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Article type : Review Article

Topical preparations for the treatment of mild to moderate acne vulgaris: systematic review and network meta-analysis

Running head: Systematic review and network meta-analysis of topical treatments for mild to moderate acne

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/BJD.20080

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Study registration: PROSPERO 2019 CRD42019135570

Funding: This study is funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR grant number 442). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The funder played no role in any of the design of the study, collection, analysis, and interpretation of data, or writing the manuscript.

Conflicts of interests: AYF is joint copyright owner of the Cardiff Acne Disability Index. AYF was previously a member of the Galderma-funded Acne Global Alliance (paid honoraria). AML has provided unrestricted educational talks or acted as a consultant on research developments for Proctor & Gamble, Galderma Pharmaceuticals, La Roche Posay and Origimm in the last 5 years. AML was previously a member of the Acne Global Alliance (supported by Galderma Pharmaceuticals) aimed at improving outcomes in acne management. None of the other authors have any interests to declare.

What's already known about this topic?

- Guidelines suggest a number of different topical preparations as first line treatment for acne vulgaris.
- Evidence from head to head comparisons on the effectiveness of the most commonly prescribed treatments for mild to moderate acne is incomplete or lacking.
- Network meta-analysis uses all available trial data for a direct and indirect comparisons of most commonly prescribed topical preparations against mild to moderate acne vulgaris.

What does this study add?

- There is no convincing evidence that topical treatments containing antibiotics, as monotherapy or in combination, are more effective for the treatment of mild to moderate acne than those that do not.
- Combination treatment with adapalene plus benzoyl peroxide may be more effective than either treatment used alone but may cause more adverse events.
- There is no convincing evidence whether adapalene or benzoyl peroxide are less likely to cause adverse events when used alone.

ABSTRACT

Background

Acne is very common and can have substantial impact on wellbeing. Guidelines suggest first line management with topical treatments but there is little evidence regarding which are most effective.

Objectives

To identify the most effective and best tolerated topical treatments for acne using network meta-analysis.

Methods

CENTRAL, MEDLINE, EMBASE and WHO Trials Registry were searched until June 2020 for randomised trials that included participants with mild/moderate acne.

Primary outcomes were self-reported improvement in acne, and trial withdrawal. Secondary outcomes included change in lesion counts, Investigator Global Assessment, change in quality of life and total number of adverse events.

Network meta-analysis was undertaken using a frequentist approach.

Risk of bias was assessed using the Cochrane Risk of Bias Tool and confidence in evidence with CINeMA.

Results

A total of 81 papers were included, reporting 40 trials including 18,089 participants. Patient Global Assessment of Improvement was reported in 11 trials. Based on the pooled network estimates, compared with vehicle, benzoyl peroxide (BPO) was effective (35% v 26%, odds ratio (OR) 1.93, 95% confidence interval (CI) 1.45- 2.56; moderate confidence) for improving self-reported acne. The combinations of BPO with adapalene (54% v 35%, OR 1.88, 1.32-2.67; low confidence) or with clindamycin (49% v 35%; OR 1.54, 1.14-2.08; low confidence) were ranked more effective than BPO alone. Participants withdrawing from the trial was reported in 35 trials. Numbers withdrawing due to adverse events were low for all treatments. Rates of withdrawal were slightly higher for BPO with adapalene (2.5%) or clindamycin (2.7%) than BPO (1.6%) or adapalene alone (1.0%). Overall confidence in the evidence was low.

Conclusions

Adapalene+BPO may be the most effective but with a slightly higher incidence of withdrawal than monotherapy. Inconsistent reporting of trial results precluded firmer conclusions.

INTRODUCTION

Rationale

Acne vulgaris (hereafter 'acne') is very common in both adolescents and adults.[1] Acne can have significant impact on quality of life, including increased risk of depression.[2]

Guidelines differ in their recommendations and quality[3], but National Institute for Clinical Care Excellence Clinical Knowledge Summary (NICE CKS) UK guidelines suggest that first line treatment is a single agent topical, followed by combination topical treatment.[4] Guidelines in the USA, Canada and Europe are similar, recommending combination topical treatment as first line therapy.[5–7] Although topical preparations, such as benzoyl peroxide (BPO) and topical retinoids (e.g. adapalene), can be effective, there is uncertainty regarding the most appropriate strategy for initial and maintenance treatment.[2] Whilst the prescription of topical antibiotics as monotherapy in the UK is declining, topical antibiotics as monotherapy or in combination are still widely prescribed[8] and contribute to antibiotic resistance.[9,10]

A 2014 James Lind Alliance priority setting partnership for acne included the question "What is the best topical product for treating acne?" in their top ten priorities for future research.[11] There are multiple topical acne treatments and it is not feasible to review and compare them all. It is, however, reasonable to address the question set out in the Priority Setting Partnership by comparing treatments suggested in European guidelines as first line topical preparations for mild and moderate acne and that are prescribed in the UK.

Although these treatments are widely used, there are gaps in the evidence base regarding their effectiveness and tolerability. There have been two Cochrane reviews to date assessing topical treatments for acne.[12,13] But these reviews were able to provided only limited head-to-head evidence for key treatments, including adapalene+BPO, which are widely used and recommended in guidelines.

The uncertainty in the evidence base regarding optimal choice of topical treatments for acne is important because (1) topical antibiotics, alone or in combination, may be used despite being no more effective than topical non-antibiotic treatments; (2) uncertainty leads to potential delays in treating acne effectively; and (3) patients may progress to other treatments if acne is not improving, such as long courses of oral antibiotics.

Whilst traditional meta-analysis is limited to direct head-to-head comparisons, network meta-analysis techniques, sometimes also called multiple treatments meta-analysis, can overcome this by using all available data to build a network of direct and indirect comparisons. It allows estimates of effectiveness of treatment as well as estimates of incoherence (how well the whole network fits together).[14]

METHODS

Protocol and registration

The study was conducted and is reported in line with the PRISMA-NMA guideline[15] and was pre-registered on PROSPERO (CRD42019135570).

Public and Patient Involvement

Prior to undertaking this study, we convened a 'patient panel' of 10 people with current/former acne. We discussed the research question and how we might measure "effectiveness" and "adverse events". The patient panel felt strongly that a participant-reported outcome should be the primary measure; it was their assessment of their acne which mattered most to them, not a clinician's. They also helped decide on the scope of the review, stressing the importance of understanding whether prescribed topical medications actually worked. They saw little value in including medications not currently available to them in the UK. One member of the patient panel joined the study team and is a co-author on this manuscript.

Search strategy and information sources

We searched the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE, from inception to June 2020, for relevant journal articles, conference abstracts, and systematic reviews (Appendix S1). Our search was not limited by language. We also searched the World Health Organization International Clinical Trials Registry for relevant registered trials; hand searched references from included papers and relevant

systematic reviews for additional relevant trials; and contacted experts and pharmaceutical companies to find any unpublished trials.

Study selection

We included randomised controlled trials (RCTs) but excluded split-face and split-body trials due to concerns about contamination, and quasi-randomised trials as well as any non-randomised designs.

Two reviewers independently screened all titles, abstracts and full papers, using the eligibility criteria below, with any disagreements resolved through discussion. We only obtained and assessed full papers or conference abstracts for inclusion in the review if they were written in English. However, we kept a record of foreign language papers whose title and abstract were potentially relevant for inclusion in future updates if possible.

Eligibility criteria

Population: We included all trials where participants had mild to moderate acne (as defined by trial authors), regardless of age, gender, setting or previous treatments. We included trials in which there were mixed populations of acne severity, provided ≤50% of participants had severe acne. We excluded trials in which severity was not reported, or where it was unclear from source material whether the trial was randomised or not.

We excluded trials in which all participants: had truncal acne only, were diagnosed with: rosacea, unusual forms of acne, chloracne, acne inversa, acne fulminans, neonatal acne, infantile acne, occupational acne, drug-induced acne and acne specifically associated with endocrinopathies, including polycystic ovary syndrome, had previously received oral isotretinoin, or were only using the trial treatment as maintenance therapy directly following another acne treatment.

Intervention: This review compares topical preparations for mild/moderate acne described in the NICE CKS or European guidelines. The list was refined by a panel of dermatologists, general practitioners and patients for relevance to clinical practice and patient needs. Treatment regimens available in the UK at any dose, formulation or duration were included. Preparations no longer manufactured or available in the UK, or studies comparing different strengths or dosages of the same preparation were excluded (Box 1).

Comparator: Placebo/vehicle or any treatment regimen, dose, duration of the topical treatments listed in box 1.

Outcomes: The primary outcomes were:

- Proportion of participants self-reporting moderate or better global improvement in acne; and
- Proportion of participants withdrawing from trial or stopping of trial medication due to adverse events

Secondary outcomes were:

- Change in mean total lesion count from baseline as assessed by an investigator
- Proportion of participants rated 'clear' or 'almost clear' on the Investigator Global Assessment (IGA) scale of acne severity
- Proportion of participants rated as having at least two grades improvement from baseline on the Investigator Global Assessment (IGA) scale of acne severity
- Change in quality of life from baseline (assessed with a validated instrument such as Skindex-16, Skindex-29 or Cardiff Acne Disability Index)
- Reduction in *C. acnes* strains
- Total number of adverse events
- Participant satisfaction with treatment

Data collection and data items

A data extraction form was developed in Excel and piloted on two randomly selected papers to ensure consistency. Data available in graph format only were not extracted.

Data extraction was performed by one reviewer and checked by a second.

All outcomes were reported in the medium term, defined as 5 weeks to 16 weeks (with closest data point to 16 weeks used), with planned sensitivity analysis for short term (from 2 to 4 weeks) and long term (from 17 weeks to 12 months) outcomes. Trial arms that reported different strengths or dosages of the same medication were pooled.

Risk of bias in individual studies

Risk of bias was assessed using the Cochrane Risk of Bias tool, covering patient allocation sequence generation, allocation concealment, blinding, and selective outcome reporting.[16]

Statistical analyses

The network geometry has been presented graphically and describes the number of included interventions and the extent to which there are trials comparing different pairs of interventions.[17,18]

The network meta-analysis (NMA) was performed using a frequentist approach using a version of the R package netmeta, implemented in MetaInsight.[19] We anticipated heterogeneity between trials and therefore used random effects models and a common variance approach was used.[20] Equal heterogeneity across all comparators was assumed and a consistency model adopted.

For continuous outcomes, the effects were summarised using mean difference if included trials used the same outcome metric or using standardised mean difference (SMD) if trials reported different outcome metrics. Continuous outcomes were modelled using normal likelihood and dichotomous outcomes using binomial likelihood models to produce odds ratios. A reduced weights approach was used to account for correlation between arms in multi-arm trials.[21] Ranking of treatments was undertaken using the P-Score approach.[22]

We used the design-by-treatment test to evaluate global inconsistency and node splitting was used to examine inconsistency between direct and indirect effects, with a p-value of <0.05 taken as suggestive of conflicting evidence.[19]

Confidence in evidence

The confidence in the evidence across trials was assessed using Confidence in Network Meta-Analysis (CINeMA) approach[23] with ratings were conducted in the CINeMA app.[23,24]
CINeMA considers 6 domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. These are rated as no concerns, some concerns, or major concerns, with the exception of reporting bias which is rated as suspect or undetected. Judgements are then summarised across these 6 domains as very low, low, moderate or high confidence for each treatment comparison.[23]

Comparisons were considered at suspected risk of reporting bias if all or most of the comparisons were from industry funded trials. Indirectness was downgraded for comparisons that were poorly connected in the network. For imprecision, the threshold was set at an odds ratio of 1.5 for binary comparisons and a difference of 10 for lesion counts based on discussion.

RESULTS

Study selection and network structure

We identified 3717 references and, after removing duplicates, 2236 were screened by 2 reviewers for eligibility. We obtained 329 full texts and identified 133 eligible full texts reporting on 82 trials. An updated search in June 2020 identified a further 23 full texts of which 9 were eligible. We excluded 54 full texts, comprising 5126 participants, because the outcomes of interest could not be extracted. Of the trials identified by the original and updated searches, 81 full texts reporting on 40 trials including a total of 18,089 participants provided outcome data for meta-analysis (Figure 1).[25-62]

Figure 2 shows network plots for direct evidence between treatments. In all analyses, the main comparator was vehicle. For all outcomes, the most common treatment studied was BPO compared to vehicle, followed by adapalene and adapalene+BPO compared to vehicle. Fewer trials compared clindamycin+tretinoin, erythromycin+zinc or tretinoin, tretinoin alone or azelaic acid to any other treatment.

Trial characteristics and risk of bias

Key trial characteristics and risk of bias are detailed in Table S1 and Figures S1 and S2. The mean sample size was 454 participants (s.d. 524). Average age was 19.77 years (s.d. 3.13) and 57.7% were females. 50% recruited participants from North America, 29% from Europe, 24% from Asia, 5% from South America and 3% from Australia but the ethnicity of these populations was poorly reported. Pharmaceutical companies sponsored 54% of trials and a further 38% did not report the funder.

Most trials were unclear risk of bias on at least one domain due to poor reporting and none were low risk of bias across all domains. Whilst blinding of participants was generally well-described in trials which included a vehicle, many trials were unclear in their description of the blinding of trial personnel. All trials were randomised but the generation of the randomisation sequence was poorly described in 30 trials.

Trial Results

Table 1 sets out the pooled network analysis results and confidence ratings for all treatment comparisons. Figure 3 sets out all the pooled network comparisons relative to vehicle. Below we consider the outcomes from the review for which sufficient data was available for network analysis. All treatment rankings and associated probabilities are set out in Tables S2-S5..

Patient Global Assessment of Improvement

The proportion of participants who rated their acne as "improved or much improved" was reported in 11 trials of 6947 participants. Figure 3 shows that all treatments were significantly more effective than vehicle.

Table 2 sets out direct (in white) and pooled (in grey) odds ratios and 95% confidence intervals for comparisons. Compared to vehicle, adapalene+BPO had an odds ratio of 3.65 (95%CI 2.58-5.15; moderate confidence) and network comparisons suggest that this treatment was significantly more effective than all other included treatments apart from clindamycin+BPO (OR 1.22, 95% CI 0.81-1.85; low confidence). Clindamycin+BPO was significantly more effective than BPO (OR 1.54, 95% CI 1.14-2.08; low confidence) or clindamycin alone (OR 1.91, 95% CI 1.36-2.68; moderate confidence).

Adverse events

Participants withdrawing from the trial or stopping the trial medication was reported in 35 trials of 16,735 participants. Results are out in Table 3 and the rankings suggest that the lowest odds of withdrawal were in participants using clindamycin. Clindamycin was associated with significantly lower odds of withdrawal than clindamycin+BPO (OR 2.17,95% CI 1.25-3.70; very low confidence), BPO (OR 2.38, 95% CI 1.20-4.76; moderate confidence) or adapalene+BPO. The highest odds of withdrawal/discontinuation were for adapalene+BPO (OR4.35, 95%CI 2.13-9.09; moderate confidence). Participants using adapalene+BPO had an odds ratio of 2.56 (95%CI 1.41- 4.76; moderate confidence) compared with adapalene, suggesting odds of withdrawal/discontinuation was 3 times higher with combination treatment than adapalene alone. Similarly, participants using adapalene+BPO had an odds ratio 2.22 (95% CI 0.94-5.26; moderate confidence)compared to those using tretinoin and 1.85 (95% CI 1.08-3.13; moderate confidence) compared to those using BPO. However, the numbers of participants who withdrew due to adverse events was low for all treatments (Table 4).

Total lesion counts

Mean change in total lesion counts was reported in 24 trials of 11,717 participants (Table 5). The largest change was observed in those using adapalene+BPO with a difference of 20.96 lesions (95%CI -25.02 - -16.90; moderate confidence) compared to vehicle. Network comparisons suggest significant improvements with adapalene+BPO compared to all other treatments apart from erythromycin+tretinoin, where the confidence intervals were very wide and confidence very low. Compared to the second ranked treatment, clindamycin+BPO, there were -8.27 (95%CI -13.02 - -3.52; very low confidence) fewer lesions with adapalene+BPO. Clindamycin+BPO and BPO were more effective than clindamycin alone with low and moderate confidence respectively.

Investigator Global Assessment

There were 14 trials of 13,342 participants that evaluated improvement in the IGA to clear or almost clear (Table 6). All treatments were significantly more effective than vehicle apart from tretinoin (OR 0.83,95% CI 0.46-1.52; low confidence). Adapalene+BPO was significantly more effective than all treatments apart from clindamycin+BPO, with an odds ratio of improvement of 3.83 (95%CI 2.40-6.10; moderate confidence) compared to vehicle. Based on the pooled network estimate, adapalene+BPO was approximately twice as likely to lead to improvement than either BPO or adapalene, with low and moderate confidence respectively.

Other outcomes and sensitivity analyses

There was insufficient data to undertake meta-analyses or network analyses for quality of life, patient satisfaction, *C. acnes* resistance and sensitivity analyses of outcomes in the short or long term.

Consistency

There was no evidence of global inconsistency. However, some analyses suggested local inconsistency between direct and indirect comparisons (see Tables S6-S9). The number of trials where pairs of direct and indirect estimates could be compared was very low and in all instances confidence intervals for estimates of differences were wide but there was no evidence of systematic differences with respect to potential effect modifiers. Therefore, this apparent inconsistency may represent true differences between direct and indirect effects, with indirect estimates being more precise due to coming from a network with larger trials.

Confidence in evidence

The grading of the comparisons with CINeMA (Tables S10-S13) showed mainly low to very low confidence ratings. This was due to concerns about reporting bias due to the involvement of industry in a large

number of small trials[23] and to concerns about within-study bias due to poor reporting of the randomisation and blinding procedures noted above. There were few concerns about transitivity (indirectness). Due to the strict inclusion criteria, most trials included a homogeneous population of interest. There was also evidence of heterogeneity and imprecision, usually related to the small numbers of trials available for some comparisons in the network.

DISCUSSION

This study has compared the most commonly prescribed topical treatments for acne in the UK and found no convincing evidence that topical treatments that contain antibiotics are more effective in treating acne than those that do not. Adapalene plus BPO appears to be ranked the most effective treatment on all included outcomes. It is also associated with a higher odds of withdrawal due to adverse events, but the overall incidence of this outcome was low for all treatments

Findings in context of existing research

Systematic reviews to date have not provided direct comparisons of some of the most commonly prescribed treatments. The recently published Cochrane review of BPO did not show statistically significant differences between BPO and other treatments[12]; however that study was not able to provide estimates for all other treatment comparisons. Similarly the Cochrane review including azelaic acid[13] was only able to draw on a limited number of direct trials to quantify differences between treatments.

This network analysis benefits from the additional power of indirect comparisons within the network. However, caution is still needed in interpreting these results. Findings presented here help to highlight gaps where further head-to-head trials are needed. The rankings we have reported are sensitive to inclusion criteria and may change as further evidence emerges. Moreover, the confidence in the evidence was low, with considerably uncertainty remaining about the true effect estimate due to poor reporting of study methods and the substantial number of trials with industry involvement.

The use of oral antibiotics for acne is high[62] and contributes to antibiotic resistance. Whereas resistance to topical antibiotics tends to be limited to the treated site, oral antibiotics can lead to resistance in commensal flora at all body sites.[9] This study suggests that non-antibiotic treatments are effective as first line treatment. Further research is needed to explore how these treatments compare to oral antibiotics used alone or in combination with topical treatments.

Strengths and limitations

Although we looked at many outcomes that were important to our patient panel, the study was hampered by poor and inconsistent reporting of trial outcomes. For the participant reported outcome, only 11 trials were included. The other 30 either did not report the outcome of interest (n=26) or it was reported inconsistently between trials (n=4). Efforts to harmonise the reporting of outcomes is needed, particularly as the outcomes most commonly reported, such as lesion counts, were not the ones that the patient panel felt were most meaningful.

For the purposes of this review, we considered total lesion counts. This was felt by people in our patient panel to be more meaningful than the distinction between inflammatory and non-inflammatory lesions. However, it is possible that the use of this global outcome disguises changes whereby certain phenotypes respond better to specific treatments.

Data on adverse events was particularly poorly reported and we were not able to assess this outcome. This makes it difficult to meaningfully discuss relative risks and benefits of the different treatments. Although we have been able to compare the likelihood of participants discontinuing the study, reasons were rarely reported. We were not able to compare adverse events that may concern patients starting a new treatment regimen, such as stinging, itching or peeling.

Blinding was reported in a number of trials and a suitable vehicle used. However, BPO or retinoids could cause adverse events such as redness or peeling. This might have led to participants or clinicians guessing the allocation. It is hard to quantify the extent to which this may have occurred as it is not reported but, if true, would lower the overall quality of the reported evidence.

Transitivity is one of the key assumptions of network meta-analysis. In order to achieve a population that was as homogeneous as possible, we excluded -full texts where the reported severity of acne was not clearly mild to moderate. Within the scope of the review, we did not have the resources to contact all authors of these excluded full texts to obtain clarification. It is possible that limiting the review in this way may have improved homogeneity but introduced a selection bias. Similarly, we did not have the resources to translate articles from other languages. We found 24 titles and abstracts in other languages that might potentially have been eligible. These represent a small proportion of the total title and abstracts screened but the inclusion of only English language full texts may be a source of bias.

The medications in the network analysis account for about two third of prescriptions in the UK in 2018[8] but there are notable gaps, with some treatments poorly connected to the network and comparisons based on only a single trial. Data on azelaic acid was only available for the lesion count outcome and there

were limited trials on combinations including erythromycin or erythromycin alone, which make up a substantial proportion of topical prescriptions alone or in combination with other treatments. [8,63]

We were also unable in the scope of this review to look at different concentrations of included treatments. Pooling of treatment strength into a single comparison may disguise differences in effectiveness of different formulations and strength and further research is needed to explore this question. Moreover, ethnicity was too poorly reported to explore whether there were any differences with respect to different skin types or skin colours.

Conclusions

Based on evidence mainly graded as low to very low confidence in the results, all topical treatments were more effective than vehicle and adapalene+BPO was the most effective. Clinicians need to weigh this up with patients as although withdrawal due to adverse events was uncommon, adapalene+BPO also appeared to have a slightly higher odds of this outcome. Further work is needed to compare topical treatment with oral antibiotic treatments and to consider which treatments may be most cost-effective.

Acknowledgements: We would like to thank our patient panel for their help and insights in the design of this study.

References

1 Hay RJ, Johns NE, Williams HC *et al.* The global burden of skin disease in 2010: An analysis of the prevalence and impact of skin conditions. *J Invest Dermatol* 2014; **134**:1527–34.

2 Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet* 2012; 361–72.

3 Eady EA, Layton AM, Sprakel J, *et al.* AGREE II assessments of recent acne treatment guidelines: how well do they reveal trustworthiness as defined by the U.S. Institute of Medicine criteria? *Br J Dermatol* 2017; **177**:1716–25.

4 Acne vulgaris - NICE CKS [WWW Document]. URL https://cks.nice.org.uk/acne-vulgaris#!scenarioRecommendation [accessed on 2 June 2020].

5 Zaenglein AL, Pathy AL, Schlosser BJ *et al.* Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016; **74**:945-973.e33.

6 Asai Y, Baibergenova A, Dutil M *et al.* Management of acne: Canadian clinical practice guideline. *CMAJ* 2016; **188**:118–26.

7 Nast A, Dréno B, Bettoli V *et al.* European evidence-based (S3) guideline for the treatment of acne – update 2016 – short version. *J Eur Acad Dermatol Venereol* 2016; **30**:1261–8.

8 Prescription Cost Analysis (PCA) data | NHSBSA [WWW Document]. URL https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data [accessed on 2 June 2020].

9 Walsh TR, Efthimiou J, Dréno B. Systematic review of antibiotic resistance in acne: An increasing topical and oral threat. *Lancet Infect Dis* 2016; **16**:e23–33.

10 Adler BL, Kornmehl H, Armstrong AW. Antibiotic resistance in acne treatment. *JAMA Dermatol* 2017; **153**:810–1.

11 Layton A, Eady EA, Peat M *et al.* Identifying acne treatment uncertainties via a James Lind Alliance Priority Setting Partnership. *BMJ Open* 2015; **5**:e008085.

12 Yang Z, Zhang Y, Lazic Mosler E *et al.* Topical benzoyl peroxide for acne. *Cochrane Database Syst Re*v 2020; **3**:CD011154.

13 Liu H, Yu H, Xia J *et al.* Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc and fruit acid (alpha-hydroxy acid) for acne. *Cochrane Database Syst Rev* 2020; **2020**. doi:10.1002/14651858.CD011368.pub2.

14 Cipriani A, Higgins JPT, Geddes JR *et a*l. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013; **159**:130–7.

15 Hutton B, Salanti G, Caldwell DM *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann Intern Med* 2015; **162**:777–84.

16 Higgins JPT, Altman DG, Gøtzsche PC *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**. doi:10.1136/bmj.d5928.

17 Mills EJ, Thorlund K, Ioannidis JPA. Demystifying trial networks and network meta-analysis. *BMJ* 2013; **346**. doi:10.1136/bmj.f2914.

18 Ioannidis JPA. Integration of evidence from multiple meta-analyses: A primer on umbrella reviews,

treatment networks and multiple treatments meta-analyses. *CMAJ* 2009; **181**:488–93.

19 Owen RK, Bradbury N, Xin Y *et al.* MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. *Res Synth Methods* 2019; **10**:569–81.

20 Lu G, Ades A. Modeling between-trial variance structure in mixed treatment comparisons. *Biostatistics* 2009; **10**:792–805.

21 Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* 2012; **3**:312–24.

22 Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015; **15**:58.

23 Nikolakopoulou A, Higgins JPT, Papakonstantinou T *et al.* Cinema: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020; **17**:e1003082.

24 Papakonstantinou T, Nikolakopoulou A, Higgins JPT *et al.* CINeMA: Software for semiautomated assessment of the confidence in the results of network meta-analysis. *Campbell Syst Rev* 2020; **16**. doi:10.1002/cl2.1080.

25 Guerra-Tapia A. Effects of benzoyl peroxide 5% clindamycin combination gel versus adapalene 0.1% on quality of life in patients with mild to moderate acne vulgaris: a randomized single-blind study [WWW Document]. URL https://jddonline.com/articles/dermatology/S1545961612P0714X [accessed on 13 July 2020].

26 Zouboulis CC, Fischer TC, Wohlrab J *et al.* Study of the efficacy, tolerability, and safety of 2 fixed-dose combination gels in the management of acne vulgaris. *Cutis* 2009; **84**:223-9

27 Eichenfield LF, Draelos Z, Lucky AW *et al.* Preadolescent moderate acne vulgaris: a randomized trial of the efficacy and safety of topical adapalene-benzoyl peroxides. *J Drugs Dermatol* 2013; **12**:611–8.

28 Leyden JJ, Hickman JG, Jarratt MT *et al.* The efficacy and safely of a combination benzoyl peroxide/clindamycin topical gel compared with benzoyl peroxide alone and a benzoyl peroxide/erythromycin combination product. *J Cutan Med Surg* 2001; **5**:37–42.

29 Pazoki-Toroudi H, Nilforoushzadeh MA, Ajami M *et al.* Combination of azelaic acid 5% and

clindamycin 2% for the treatment of acne vulgaris. *Cutan Ocul Toxicol* 2011; **30**:286–91.

30 Hughes BR, Norris JFB, Cunliffe WJ. A double-blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. *Clin Exp Dermatol* 1992; **17**:165–8.

31 Hunt MJ, Barnetson RS. A comparative study of gluconolactone versus benzoyl peroxide in the treatment of acne. *Australas J Dermatol* 1992; **33**:131–4.

32 Alirezaï M, Gerlach B, Horvath A *et al.* Results of a randomised, multicentre study comparing a new water-based gel of clindamycin 1% versus clindamycin 1% topical solution in the treatment of acne vulgaris. *Eur J Dermatol* 2005; **15**:274–8.

33 Pariser DM, Thiboutot DM, Clark SD *et al.* The efficacy and safety of adapalene gel 0.3% in the treatment of acne vulgaris: A randomized, multicenter, investigator-blinded, controlled comparison study versus adapalene gel 0.1% and vehicle. *Cutis* 2005; **76**:145–51.

34 Jawade SA, Vaidehi AS, Ambika RK. Efficacy and tolerability of adapalene 0.1%-benzoyl peroxide 2.5% combination gel in treatment of acne vulgaris in Indian patients: A randomized investigator-blind controlled trial. Iranian Society of Dermatology, 2016. URL http://iranjd.ir/article_98294.html [accessed on 13 July 2020].

35 Lyons RE. Comparative effectiveness of benzoyl peroxide and tretinoin in acne vulgaris. *Int J Dermatol* 1978; **17**:246–51.

36 Stinco G, Bragadin G, Trotter D *et al.* Relationship between sebostatic activity, tolerability and efficacy of three topical drugs to treat mild to moderate acne. *J Eur Acad Dermatology Venereol* 2007; **21**:320–5.

37 Langner A, Chu A, Goulden V *et al*.A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide and adapalene in the treatment of mild to moderate facial acne vulgaris. *Br J Dermatol* 2007; **158**:122–9.

38 Thielitz A, Lux A, Wiede A *et al.* A randomized investigator-blind parallel-group study to assess efficacy and safety of azelaic acid 15% gel vs. adapalene 0.1% gel in the treatment and maintenance treatment of female adult acne. *J Eur Acad Dermatol Venereol* 2015; **29**:789–96.

39 Tirado-Sánchez A, Espíndola YS, Ponce-Olivera RM *et al*. Efficacy and safety of adapalene gel 0.1% and 0.3% and tretinoin gel 0.05% for acne vulgaris: results of a single-center, randomized, double-blinded, placebo-controlled clinical trial on Mexican patients (skin type III-IV). *J Cosmet Dermatol*

2013; **12**:103–7.

40 Leyden JJ, Berger RS, Dunlap FE *et al.* Comparison of the efficacy and safety of a combination topical gel formulation of benzoyl peroxide and clindamycin with benzoyl peroxide, clindamycin and vehicle gel in the treatments of acne vulgaris. *Am J Clin Dermatol* 2001; **2**:33–9.

41 Gold LS, Tan J, Cruz-Santana A,*et al.* A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. *Cutis* 2009; **84**:110–6.

42 Jarratt MT, Brundage T. Efficacy and safety of clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: A randomized, double-blind, vehicle-controlled study. *J Drugs Dermatology* 2012; **11**:318–26.

43 Gollnick HPM, Draelos Z, Glenn MJ *et al.* Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. *Br J Dermatol* 2009; **161**:1180–9.

44 Eichenfielda LF, Alió Sáenz AB. Safety and efficacy of clindamycin phosphate 1.2%-benzoyl peroxide 3% fixed-dose combination gel for the treatment of acne vulgaris: A phase 3, multicenter, randomized, double-blind, active- and vehicle-controlled study. *J Drugs Dermatol* 2011; **10**:1382–96.

45 Anadolu RY, Sen T, Tarımcı N *et al*. Improved efficacy and tolerability of retinoic acid in acne vulgaris. *J Am Acad Dermatol* 2004; **50**:P20.

46 Schaller M, Sebastian M, Ress C *et al.* A multicentre, randomized, single-blind, parallel-group study comparing the efficacy and tolerability of benzoyl peroxide 3%/clindamycin 1% with azelaic acid 20% in the topical treatment of mild-to-moderate acne vulgaris. *J Eur Acad Dermatol Venereol* 2016; **30**:966–73.

47 Xu JH, Lu QJ, Huang JH *et al.* A multicentre, randomized, single-blind comparison of topical clindamycin 1%/benzoyl peroxide 5% once-daily gel versus clindamycin 1% twice-daily gel in the treatment of mild to moderate acne vulgaris in Chinese patients. *J Eur Acad Dermatol Venereol* 2016; **30**:1176–82.

48 Nyirady J, Grossman RM, Nighland M *et al.* A comparative trial of two retinoids commonly used in the treatment of acne vulgaris. *J Dermatolog Treat* 2001; **12**:149–57.

49 Tu P, Li GQ, Zhu XJ *et al.* A comparison of adapalene gel 0.1% vs. tretinoin gel 0.025% in the

treatment of acne vulgaris in China. *J Eur Acad Dermatol Venereol* 2001; **15**:31–6.

50 Tschen EH, Katz HI, Jones TM *et al.* A combination benzoyl peroxide and clindamycin topical gel compared with benzoyl peroxide, clindamycin phosphate, and vehicle in the treatment of acne vulgaris. *Cutis* 2001; **67**:165–9.

51 Babaeinejad SH, Fouladi RF. The efficacy, safety, and tolerability of adapalene versus benzoyl peroxide in the treatment of mild acne vulgaris; a randomized trial. *J Drugs Dermatol* 2013; **12**:1033–8.

52 Cunliffe WJ, Danby FW, Dunlap F *et al.* Randomised, controlled trial of the efficacy and safety of adapalene gel 0.1% and tretinoin cream 0.05% in patients with acne vulgaris. *Eur J Dermatol* 2002; **12**:350-4

53 Thiboutot DM, Weiss J, Bucko A *et al.* Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: Results of a multicenter, randomized double-blind, controlled study. *J Am Acad Dermatol* 2007; **57**:791–9.

54 Thiboutot D, Pariser DM, Egan N *et al.* Adapalene gel 0.3% for the treatment of acne vulgaris: A multicenter, randomized, double-blind, controlled, phase III trial. *J Am Acad Dermatol* 2006; **54**:242–50.

55 Dogra S, Sumathy TK, Nayak C *et al.* Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin versus their monotherapy in patients with acne vulgaris: a phase 3, randomized, double-blind study. *J Dermatolog Treat* 2020; 1–9.

56 Mohammadi S, Pardakhty A, Khalili M *et al.* Niosomal benzoyl peroxide and clindamycin lotion versus niosomal clindamycin lotion in treatment of acne vulgaris: A randomized clinical trial. *Adv Pharm Bull* 2019; **9**:578–83.

57 Iftikhar U, Aman S, Nadeem M *et al*. A comparison of efficacy and safety of topical 0.1% adapalene and 4% benzoyl peroxide in the treatment of mild to moderate acne vulgaris. *J Pak Assoc Derma* 2009; **19**:141-5

58 Pariser DM. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 3.75% for the once-daily treatment of moderate to severe acne vulgaris [WWW Document]. URL https://jddonline.com/articles/dermatology/S1545961614P1083X [accessed on 13 July 2020].

59 Khanna. Topical clindamycin hydrochloride 1% in acne vulgaris. *Indian J Dermatol Venereol Leprol* 1990; **56**:377.

60 Lucky A, Jorizzo JL, Rodriguez D *et al.* Efficacy and tolerance of adapalene cream 0.1% compared with its cream vehicle for the treatment of acne vulgaris. *Cutis* 2001; **68**:34–40.

61 Kawashima M, Hashimoto H, Alio Sáenz AB *et al.* Is benzoyl peroxide 3% topical gel effective and safe in the treatment of acne vulgaris in Japanese patients? A multicenter, randomized, double-blind, vehicle-controlled, parallel-group study. *J Dermatol* 2014; **41**:795–801.

62 Berger R, Barba A, Fleischer A *et al.* A double-blinded, randomized, vehicle-controlled, multicenter, parallel-group study to assess the safety and efficacy of tretinoin gel microsphere 0.04% in the treatment of acne vulgaris in adults. *Cutis* 2007; **80**:152-7.

63 Francis NA, Entwistle K, Santer M *et al.* The management of acne vulgaris in primary care: a cohort study of consulting and prescribing patterns using the Clinical Practice Research Datalink. *Br J Dermatol* 2017; **176**:107–15.

Box 1. List of included topical treatments

Generic name	**Examples of brand names**
Vehicle	
Azelaic acid	Skinoren®
Adapalene	Differin®
Adapalene+Benzoyl Peroxide (BPO)	Epiduo®
BPO	Acnecide®
Clindamycin	Dalacin T®
Clindamycin+BPO	Duac®
Clindamycin+zinc	Zindaclin®
Erythromycin+zinc	Zineryt®
Isotretinoin+erythromycin	Isotrexin®
Tretinoin	
Tretinoin+clindamycin	Treclin®
Tretinoin+erythromycin	Aknemycin Plus®

Table 1. Summary of network pooled results and confidence in evidence

	Patient Global Assessment of Improvement		**Withdrawal**		**Total Lesion Counts**		**Investigator's Global Assessment**	
	NMA estimate Odds ratio (95% CI)	CINEMA confidence rating	NMA estimate Odds ratio (95% CI)	CINEMA confidence rating	NMA estimate Mean difference (95% CI)	CINEMA confidence rating	NMA estimate Odds ratio (95% CI)	CINEMA confidence rating
Adapalene +BPO v Clindamycin + BPO	1.22 (0.81, 1.85)	Low	2.04 (1.03, 4.00)	Moderate	-8.27 (-13.02, -3.52)	Very Low	1.23 (0.62, 2.42)	Very Low
Adapalene +BPO v Azelaic acid	N/A	N/A	3.33 (0.49, 25.00)	Very Low	-7.35 (-13.74, -0.96)	Very Low	N/A	N/A
Adapalene +BPO v BPO	1.88 (1.32, 2.67)	Low	1.85 (1.08, 3.13)	Moderate	-11.35 (-15.40, -7.30)	Moderate	1.68 (1.03 2.75)	Low
Adapalene +BPO v Adapalene	1.49 (1.01, 2.20)	Very low	2.56 (1.41, 4.76)	Moderate	-9.99 (-14.05, -5.93)	Moderate	2.01 (1.20, 3.36)	Moderate
Adapalene +BPO v Clindamycin	2.34 (1.50, 3.64)	Moderate	4.35 (2.13, 9.09)	Moderate	-12.78 (-17.35, -8.20)	Very Low	1.91 (0.99, 3.70)	Very Low
Adapalene +BPO v Clindamycin + tretinoin	2.13 (1.26, 3.60)	Moderate	3.33 (0.49, 25.00)	Low	-13.52 (-19.20, -7.85)	Very Low	2.05 (0.92, 4.55)	Very Low
Adapalene +BPO v Clindamycin + zinc	N/A	N/A	5.26 (1.03, 24.00)	Low	N/A	N/A	N/A	N/A
Adapalene +BPO v Tretinoin	1.74 (0.68, 4.47)	Low	2.22 (0.94, 5.26)	Moderate	-10.41 (-15.21, -5.61)	Very Low	4.61 (2.27, 9.35)	Very Low
Adapalene +BPO v Erythromycin + tretinoin	N/A	N/A	1.11 (0.10, 11.86)	Very Low	-2.23 (-22.41, 17.95)	Very Low	N/A	N/A
Adapalene +BPO v Erythromycin + zinc	N/A	N/A	2.08 (0.26, 16.67)	Very Low	-14.37 (-27.32, -1.42)	Very Low	N/A	N/A
Adapalene +BPO v Vehicle	3.65 (2.58, 5.15)	Moderate	2.94 (1.69, 5.00)	Moderate	-20.96 (-25.02, -16.90)	Moderate	3.83 (2.40, 6.10)	Moderate
Clindamycin + BPO v Azelaic acid	N/A	N/A	1.67 (0.24, 11.11)	Very Low	0.92 (-4.12, 5.96)		N/A	N/A
Clindamycin + BPO v BPO	1.54 (1.14, 2.08)	Low	0.90 (0.46, 1.77)	Very Low	-3.08 (-6.41, 0.24)	Moderate	1.37 (0.76, 2.49)	Low
Clindamycin + BPO v Adapalene	1.22 [0.78; 1.90]	Very Low	1.28 (0.62, 2.63)	Very Low	-1.72 (-5.36, 1.91)	Low	1.64 (0.82, 3.26)	Very Low
Clindamycin + BPO v Clindamycin	1.91 (1.36, 2.68)	Moderate	2.17 (1.25, 3.70)	Very Low	-4.51 (-7.08, -1.95)	Low	1.56 (0.93, 2.63(	Low
Clindamycin +BPO v Clindamycin + tretinoin	1.74 (1.13, 2.67)	Low	1.49 (0.56, 4.00)	Very Low	-5.26 (-9.71, -0.80)	Low	1.67 (0.87, 3.21)	Very Low
Clindamycin +BPO v Clindamycin + zinc	N/A	N/A	2.56 (0.54, 12.50)	Very Low	N/A	N/A	N/A	N/A

Clindamycin + BPO v Tretinoin	1.42 (0.56, 3.59)	Very low	1.09 (0.48, 2.50)	Very Low	-2.14 (-5.90, 1.63)	Very Low	3.76 (1.93, 7.33)	Low
Clindamycin +BPO v Erythromycin + tretinoin	N/A	N/A	0.44 (0.04, 4.86)	Very Low	6.04 (-13.99, 26.07)	Very Low	N/A	N/A
Clindamycin +BPO v Erythromycin + zinc	N/A	N/A	1.03 (0.14, 7.69)	Very Low	-6.10 (-18.14, 5.94)	Very Low	N/A	N.A
Clindamycin + BPO v Vehicle	2.98 (2.22, 4.01)	Moderate	1.43 (0.76, 2.70)	Very low	-12.69 (-15.92, -9.47)	Low	3.12 (1.82, 5.37)	Moderate
Azelaic acid v BPO	N/A	N/A	0.55 (0.08, 3.65)	Very Low	-4.00 (-9.46, 1.45)	Very Low	N/A	N/A
Azelaic acid v Adapalene	N/A	N/A	0.77 (0.11, 5.17)	Very Low	-2.64 (-8.20, 2.91)	Very Low	N/A	N/A
Azelaic acid v Clindamycin	N/A	N/A	1.30 (0.20, 8.33)	Very Low	-5.43 (-10.14, -0.73)	Very Low	N/A	N/A
Azelaic acid v Clindamycin + tretinoin	N/A	N/A	0.90 (0.11, 7.26)	Very Low	-6.17 (-12.17, -0.18)	Very Low	N/A	N/A
Azelaic acid v Clindamycin + zinc	N/A	N/A	1.54 (0.14, 16.67)	Very Low	N/A	N/A	N/A	N/A
Azelaic acid v Tretinoin	N/A	N/A	0.66 (0.09, 4.75)	Very Low	-3.06 (-8.64, 2.52)	Very Low	N/A	N/A
Azelaic acid v Erythromycin + tretinoin	N/A	N/A	0.27 (0.01, 5.34)	Very Low	5.12 (-15.37, 25.60)	Very Low	N/A	N/A
Azelaic acid v Erythromycin + zinc	N/A	N/A	0.62 (0.04, 9.88)	Very Low	-7.02 (-20.08, 6.04)	Very Low	N/A	N/A
Azelaic acid v Vehicle	N/A	N/A	1.15 (0.17, 7.75)	Very Low	-13.61 (-18.99, -8.24)	Very Low	N/A	N/A
BPO v Adapalene	1.27 (0.86, 1.85)	Low	1.41 (0.77, 2.56)	Low	1.36 (-1.34, 4.06)	Moderate	1.19 (0.72, 1.97)	Low
BPO v Clindamycin	1.24 [0.87; 1.75]	Low	2.38 (1.20, 4.76)	Moderate	-1.43 (-4.56, 1.70)	Moderate	1.14 (0.65, 2.00)	Low
BPO v Clindamycin + tretinoin	1.13 (0.71, 1.78)	Low	1.64 (0.56, 5.00)	Very Low	-2.17 (-6.81, 2.47)	Very Low	1.22 (0.59, 2.50)	Very Low
BPO v Tretinoin	1.09 (0.43, 2.73)	Very low	1.20 (0.53, 2.78)	Very Low	0.95 (-2.68, 4.58)	Very Low	2.74 (1.50, 5.00)	Low
BPO v Clindamycin + zinc	N/A	N/A	2.86 (0.56,14.29)	Very Low	N/A	N/A	N/A	N/A
BPO v Erythromycin + tretinoin	N/A	N/A	0.49 (0.05, 5.17)	Very Low	9.12 (-10.85, 29.09)	Very Low	N/A	N/A

BPO v Erythromycin + zinc	N/A	N/A	1.14 (0.77, 2.56)	Very Low	-3.02 (-15.51, 9.48)	Very Low	N/A	N/A
BPO v Vehicle	1.93 (1.45, 2.56)	Moderate	1.59 (0.98, 2.56)	Moderate	-9.61 (-12.44, -6.78)	Moderate	2.28 (1.51, 3.44)	Moderate
Adapalene v Clindamycin	1.57 (0.98, 2.51)	Low	1.69 (0.82, 3.57)	Low	-2.79 (-6.19, 0.60)	Very Low	0.95 (0.49, 1.85)	Very Low
Adapalene v Clindamycin + tretinoin	1.43 (0.82, 2.48)	Very Low	1.18 (0.39, 3.57)	Very Low	-3.53 (-8.24, 1.18)	Very Low	1.02 (0.46, 2.28)	Very Low
Adapalene v Tretinoin	1.17 (0.45, 3.04)	Very Low	0.86 (0.39, 1.89)	Very low	-0.41 (-3.89, 3.06)	Low	2.29 (1.12, 4.68)	Very Low
Adapalene v Erythromycin + tretinoin	N/A	N/A	0.35 (0.03, 3.75)	Very Low	7.76 (-12.24, 27.76)	Very Low	N/A	N/A
Adapalene v Erythromycin + zinc	N/A	N/A	0.81 (0.10, 6.68)	Very Low	-4.38 (-16.96, 5.94)	Very Low	N/A	N/A
Adapalene v Vehicle	2.44 (1.66, 3.60)	Moderate	1.12 (0.64, 2.00)	Very low	-10.97 (-13.99, -7.95)	Moderate	1.91 (1.19, 3.09)	Moderate
Clindamycin v Clindamycin + tretinoin	1.10 (0.72, 1.68)	Low	0.69 (0.28, 1.71)	Very low	-0.74 (-4.52, 3.04)	Moderate	1.07 (0.61, 1.87)	Very Low
Clindamycin v Tretinoin	1.34 (0.53, 3.43)	Very low	0.50 (0.25, 1.04)	Very low	2.38 (-0.84, -5.59)	Moderate	2.41 (1.38, 4.21)	Low
Clindamycin v Erythromycin + tretinoin	N/A	N/A	0.20 (0.02, 2.25)	Very Low	10.55 (-9.43, 30.53)	Very Low	N/A	N/A
Clindamycin v Erythromycin + zinc	N/A	N/A	0.48 (0.06, 3.73)	Very Low	-1.59 (-13.90, 10.73)	Very Low	N/A	N/A
Clindamycin v Vehicle	1.56 (1.13, 2.16)	Low	0.66 (0.35, 1.27)	Very low	-8.18 (-11.11, -5.25)	Low	2.00 (1.19, 3.37)	Low
Tretinoin v Clindamycin + tretinoin	1.22 (0.46, 3.24)	Very low	1.37 (0.46, 4.00)	Very Low	-3.12 (-7.23, 0.99)	Very Low	0.45 (0.23, 0.89)	Low
Tretinoin v Erythromycin + tretinoin	N/A	N/A	0.41 (0.04, 4.64)	Very Low	8.17 (-11.87, 28.33)	Very Low	N/A	N/A
Tretinoin v Erythromycin + zinc	N/A	N/A	1.03 (0.14, 7.69)	Very Low	-3.96 (-16.58, 8.66)	Very Low	N/A	N/A
Tretinoin v Vehicle	2.10 (0.87, 5.04)	Very low	1.32 (0.60, 2.86)	Very Low	-10.56 (-13.87, -7.24)	Moderate	0.83 (0.46,1.52)	Low
Clindamycin + tretinoin v Erythromycin + tretinoin	N/A	N/A	3.33 (0.27, 50.00)	Very Low	10.55 (-9.43, 30.53)	Very Low	N/A	N/A
Clindamycin + tretinoin v Erythromycin + zinc	N/A	N/A	0.69 (0.07, 6.33)	Very Low	-0.84 (-13.69, 12.00)	Very Low	N/A	N/A
Clindamycin + tretinoin v Vehicle	1.71 (1.12, 2.62)	Low	1.04 (0.36, 3.02)	Very Low	-7.44 (-11.90, -2.97)	Very Low	1.87 (0.94, 3.72)	Very Low

Erythromycin + zinc v Erythromycin + tretinoin	N/A	N/A	0.43 (0.02, 9.68)	Very Low	12.14 (-11.24, 35.51)	Very Low	N/A	N/A
Erythromycin + zinc v Vehicle	N/A	N/A	1.41 (0.17, 11.11)	Very Low	-6.59 (-19.06, 5.88)	Very Low	N/A	N/A
Erythromycin + tretinoin v Vehicle	N/A	N/A	3.23 (0.23, 33.33)	Very Low	-18.73 (-38.50, 1.04)	Very Low	N/A	N/A

Table 2. Direct and pooled comparisons and rankings for patient-reported global improvement

Odds Ratio (95% confidence interval)*

	Adapalene+BPO	Clindamycin+BPO	Adapalene	Tretinoin	BPO	Clindamycin+tretinoin	Clindamycin	Vehicle
Adapalene+BPO		.	1.31 [0.88; 1.97]	.	1.58 [1.05; 2.37]	.	.	3.90 [2.67; 5.68]
Clindamycin+BPO	1.22 [0.81; 1.85]		.	.	1.60 [1.14; 2.25]	1.86 [0.92; 3.74]	1.85 [1.22; 2.80]	2.75 [1.90; 3.99]
Adapalene	1.49 [1.01; 2.21]	1.22 [0.78; 1.90]		.	1.20 [0.80; 1.81]	.	.	2.23 [1.42; 3.51]
Tretinoin	1.74 [0.68; 4.47]	1.42 [0.56; 3.59]	1.17 [0.45; 3.04]		.	.	.	2.10 [0.87; 5.04]
BPO	1.89 [1.32; 2.70]	1.54 [1.15; 2.08]	1.27 [0.86; 1.85]	1.09 [0.43; 2.73]		.	1.17 [0.76; 1.80]	1.90 [1.36; 2.64]
Clindamycin+tretinoin	2.13 [1.26; 3.60]	1.74 [1.13; 2.67]	1.43 [0.82; 2.48]	1.22 [0.46; 3.24]	1.13 [0.71; 1.78]		1.13 [0.67; 1.90]	1.76 [1.02; 3.04]
Clindamycin	2.34 [1.50; 3.64]	1.91 [1.36; 2.68]	1.57 [0.98; 2.51]	1.34 [0.53; 3.43]	1.24 [0.87; 1.75]	1.10 [0.72; 1.68]		1.50 [1.04; 2.16]
Vehicle	3.65 [2.58; 5.15]	2.98 [2.22; 4.01]	2.44 [1.66; 3.60]	2.10 [0.87; 5.04]	1.93 [1.45; 2.56]	1.71 [1.12; 2.62]	1.56 [1.13; 2.16]	

*direct comparisons in white, indirect comparisons in grey and treatment rankings in black

Table 3. Direct and pooled comparisons and rankings for withdrawal due to adverse events

Odds Ratio (95% confidence interval)*

	Clindamycin	Clindamycin +zinc	Vehicle	Azelaic acid	Clindamycin+tretinoin	Adapalene	Erythromycin +zinc	Tretinoin	Clindamycin +BPO	BPO	Erythromycin+tretinoin	Adapalene+ BPO
Clindamycin		1.19 [0.28; 5.08]	0.95 [0.37; 2.44]	1.00 [0.06; 17.18]	0.74 [0.26; 2.09]	.	.	0.92 [0.37; 2.27]	0.34 [0.18; 0.63]	0.67 [0.19; 2.35]	.	.
Clindamycin+zinc	0.85 (0.2,3.57)		.	.	.	.	.	.	.	.	.	.
Vehicle	1.52 (0.79,2.86)	1.79 (0.36,9.09)		.	.	0.89 [0.44; 1.81]	.	0.48 [0.12; 1.93]	1.75 [0.61; 5.03]	0.64 [0.38; 1.07]	0.31 [0.03; 3.10]	0.37 [0.18; 0.76]
Azelaic acid	1.3 (0.2,8.33)	1.54 (0.14,16.67)	0.87 (0.13,5.88)		.	0.79 [0.05; 13.50]	.	.	.	0.79 [0.05; 13.50]	.	.
Clindamycin+tretinoin	1.45 (0.58,3.57)	1.72 (0.31,9.09)	0.96 (0.33,2.78)	1.11 (0.14,9.09)		.	.	0.33 [0.03; 3.20]	0.99 [0.14; 7.16]	.	.	.
Adapalene	1.69 (0.82,3.57)	2 (0.4,10)	1.12 (0.64,2)	1.3 (0.19,9.09)	1.18 (0.39,3.57)		.	0.48 [0.15; 1.50]	1.00 [0.14; 7.32]	0.73 [0.33; 1.58]	.	0.39 [0.18; 0.83]

Erythromycin+zinc	2.08 (0.27,16.67)	2.5 (0.2,33.33)	1.41 (0.17,11.11)	1.61 (0.1,25)	1.45 (0.16,14.29)	1.23 (0.15,10)		.	0.97 [0.13; 7.09]	.	.	.
Tretinoin	2 (0.96,4)	2.33 (0.46,12.5)	1.32 (0.6,2.86)	1.52 (0.21,11.11)	1.37 (0.46,4)	1.16 (0.53,2.56)	0.94 (0.11,8.33)		.	.	.	.
Clindamycin+BPO	2.17 (1.25,3.7)	2.56 (0.54,12.5)	1.43 (0.76,2.7)	1.67 (0.24,11.11)	1.49 (0.56,4)	1.28 (0.62,2.63)	1.03 (0.14,7.69)	1.09 (0.48,2.5)		0.71 [0.22; 2.27]	.	0.39 [0.12; 1.27]
BPO	2.38 (1.2,4.76)	2.86 (0.56,14.29)	1.59 (0.98,2.56)	1.82 (0.27,12.5)	1.64 (0.56,5)	1.41 (0.77,2.56)	1.14 (0.14,9.09)	1.2 (0.53,2.78)	1.11 (0.56,2.17)		.	0.55 [0.29; 1.04]
Erythromycin+tretinoin	5 (0.44,50)	5.88 (0.35,100)	3.23 (0.32,33.33)	3.7 (0.19,100)	3.33 (0.27,50)	2.86 (0.27,33.33)	2.33 (0.1,50)	2.44 (0.22,25)	2.27 (0.21,25)	2.04 (0.19,20)		.
Adapalene+BPO	4.35 (2.13,9.09)	5.26 (1.03,25)	2.94 (1.69,5)	3.33 (0.49,25)	3.03 (1,9.09)	2.56 (1.41,4.76)	2.08 (0.26,16.67)	2.22 (0.94,5.26)	2.04 (1.03,4)	1.85 (1.08,3.13)	0.9 (0.08,10)	

*direct comparisons in white, pooled comparisons in grey and treatment rankings in black

Table 4. Number of reported withdrawals for each treatment

	Number of withdrawals	Total number of participants	%
Clindamycin	24	3431	0.7%
Vehicle	19	2779	0.7%

Adapalene	22	2133	1.0%
Tretinoin	15	689	2.2%
Clindamycin + BPO	60	2231	2.7%
BPO	30	1872	1.6%
Adapalene + BPO	34	1358	2.5%

Table 5. Direct and pooled comparisons and rankings for total lesion counts

Mean difference (95% confidence interval)*

	Adapalene+BPO	Erythromycin+tretinoin	Azelaic acid	Clindamycin+BPO	Adapalene	Tretinoin	BPO	Erythromycin+zinc	Clindamycin	Clindamycin+tretinoin	Vehicle
Adapalene+BPO		.	.	.	-8.51 [-13.55; -3.47]	.	-10.37 [-15.58; -5.16]	.	.	.	-23.19 [-28.42; -17.97]
Erythromycin+tretinoin	-2.23 [-22.41; 17.95]		.	.	.	.	.	.	.	.	-18.73 [-38.50; 1.04]
Azelaic acid	-7.35 [-13.74; -0.96]	-5.12 [-25.60; 15.37]		14.10 [4.36; 23.84]	12.58 [-4.62; 29.78]	.	.	.	-11.95 [-17.52; -6.38]	.	.
Clindamycin+BPO	-8.27 [-13.02; -3.52]	-6.04 [-26.07; 13.99]	-0.92 [-5.96; 4.12]		-17.60 [-29.93; -5.27]	.	-1.87 [-6.11; 2.36]	-6.10 [-18.14; 5.94]	-3.52 [-6.25; -0.79]	.	-8.17 [-12.46; -3.88]
Adapalene	-9.99 [-14.05; -5.93]	-7.76 [-27.76; 12.24]	-2.64 [-8.20; 2.91]	-1.72 [-5.36; 1.91]		4.03 [-0.51; 8.56]	-2.95 [-6.10; 0.21]	.	.	.	-11.68 [-16.05; -7.31]
Tretinoin	-10.41 [-15.21; -5.61]	-8.17 [-28.22; 11.87]	-3.06 [-8.64; 2.52]	-2.14 [-5.90; 1.63]	-0.41 [-3.89; 3.06]		.	.	-0.08 [-4.29; 4.13]	1.96 [-3.07; 6.99]	-12.45 [-16.78; -8.13]
BPO	-11.35 [-15.40; -7.30]	-9.12 [-29.09; 10.85]	-4.00 [-9.46; 1.45]	-3.08 [-6.41; 0.24]	-1.36 [-4.06; 1.34]	-0.95 [-4.58; 2.68]		.	-1.68 [-5.92; 2.56]	.	-9.95 [-13.33; -6.57]
Erythromycin+zinc	-14.37 [-27.32; -1.42]	-12.14 [-35.51; 11.24]	-7.02 [-20.08; 6.04]	-6.10 [-18.14; 5.94]	-4.38 [-16.96; 8.20]	-3.96 [-16.58; 8.66]	-3.02 [-15.51; 9.48]		.	.	.
Clindamycin	-12.78 [-17.36; -8.20]	-10.55 [-30.53; 9.43]	-5.43 [-10.14; -0.73]	-4.51 [-7.08; -1.95]	-2.79 [-6.19; 0.60]	-2.38 [-5.59; 0.84]	-1.43 [-4.56; 1.70]	1.59 [-10.73; 13.90]		-3.05 [-7.12; 1.02]	-5.05 [-8.68; -1.41]
Clindamycin+tre	-13.52 [-19.20;	-11.29 [-31.56;	-6.17 [-12.17;	-5.26 [-9.71; -	-3.53 [-8.24;	-3.12 [-7.23;	-2.17 [-6.81;	0.84 [-12.00;	-0.74 [-4.52;		.

tinoin	-7.85]	8.98]	-0.18]	0.80]	1.18]	0.99]	2.47]	13.69]	3.04]		
Vehicle	-20.96 [-25.02; -16.90]	-18.73 [-38.50; 1.04]	-13.61 [-18.99; -8.24]	-12.69 [-15.92; -9.47]	-10.97 [-13.99; -7.95]	-10.56 [-13.87; -7.24]	-9.61 [-12.44; -6.78]	-6.59 [-19.06; 5.88]	-8.18 [-11.11; -5.25]	-7.44 [-11.90; -2.97]	

*direct comparisons in white, indirect comparisons in grey and treatment rankings in black

Table 6. Direct and pooled comparisons and rankings for IGA

Odds ratio (95% Confidence interval)*

	Adapalene+BPO	Clindamycin+BPO	BPO	Clindamycin	Adapalene	Clindamycin+tretinoin	Vehicle	Tretinoin
Adapalene+BPO		.	1.71 [0.99; 2.96]	.	1.98 [1.14; 3.44]	.	3.53 [2.13; 5.85]	.
Clindamycin+BPO	1.23 [0.62; 2.42]		1.51 [0.60; 3.79]	1.93 [1.01; 3.68]	.	2.38 [0.81; 6.95]	2.18 [1.12; 4.26]	.
BPO	1.68 [1.03; 2.75]	1.37 [0.76; 2.49]		1.43 [0.56; 3.59]	1.16 [0.67; 2.03]	.	2.26 [1.42; 3.59]	1.91 [0.75; 4.84]
Clindamycin	1.91 [0.99; 3.70]	1.56 [0.93; 2.63]	1.14 [0.65; 2.00]		.	1.32 [0.69; 2.52]	1.64 [0.85; 3.16]	3.41 [1.76; 6.60]
Adapalene	2.01 [1.20; 3.36]	1.64 [0.82; 3.26]	1.19 [0.72; 1.97]	1.05 [0.54; 2.04]		.	1.74 [1.04; 2.91]	.
Clindamycin+tretinoin	2.05 [0.92; 4.55]	1.67 [0.87; 3.21]	1.22 [0.59; 2.50]	1.07 [0.61; 1.87]	1.02 [0.46; 2.28]		.	4.39 [1.69; 11.38]
Vehicle	3.83 [2.40; 6.10]	3.12 [1.82; 5.37]	2.28 [1.51; 3.44]	2.00 [1.19; 3.37]	1.91 [1.19; 3.06]	1.87 [0.94; 3.72]		0.58 [0.23; 1.46]
Tretinoin	4.61 [2.27; 9.35]	3.76 [1.93; 7.33]	2.74 [1.50; 5.00]	2.41 [1.38; 4.21]	2.29 [1.12; 4.68]	2.25 [1.14; 4.43]	1.20 [0.66; 2.18]	

*direct comparisons in white, pooled comparisons in grey and treatment rankings in black

Figure 1. PRISMA flow diagram

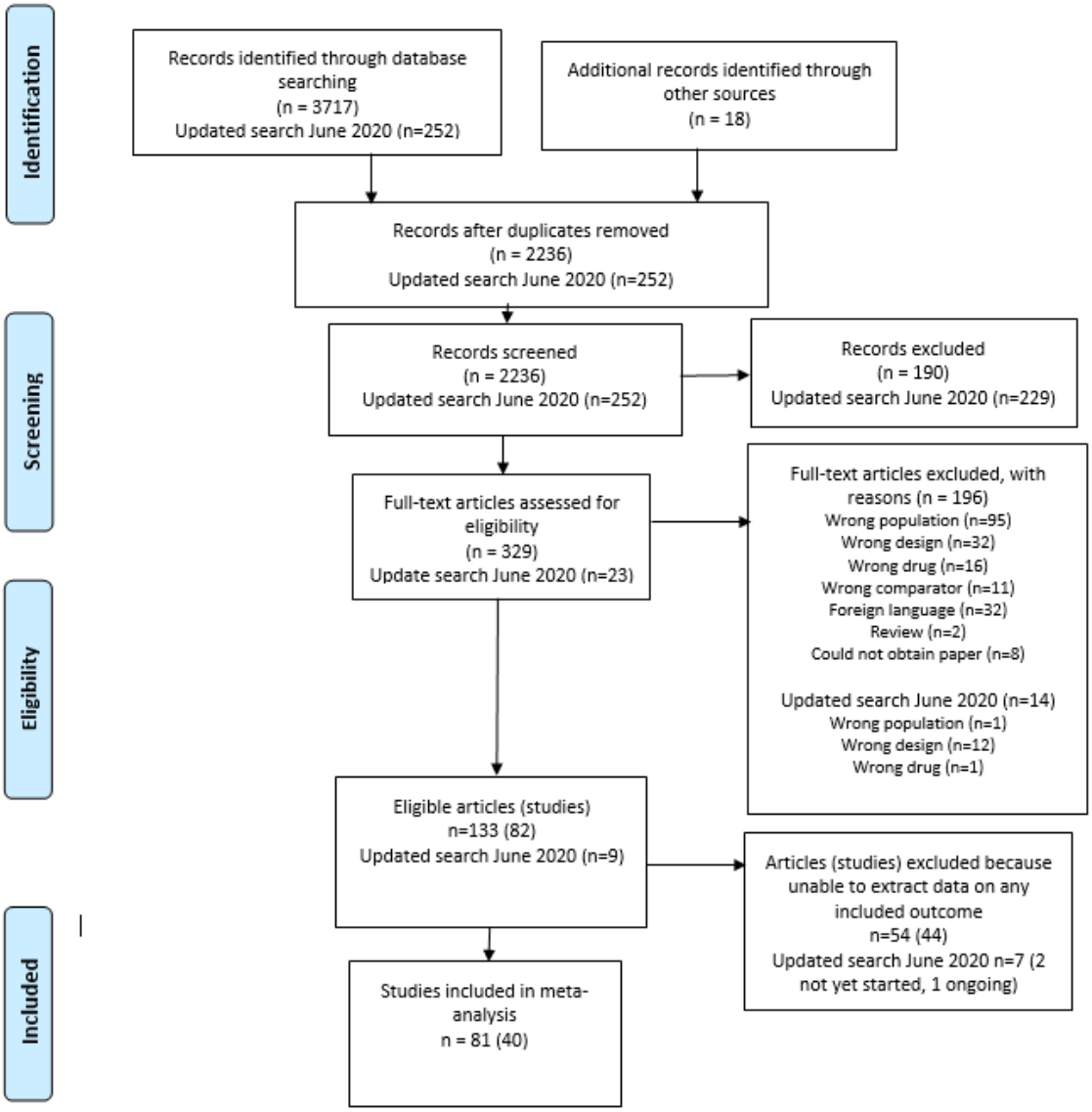
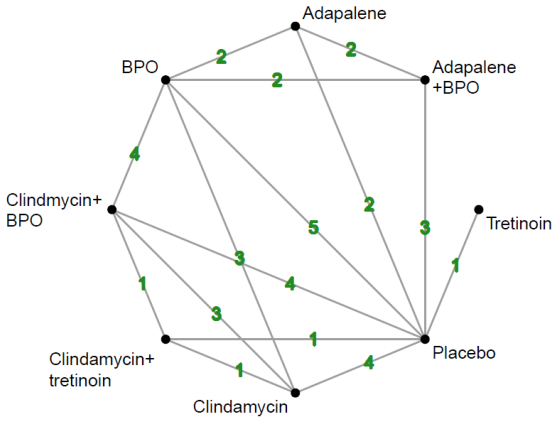
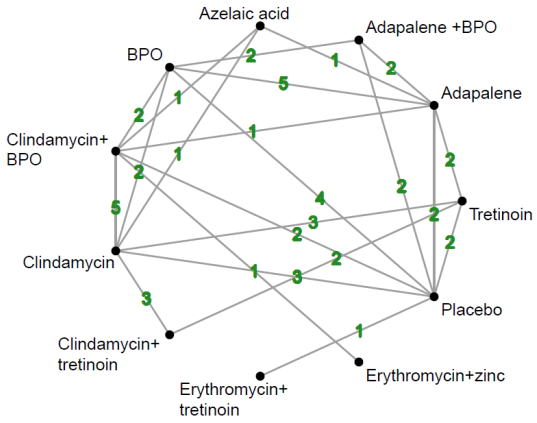


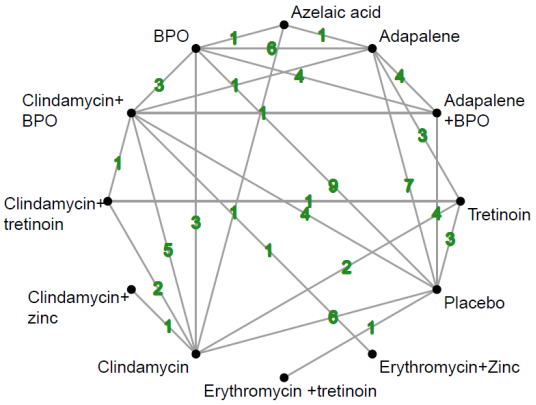
Figure 2. Network plots of direct evidence



Patient global assessment of improvement



Lesion count



Withdrawal due to adverse events

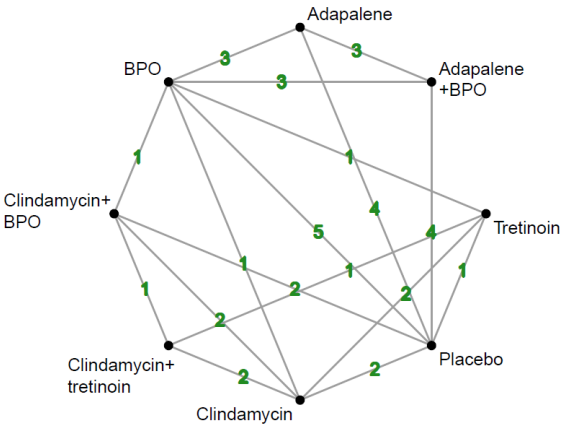


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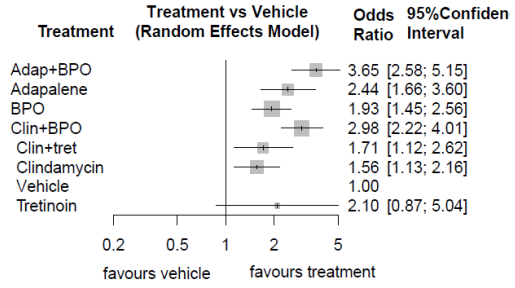
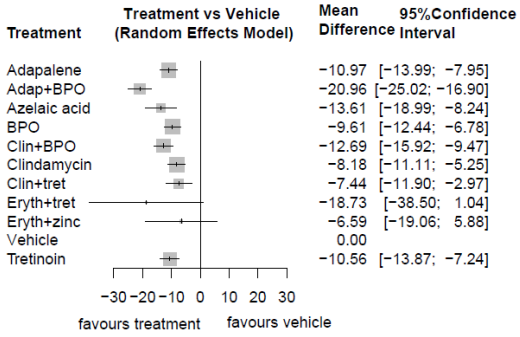
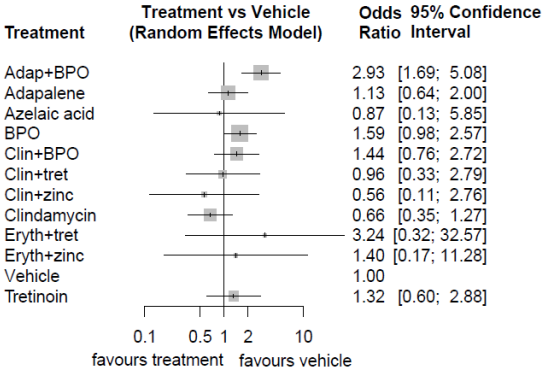
Figure 3. All treatments compared to vehicle (pooled network estimates)



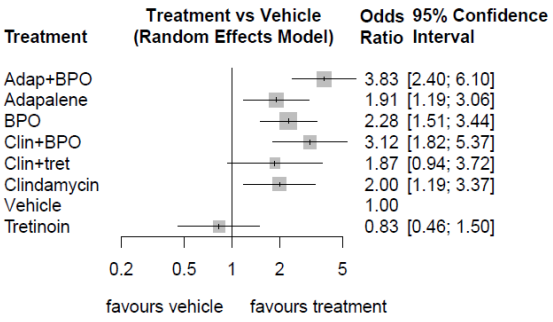
Patient global assessment of improvement



Lesion count



Withdrawal due to adverse events



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