lesions, and the number of the papules, and pustules to be < 10 without any nodules or cysts; moderate acne: the presence of non-inflammatory lesions and the number of the papules and pustules to be < 20 without any nodules or cysts)
Shalita 1981	Mild to moderate	Grade Ⅰ or Ⅱ, Pillsbury classification system
Shalita 1989	Mild to moderate	Self-defined grading system (the presence of at least 10 papulopustular lesions on the face accompanied by a minimum of 5 comedones, as well as a grade of 4 to 6 on the Allen-Smith Acne Severity Scale)
Shalita 1995	Moderate inflammatory acne	Self-defined grading system (the presence of at least 15 papules and/or pustules on the face)
Sharquie 2008	Mild to moderate	Mild acne: the count of pustules < 20 and the count of papules < 10; moderate acne: the count of pustules ranged between 20 and 40 and the count of papules ranged between 10 and 30
Stinco 2007	Mild to moderate	Participants with mild or moderate comedonic or papulopustular acne, a minimum of 20 facial non-inflammatory lesions and 10 inflamed lesions
Techapichetvanich 2011	Mild to moderate	Acne severity grading method not reported, this study was published as an abstract
Thielitz 2015	Mild to moderate	Graded using a modified Investigators' Static Global assessment (grades of 2 to 4) and the Leeds Revised Acne Grading Scale (grades of 2 to 7)
Vasarinsh 1969	Not reported	Not reported
Weltert 2004	Moderate inflammatory acne	Participants with moderate inflammatory ance on face (≥ 5 inflammatory elements, papules or pustules)

[a]Possible acne severity, graded by using a simple system based on the predominant lesions present (Dayal 2017), grade 1 (mild): comedones, occasional papules; grade 2 (moderate): papules, comedones, few pustules; grade 3 (severe): predominant pustules, nodules, abscesses; grade 4 (cystic): mainly cysts, abscesses, widespread scarring.

Table 4. Azelaic acid compared to benzoyl peroxide/clindamycin

Azelaic acid compared to benzoyl peroxide/clindamycin for acne						
Patient or population: participants with acne **Settings:** 11 study centres in Germany **Intervention:** topical azelaic acid **Comparison:** topical benzoyl peroxide/clindamycin						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Topical benzoyl peroxide/clindamycin	**Topical azelaic acid**				
Participants' global self-assessment of acne improvement *Much to very much improved* (long term: treatment duration > 8 weeks)	**559 per 1000**	**419 per 1000** (318 to 553)	**RR 0.75** (0.57 to 0.99)	221 (1 study)	⊕⊕⊖⊖ **Low** [a]	-
Withdrawal for any reason (long term: treatment duration > 8 weeks)	63 per 1000	73 per 1000	RR 1.15 (0.43 to 3.07)	221 (1 study)	⊕⊕⊖⊖ **Low** [b]	-
Total number of participants who experienced at least one minor adverse event (long term: treatment duration > 8 weeks)	**559 per 1000**	**693 per 1000** (564 to 849)	**RR 1.24** (1.01 to 1.52)	221 (1 study)	⊕⊕⊖⊖ **Low**[b]	The common application site reactions include pruritus, pain, erythema and dryness.
Quality of life *CDLQI* (long term: treatment duration > 8 weeks)	The authors reported that a greater mean (SD) change in CDLQI was noted with benzoyl peroxide 3% + clindamycin 1% gel (-60.5% ± 70.6, n = 107) versus azelaic acid 20% cream (-36.8% ± 74.8, n = 108).			215 (1 study)	⊕⊕⊖⊖ **Low** [c]	Skewed data reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CDLQI: Children's Dermatology Life Quality Index; **CI:** confidence interval; **RR:** risk ratio; **SD**: standard deviation

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.

Table 4. Azelaic acid compared to benzoyl peroxide/clindamycin *(Continued)*

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of performance bias and with unclear risk of allocation concealment and other bias. One level for imprecision: optimal sample size not met.
[b]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of performance bias and with unclear allocation concealment and other bias. One level for imprecision: wide CI and optimal sample size not met.
[c]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of performance bias and unclear risk of allocation concealment and other bias. One level for imprecision: total population size is less than 400 and wide CI.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Table 5. Azelaic acid compared to placebo

Azelaic acid compared to placebo for acne						
Patient or population: participants with acne **Settings:** not described (4 studies) **Intervention:** topical azelaic acid **Comparison:** placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo/no treatment	**Topical azelaic acid**				
Participants' global self-assessment of acne improvement	-	-	-	-	-	Not measured
Withdrawal for any reason (long term: treatment duration > 8 weeks)	**63 per 1000**	**101 per 1000** (35 to 295)	**RR 1.60** (0.55 to 4.66)	152 (3 studies)	⊕⊕⊖⊖ **Low** [a]	-
Total number of participants who experienced at least one minor adverse event (medium term: treatment duration from 5 to 8 weeks)	See comment	See comment	**RR 19.00** (1.16 to 312.42)	60 (1 study)	⊕⊖⊖⊖ **Very low** [b]	9/30 versus 0/30 experienced minor adverse events. In the other studies in this comparison, events such as scaling, dry skin, erythema, oiliness, and pruritus were reported, but the number of participants with these events were low and similar across groups.
Quality of life	-	-	-	-	-	Not measured

Table 5. Azelaic acid compared to placebo *(Continued)*

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: three studies included, two with unclear risk of selection bias and one with unclear risk of allocation concealment, one study with high risk of reporting bias and one with high risk of attrition bias. One level for imprecision: wide CI and optimal sample size not met.
[b]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included, and study with unclear random sequence generation and allocation concealment. Two levels for imprecision: wide CI and optimal sample size not met.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Table 6. Salicylic acid compared to no treatment

Salicylic acid compared to no treatment for acne

Patient or population: participants with acne
Settings: Skin Disease and Leishmaniasis Research Center and Isfahan University of Medical Sciences clinics (1 study); a tertiary care hospital of Eastern India (1 study); not described (1 study)
Intervention: topical salicylic acid
Comparison: no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no treatment	Topical salicylic acid				
Participants' global self-assessment of acne improvement *Moderate to excellent improvement* (long term: treatment duration > 8 weeks)	**1000 per 1000**	**960 per 1000** (860 to 1000)	**RR 0.96** (0.86 to 1.07)	50 (1 study)	⊕⊕⊖⊖ **Low** [a]	Clindamycin/benzoyl peroxide was a co-intervention given in both arms.
Withdrawal for any reason (long term: treatment duration > 8 weeks)	-	-	**RR 3.0** (0.13 to 70.30)	138 (3 studies)	⊕⊖⊖⊖ **Very low** [b]	Two studies had no withdrawals.

Table 6. Salicylic acid compared to no treatment *(Continued)*

Total number of participants who experienced at least one minor adverse event (long term: treatment duration > 8 weeks)	**436 per 1000**	**1000 per 1000** (61 to 1000)	**RR 3.43** (0.14 to 82)	78 (2 studies)	⊕⊖⊖⊖ **Very low** [c]	All side effects reported in the study were of mild to moderate intensity and transient.
Quality of life *AQOL* (long term: treatment duration > 8 weeks)	The authors reported no "significant differences" in AQOL between treatment groups (salicylic acid/clindamycin/benzoyl peroxide group versus clindamycin/benzoyl peroxide group) at baseline and the end of the study.			50 (1 study)	⊕⊖⊖⊖ **Very low**[d]	Median and 95% CI reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AQOL: acne quality of life; **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of performance bias and unclear risk of selection bias. One level for imprecision: optimal sample size not met.
[b]Downgraded by three levels to very low quality evidence. One level for risk of bias: three studies included and all with unclear risk of allocation concealment and high risk of performance bias, two studies with unclear risk of random sequence generation. Two levels for imprecision: very wide CI and optimal sample size not met.
[c]Downgraded by three levels to very low quality evidence. One level for risk of bias: two studies included and both with unclear risk of selection and high risk of performance bias, one with unclear risk of reporting bias. Two levels for imprecision: very wide CI and optimal sample size not met.
[d]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with high risk of performance bias and unclear risk of selection bias. One level for imprecision: very small total sample size.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Table 7. Sulphur compared to benzoyl peroxide

Sulphur compared to benzoyl peroxide for acne						
Patient or population: participants with acne **Settings:** Wayne State University Health Service **Intervention:** topical sulphur **Comparison:** topical benzoyl peroxide						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

Table 7. Sulphur compared to benzoyl peroxide *(Continued)*

	Topical benzoyl peroxide	Topical sulphur				
Participants' global self-assessment of acne improvement *Numerical point system defined by investigator, high = well* (medium term: treatment duration from 5 to 8 weeks)	The score (high = well) was 0.75 in sulphur group and 0.66 in benzoyl peroxide group.			34 (1 study)	⊕⊖⊖⊖ **Very low** [a]	SDs were missing.
Withdrawal for any reason (medium term: treatment duration from 5 to 8 weeks)	**125 per 1000**	**334 per 1000** (78 to 1000)	**RR 2.67** (0.62 to 11.39)	34 (1 study)	⊕⊖⊖⊖ **Very low** [b]	-
Total number of participants who experienced at least one minor adverse event	See comment	See comment	See comment	See comment	See comment	Total number of participants who experienced at least one adverse event not reported. But the authors reported that five patients in the benzoyl peroxide group (5/16) versus zero in sulphur group (0/18) developed erythema and drying.
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **SD**: standard deviation.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by four levels to very low quality evidence. Two levels for risk of bias: only one study included with high risk of attrition bias and unclear risk of selection, performance, detection, and reporting bias. Two levels for imprecision: very small sample size.
[b]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with high risk of attrition bias and unclear risk of selection, performance, detection, and reporting bias. Two levels for imprecision: wide CI and optimal sample size not met.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Table 8. Sulphur compared to placebo

Sulphur compared to placebo for acne						
Patient or population: participants with acne **Settings:** Wayne State University Health Service **Intervention:** topical sulphur **Comparison:** placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo/no treatment	**Topical sulphur**				
Participants' global self-assessment of acne improvement *Numerical point system defined by investigator, high = well* (medium term: treatment duration from 5 to 8 weeks)	The score (high = well) was 0.75 in participants receiving sulphur treatment and 0.53 in placebo group.			37 (1 study)	⊕⊖⊖⊖ **Very low** [a]	SDs were missing.
Withdrawal for any reason (medium term: treatment duration from 5 to 8 weeks)	**211 per 1000**	**333 per 1000** (112 to 989)	**RR 1.58** (0.53 to 4.70)	37 (1 study)	⊕⊖⊖⊖ **Very low** [b]	-
Total number of participants who experienced at least one minor adverse event	See comment	See comment	See comment	See comment	See comment	Total number of participants who experienced at least one adverse event not reported. Two participants in the placebo group (2/19) versus zero in sulphur group (0/18) developed erythema and drying.
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **SD**: standard deviation.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by four levels to very low quality evidence. Two levels for risk of bias: only one study included with high risk of attrition bias and unclear risk of selection, performance, and reporting bias. Two levels for imprecision: very small sample size.
[b]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with high risk of attrition bias and unclear risk of selection, performance, and reporting bias. Two levels for imprecision: wide CI and optimal sample size not met.
*We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Table 9. Zinc compared to tea

Zinc compared to tea for acne						
Patient or population: participants with acne **Settings:** Department of Dermatology and Venereology, Baghdad Teaching Hospital, Baghdad, Iraq **Intervention:** topical zinc **Comparison:** topical tea						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Topical tea	**Topical zinc**				
Participants' global self-assessment of acne improvement	-	-	-	-	-	Not measured
Withdrawal for any reason (medium term: treatment duration from 5 to 8 weeks)	**167 per 1000**	**130 per 1000** (33 to 520)	**RR 0.78** (0.20 to 3.12)	47 (1 study)	⊕⊖⊖⊖ **Very low** [a]	-
Total number of participants who experienced at least one minor adverse event (medium term: treatment duration from 5 to 8 weeks)	**208 per 1000**	**304 per 1000** (113 to 823)	**RR 1.46** (0.54 to 3.95)	47 (1 study)	⊕⊖⊖⊖ **Very low** [b]	Five people experienced burning and two experienced itching in the zinc sulphate treatment group, in contrast, five people had mild itching in the tea lotion treatment group.
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Table 9. Zinc compared to tea *(Continued)*

Very low quality: we are very uncertain about the estimate.

[a]Downgraded by three levels to very low quality evidence. One level for risk of bias: only one study included with unclear risk of selection, performance, and reporting bias. Two levels for imprecision: wide CI and optimal sample size not met.

[b]Downgraded by four levels to very low quality evidence. Two levels for risk of bias: only one study included with high risk of attrition bias and with unclear risk of selection, performance, detection, and reporting bias. Two levels for imprecision: wide CI and optimal sample size not met.

[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Table 10. Zinc compared to no treatment

Zinc compared to no treatment for acne						
Patient or population: participants with acne **Settings:** eight centres in the UK, one in France and one in Germany **Intervention:** topical zinc plus clindamycin 1% gel **Comparison:** no treatment plus clindamycin 1% gel						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo/no treatment	**Topical zinc**				
Participants' global self-assessment of acne improvement *Visual analogue scale* (long term: treatment duration > 8 weeks)	The study authors only reported no significant difference between treatment groups.			163 (1 study)	⊕⊕⊝⊝ **Low** [a]	Clindamycin 1% gel was a co-intervention given in both arms. No numerical data provided.
Withdrawal for any reason (long term: treatment duration > 8 weeks)	**72 per 1000**	**87 per 1000** (31 to 249)	**RR 1.21** (0.43 to 3.45)	163 (1 study)	⊕⊕⊝⊝ **Low** [b]	Clindamycin 1% gel was a co-intervention given in both arms.
Total number of participants who experienced at least one minor adverse event (long term: treatment duration > 8 weeks)	See comment	See comment	Not estimable	163 (1 study)	⊕⊕⊝⊝ **Low** [c]	Clindamycin 1% gel was a co-intervention given in both arms. The authors only report number of adverse events, not number of participants - 91 adverse events in 80 zinc/clindamycin participants and 117 adverse events in 83 clindamycin participants.
Quality of life	-	-	-	-	-	Not measured

Table 10. Zinc compared to no treatment *(Continued)*

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of performance bias and unclear risk of selection bias. One level for imprecision: small sample size.
[b]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of performance bias and unclear risk of selection bias. One level for imprecision: wide CI and optimal sample size not met.
[c]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of performance bias and unclear risk of selection bias. One level for imprecision: small sample size.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Table 11. Gluconolactone (alpha-hydroxy acid) compared to benzoyl peroxide

Gluconolactone (alpha-hydroxy acid) compared to benzoyl peroxide for acne

Patient or population: participants with acne
Settings: not described
Intervention: topical gluconolactone (alpha-hydroxy acid)
Comparison: topical benzoyl peroxide

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Topical benzoyl peroxide	Topical gluconolactone				
Participants' global self-assessment of acne improvement	-	-	-	-	-	Not measured
Withdrawal for any reason (long term: treatment duration > 8 weeks)	**120 per 1000**	**100 per 1000** (32 to 306)	**RR 0.83** (0.27 to 2.55)	100 (1 study)	⊕⊕⊖⊖ **Low** [a]	-
Total number of participants who experienced at least one minor adverse event (long term: treatment duration > 8 weeks)	**500 per 1000**	**240 per 1000** (135 to 425)	**RR 0.48** (0.27 to 0.85)	100 (1 study)	⊕⊕⊖⊖ **Low** [b]	Dryness was the most commonly reported problem in treatment groups

Table 11. Gluconolactone (alpha-hydroxy acid) compared to benzoyl peroxide *(Continued)*

Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of other bias, and with unclear risk of selection bias and reporting bias. One level for imprecision: wide CI and optimal sample size not met.
[b]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of other bias and unclear risk of selection and reporting bias. One level for imprecision: optimal sample size not met.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

Table 12. Gluconolactone (alpha-hydroxy acid) compared to placebo

Gluconolactone (alpha-hydroxy acid) compared to placebo for acne

Patient or population: participants with acne
Settings: not described
Intervention: topical gluconolactone (alpha-hydroxy acid)
Comparison: placebo

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo/no treatment	**Topical gluconolactone**				
Participants' global self-assessment of acne improvement	-	-	-	-	-	Not measured
Withdrawal for any reason (long term: treatment duration > 8 weeks)	**80 per 1000**	**100 per 1000** (29 to 350)	**RR 1.25** (0.36 to 4.38)	100 (1 study)	⊕⊕⊖⊖ **Low** [a]	-
Total number of participants who experienced at least one minor adverse event (long term: treatment duration > 8 weeks)	**100 per 1000**	**240 per 1000** (91 to 631)	**RR 2.40** (0.91 to 6.31)	100 (1 study)	⊕⊕⊖⊖ **Low** [b]	Participants in gluconolactone group reported more erythema, burning and stinging, pruritus and scal-

Table 12. Gluconolactone (alpha-hydroxy acid) compared to placebo *(Continued)*

						ing than those in the placebo group, but these differences were not "significant".
Quality of life	-	-	-	-	-	Not measured

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of other bias and unclear risk of selection and reporting bias. One level for imprecision: wide CI and optimal sample size not met.
[b]Downgraded by two levels to low quality evidence. One level for risk of bias: only one study included with high risk of other bias and unclear risk of selection and reporting bias. One level for imprecision: wide CI and optimal sample size not met.
[*]We choose a mean baseline risk from the studies included in meta-analysis, calculated as number of participants in the control groups with event divided by total number of participants in control groups (study population) as assumed risk.

APPENDICES

Appendix 1. Skin Group Specialised Register/CRS search strategy

acne and (azelaic or azeleic or salicylic or niacinamide or nicotinamide or sulfur or sulphur or ascorbic or fruit or zinc)

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Acne Vulgaris] explode all trees
#2 acne:ti,ab,kw
#3 #1 or #2
#4 MeSH descriptor: [Dicarboxylic Acids] explode all trees
#5 ((azelaic or azeleic) and acid*):ti,ab,kw
#6 MeSH descriptor: [Salicylic Acid] explode all trees
#7 salicylic acid*:ti,ab,kw
#8 o-hydroxybenzoic acid*:ti,ab,kw
#9 MeSH descriptor: [Niacinamide] explode all trees
#10 niacinamide:ti,ab,kw
#11 nicotinamide:ti,ab,kw
#12 MeSH descriptor: [Sulfur] explode all trees
#13 sulphur:ti,ab,kw
#14 sulfur:ti,ab,kw
#15 MeSH descriptor: [Ascorbic Acid] explode all trees
#16 ascorbic acid*:ti,ab,kw
#17 fruit acid*:ti,ab,kw
#18 MeSH descriptor: [Fruit] explode all trees
#19 (topical and zinc):ti,ab,kw
#20 MeSH descriptor: [Zinc] explode all trees
#21 {or #4-#20}
#22 #3 and #21

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Acne Vulgaris/
2. acne.ti,ab.
3. 1 or 2
4. exp Dicarboxylic Acids/
5. azelaic acid$.ti,ab.
6. azeleic acid$.ti,ab.
7. exp Salicylic Acid/
8. salicylic acid$.ti,ab.
9. o-hydroxybenzoic acid$.ti,ab.
10. exp Niacinamide/
11. niacinamide.ti,ab.
12. nicotinamide.ti,ab.
13. Sulfur/
14. sulphur.ti,ab.
15. sulfur.ti,ab.
16. exp Ascorbic Acid/
17. ascorbic acid$.ti,ab.
18. fruit acid$.ti,ab.
19. Fruit/
20. Zinc/ and topical.ti,ab.
21. (topical and zinc).ti,ab.
22. or/4-21
23. randomized controlled trial.pt.
24. controlled clinical trial.pt.
25. randomized.ab.
26. placebo.ab.
27. clinical trials as topic.sh.
28. randomly.ab.
29. trial.ti.
30. 23 or 24 or 25 or 26 or 27 or 28 or 29
31. exp animals/ not humans.sh.
32. 30 not 31
33. 3 and 22 and 32

[Lines 23-32: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 4. Embase (Ovid) search strategy

1. exp acne vulgaris/
2. acne.mp.
3. 1 or 2
4. exp dicarboxylic acid/
5. azelaic acid$.ti,ab.
6. azeleic acid$.ti,ab.
7. azelaic acid/
8. salicylic acid/
9. salicylic acid$.ti,ab.
10. o-hydroxybenzoic acid$.ti,ab.
11. exp nicotinamide/
12. niacinamide.ti,ab.
13. nicotinamide.ti,ab.
14. sulfur/
15. sulphur.ti,ab.
16. sulfur.ti,ab.
17. exp ascorbic acid/
18. fruit acid$.ti,ab.
19. exp fruit/
20. (topical and zinc).ti,ab.
21. zinc/ and topical.ti,ab.
22. ascorbic acid$.ti,ab.

23. or/4-22
24. crossover procedure.sh.
25. double-blind procedure.sh.
26. single-blind procedure.sh.
27. (crossover$ or cross over$).tw.
28. placebo$.tw.
29. (doubl$ adj blind$).tw.
30. allocat$.tw.
31. trial.ti.
32. randomized controlled trial.sh.
33. random$.tw.
34. or/24-33
35. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
36. human/ or normal human/
37. 35 and 36
38. 35 not 37
39. 34 not 38
40. 3 and 23 and 39

Appendix 5. LILACS search strategy

acne and (azelaic or azeleic or azelaico or salicilico or salicylic or niacinamide or nicotinamide or sulfur or sulphur or azufre or ascorbic or ascorbico or fruit or zinc or cinc)

These terms combined with the Controlled clinical trials topic-specific query filter.

FEEDBACK

Intention to treat analysis, 21 July 2020

Summary

A comment was received from Sarah King who has conducted a systematic review on AA for acne, querying whether the authors conducted ITT analysis. She cites an example: in Katsambas 1989a, they have used the full data set (i.e. n = 92 in their Analysis 2.9), but it does not appear that the primary study authors conducted ITT analysis (n = 80 as there were drop-outs reported). Did the authors use the full numbers in other analyses as well or use numbers analysed by study authors? If they used ITT analysis, how did they impute the data - if they did this?

Reply

As suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011; 16.2.2 Intention-to-treat issues for dichotomous data), for dichotomous data, there are two options for this issue: 1) available case analysis; 2) ITT analysis using imputation, based on analysis of the total number of randomized participants, irrespective of how the original study authors analysed the data. We used the second one. This is to say, we extracted data on ITT basis (once-randomised-always-analyse) as stated in our protocol. Thus, we used the 'full data set' in our review for dichotomous data. We assumed that all the missing participants 'did not experience the event'. For example, in Analysis 2.9, all the drop-outs did not experience 'Good to excellent improvement'. There is no consensus on the best way to handle these missing participants in an analysis. The choice of imputation methods should be based on clinical judgement.

Contributors

Lead author Haibo Liu and Cochrane Skin feedback editor Urbà González.

WHAT'S NEW

Date	Event	Description
8 December 2020	Amended	Feedback received 21 July 2020; response published.

HISTORY

Protocol first published: Issue 11, 2014
Review first published: Issue 5, 2020

CONTRIBUTIONS OF AUTHORS

HS was the contact person with the editorial base.
HL, HS, JX, and FP co-ordinated contributions from the co-authors and wrote the final draft of the review.
HL and HY screened papers against eligibility criteria.
HY obtained data on ongoing and unpublished studies.
HL and HS appraised the quality of papers.
HL, HY, and FP extracted data for the review and sought additional information about papers.
HL and HY entered data into RevMan.
HL and HS analysed and interpreted data.
HL, JX and FP worked on the methods sections.
HL and HS drafted the clinical sections of the background and responded to the clinical comments of the referees.
GL responded to the methodology and statistics comments of the referees.
LL was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.
HL is the guarantor of the update.

Disclaimer

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DECLARATIONS OF INTEREST

Haibo Liu: nothing to declare
Haiyan Yu: nothing to declare
Jun Xia: nothing to declare
Ling Liu: nothing to declare
Guan J Liu: nothing to declare
Hong Sang: nothing to declare
Frank Peinemann: nothing to declare
Jerry Tan, clinical referee: advisor, consultant, and/or investigator for Allergan, Almirall, Cipher, Galderma, and Valeant

SOURCES OF SUPPORT

Internal sources

- Jinling Hospital, Nanjing, China
- Zhejiang University, Hangzhou, China

External sources

- The National Institute for Health Research (NIHR), UK

  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Types of interventions/Objectives: we added topical zinc and fruit acid (alpha-hydroxy acid) as included interventions, as the aim of this review was to include all topical treatments other than antimicrobials/retinoids.
- Types of outcome measures/Secondary outcomes: we assessed 'minor adverse events' as 'total number of participants who experienced at least one minor adverse event' which would be more clear and precise.
- Types of outcome measures: we clarified the timing definitions.
- Measures of treatment effect: in the protocol, we planned to conduct a sensitivity analysis using different cut-off points (e.g. 'greatly improved' or 'not greatly improved'). We did not do this because of the limited number of trials included in each comparison.
- Several trials compared one of the six topical treatments plus drug X to drug X alone. In this case, we considered drug X as the concomitant medication in both treatment arms and we deemed this kind of comparison to be: one of six topical treatments versus no treatment. We extracted and analysed these data in the comparisons of 'topical treatments versus no treatment'.
- Data synthesis: in the protocol, we planned to employ a fixed-effect model for pooled analyses unless the I^2 statistic measure of heterogeneity was equal to or greater than 30%, in which case we used the random-effects model. However, we used the random-effect model throughout all analyses, as suggested by the reviewer, as it would be likely there would be clinical and methodological heterogeneity between any pooled studies.

- Data collection and analysis: in the protocol, we planned to create 'Summary of findings' tables for primary outcomes. We also summarised the secondary outcome of 'minor adverse events - total events' and 'quality of life'.
- We edited the title so that the scientific term for 'fruit acid' was included, to enable visibility of the review in search results.
- We excluded trials in which participants had a diagnosis of neonatal and infantile acne.

INDEX TERMS

Medical Subject Headings (MeSH)

Acne Vulgaris [*drug therapy]; Adapalene [adverse effects] [therapeutic use]; Anti-Bacterial Agents [therapeutic use]; Benzoyl Peroxide [therapeutic use]; Bias; Clindamycin [adverse effects] [therapeutic use]; Dermatologic Agents [adverse effects] [*therapeutic use]; Dicarboxylic Acids [adverse effects] [therapeutic use]; Erythromycin [adverse effects] [therapeutic use]; Glycolates [therapeutic use]; Keratolytic Agents [therapeutic use]; Mandelic Acids [therapeutic use]; Niacinamide [adverse effects] [therapeutic use]; Patient Dropouts [statistics & numerical data]; Pyruvic Acid [adverse effects] [therapeutic use]; Quality of Life; Salicylic Acid [therapeutic use]; Sulfur [therapeutic use]; Tretinoin [therapeutic use]; Zinc [therapeutic use]

MeSH check words

Adolescent; Adult; Child; Female; Humans; Male; Young Adult