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A systematic review and network meta-analysis of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris*

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Summary

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Background Various treatments for acne vulgaris exist, but little is known about their comparative effectiveness in relation to acne severity.
Objectives To identify best treatments for mild-to-moderate and moderate-to-severe acne, as determined by clinician-assessed morphological features.
Methods We undertook a systematic review and network meta-analysis of randomized controlled trials (RCTs) assessing topical pharmacological, oral pharmacological, physical and combined treatments for mild-to-moderate and moderate-to-severe acne, published up to May 2020. Outcomes included percentage change in total lesion count from baseline, treatment discontinuation for any reason, and discontinuation owing to side-effects. Risk of bias was assessed using the Cochrane risk-of-bias tool and bias adjustment models. Effects for treatments with ≥ 50 observations each compared with placebo are reported below.
Results We included 179 RCTs with approximately 35 000 observations across 49 treatment classes. For mild-to-moderate acne, the most effective options for each treatment type were as follows: topical pharmacological – combined retinoid with benzoyl peroxide (BPO) [mean difference 26·16%, 95% credible interval (CrI) 16·75–35·36%]; physical – chemical peels, e.g. salicylic or mandelic acid (39·70%, 95% CrI 12·54–66·78%) and photochemical therapy (combined blue/red light) (35·36%, 95% CrI 17·75–53·08%). Oral pharmacological treatments (e.g. antibiotics, hormonal contraceptives) did not appear to be effective after bias adjustment. BPO and topical retinoids were less well tolerated than placebo. For moderate-to-severe acne, the most effective options for each treatment type were as follows: topical pharmacological – combined retinoid with lincosamide (clindamycin) (44·43%, 95% CrI 29·20–60·02%); oral pharmacological – isotretinoin of total cumulative dose ≥ 120 mg kg^{-1} per single course (58·09%, 95% CrI 36·99–79·29%); physical – photodynamic therapy (light therapy enhanced by a

photosensitizing chemical) (40·45%, 95% CrI 26·17–54·11%); combined – BPO with topical retinoid and oral tetracycline (43·53%, 95% CrI 29·49–57·70%). Topical retinoids and oral tetracyclines were less well tolerated than placebo. The quality of included RCTs was moderate to very low, with evidence of inconsistency between direct and indirect evidence. Uncertainty in findings was high, in particular for chemical peels, photochemical therapy and photodynamic therapy. However, conclusions were robust to potential bias in the evidence.

Conclusions Topical pharmacological treatment combinations, chemical peels and photochemical therapy were most effective for mild-to-moderate acne. Topical pharmacological treatment combinations, oral antibiotics combined with topical pharmacological treatments, oral isotretinoin and photodynamic therapy were most effective for moderate-to-severe acne. Further research is warranted for chemical peels, photochemical therapy and photodynamic therapy for which evidence was more limited.

What is already known about this topic?

- Acne vulgaris is the eighth most common disease globally.
- Several topical, oral, physical and combined treatments for acne vulgaris exist.
- Network meta-analysis (NMA) synthesizes direct and indirect evidence and allows simultaneous inference for all treatments forming an evidence network.
- Previous NMAs have assessed a limited range of treatments for acne vulgaris and have not evaluated effectiveness of treatments for moderate-to-severe acne.

What does this study add?

- For mild-to-moderate acne, topical treatment combinations, chemical peels, and photochemical therapy (combined blue/red light; blue light) are most effective.
- For moderate-to-severe acne, topical treatment combinations, oral antibiotics combined with topical treatments, oral isotretinoin and photodynamic therapy (light therapy enhanced by a photosensitizing chemical) are most effective.
- Based on these findings, along with further clinical and cost-effectiveness considerations, National Institute for Health and Care Excellence (NICE) guidance recommends, as first-line treatments, fixed topical treatment combinations for mild-to-moderate acne and fixed topical treatment combinations, or oral tetracyclines combined with topical treatments, for moderate-to-severe acne.

Acne vulgaris is the eighth most common disease globally, affecting over 0·5 billion people.[1,2] Acne can have a detrimental physical, psychological and social impact.[3,4] Acne severity may be determined by clinical presentation (number and type of lesions), secondary sequelae (scarring, pigmentation), and its psychological and social impact on the patient.[5] Uncertainty around acne treatment effectiveness may be a barrier to treatment.[6] Various topical, oral and physical acne treatments are available, but little is known about their comparative effectiveness, especially in relation to acne severity.

Network meta-analysis (NMA) allows simultaneous estimation of relative effects for any number of treatments, even if some have not been directly compared in randomized controlled trials (RCTs), provided that treatments create a 'network of evidence' where every treatment is linked to at least another treatment through direct comparisons.[7–10]

Two NMAs assessing the effectiveness of treatments for acne vulgaris have been published to date, both focusing on mild-to-moderate acne.[11,12] Therefore, our study examined the relative effectiveness, acceptability and tolerability of topical pharmacological, oral pharmacological, physical and combined treatments separately for mild-to-moderate and moderate-to-severe acne, as determined by clinician-assessed morphological features, to identify suitable first-line treatments.

Materials and methods

The analyses presented here informed national guidance for the management of acne vulgaris in England, published by the National Institute for Health and Care Excellence (NICE), who worked with the British Association of Dermatologists for this purpose.[13] The guideline was developed by a committee of

academics, health professionals and service users with expertise and experience in acne vulgaris.

Search strategy

Searches for RCTs of treatments for acne vulgaris were conducted in Embase, MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) from inception, using relevant medical subject headings, free-text terms and study-type filters where appropriate. The search was undertaken in August 2019 and reruns were performed in May 2020 (Appendix S1; see Supporting Information).

Selection criteria for the systematic review and the network meta-analysis

A systematic review of RCTs of topical pharmacological, oral pharmacological, physical and combined treatments for mild-to-moderate and moderate-to-severe acne vulgaris was undertaken according to PRISMA guidelines.[14,15] The study protocol was registered on PROSPERO (CRD42020154100) and is provided in full in Appendix S2 (see Supporting Information).

The review included people with acne vulgaris of all ages (except neonatal acne) and severity levels. Populations with postinflammatory dyspigmentation, polycystic ovary syndrome (PCOS), refractory acne or receiving maintenance treatment were excluded. Separate analyses were conducted for mild-to-moderate and moderate-to-severe acne. Reported severity levels in each study were used for study categorization into mild-to-moderate or moderate-to-severe acne. Based on the committee's expert advice, if severity was unclear or reported as 'moderate', the study was categorized as mild-to-moderate acne if each participant had only noninflammatory lesions, or < 35 inflammatory lesions, or if the average number of inflammatory lesions per study participant was ≤ 30, whereas the study was categorized as moderate-to-severe acne if each participant had ≥ 3 nodules (regardless of the number of other inflammatory lesions), or ≥ 35 inflammatory lesions, or if the average number of inflammatory lesions per study participant was ≥ 40. If this information could not be obtained or the mean number of inflammatory lesions per study participant was 31–39, the study was excluded from the review.

Topical pharmacological treatments included retinoids, antibiotics, benzoyl peroxide (BPO), azelaic acid and other interventions. Oral pharmacological treatments included antibiotics, isotretinoin, hormonal contraceptives and hormone-modifying agents (e.g. metformin, spironolactone). Physical treatments included chemical peels (e.g. salicylic acid, mandelic acid, Jessner's peel), and light therapies including photochemical therapies (blue, red or combined blue/red light), photodynamic therapy (i.e. therapy comprising a light source, e.g. red light, blue light, daylight, and a photosensitizing chemical, e.g. 5-aminolaevulinic acid, methyl aminolaevulinate) and other phototherapies. Combined treatments within and across treatment types were also included. Treatments were grouped into treatment classes, with each class comprising treatments with the same or very similar mechanism(s) of action. Only drug classes and interventions available in the UK were considered. All control groups (i.e. topical vehicles, oral placebos, physical 'sham' placebos) were included under a broader 'placebo' control class (Appendix S3; see Supporting Information).

Hormonal contraceptives are only suitable for females. Therefore, depending on data availability, separate analyses were conducted for males and females for some outcomes. Analyses included both parallel and split-body/face RCTs; because of inclusion of the latter, for each treatment we report number of observations rather than number of participants.

Three outcomes at treatment endpoint were analysed using NMA techniques, as they were deemed to be clinically important and were applicable to all treatments:

- efficacy, expressed as percentage change in total acne lesion count from baseline (%CFB)
- treatment discontinuation for any reason (reflecting acceptability)
- treatment discontinuation owing to side-effects (reflecting tolerability).

A fourth outcome, prevention of scarring at any follow-up, was selected for NMA, but insufficient data were identified.

Titles and abstracts of identified studies were screened by two reviewers for inclusion against protocol criteria, until a good interrater reliability was observed (agreement $\geq$ 90%). Initially 10% of references were double-screened; as interrater agreement was $>$ 90%, the remaining references were screened by one reviewer. Full texts of studies included after the first sift were acquired and checked for eligibility. The following data were extracted from included studies: country, study population, intervention details, outcome data, and potential risk of bias assessed using the Cochrane risk-of-bias tool version 2.0.[16] All data extraction was double-checked by a second reviewer. Disagreements were resolved via discussion between the two reviewers, and consultation with a senior reviewer if necessary.

Statistical analysis

NMAs were conducted within a Bayesian framework using Markov Chain Monte Carlo simulation techniques implemented in OpenBUGS 3.2.3 (efficacy) and WinBUGS 1.4.3 (discontinuation).[17–19] Details of statistical analysis and codes for evidence synthesis are reported in Appendix S3.

For efficacy, we pooled the difference in %CFB between treatments using an NMA model with normal likelihood and identity link function accounting for different reporting formats between studies.[20] For discontinuation, we pooled log-odds ratios (LORs) between pairs of treatments using an NMA model with binomial likelihood and logit link function.[9,20] Class models were used to enhance precision of the estimated effects between treatment classes and to connect networks disconnected at the treatment level.[20] Fixed and random class

models were fitted. The former assumed that treatments within each class had identical effects, whereas the latter assumed that treatments within each class had similar effects spread around the mean class effect. Within each class model, fixed and random study-specific treatment effects models were fitted. Results are reported for the most suitable models selected based on model fit.

For each analysis we estimated mean relative effects (difference in %CFB; LOR) between treatment classes, with 95% credible intervals (CrIs). We also estimated mean ranks with 95% CrI for every treatment class, where a rank of 1 indicates best treatment. In every analysis, we considered only results for treatment classes with $\geq$ 50 observations each (i.e. the minimum size of evidence that was deemed adequate to support recommendations). We interpreted results in terms of 'evidence of effect', determined based on whether the 95% CrI crossed the line of no effect.

Transitivity and inconsistency checks

A basic NMA assumption is that the distribution of effect modifiers is the same across treatment comparisons ('transitivity' assumption). To control for potential effect modifiers, we aimed to reduce heterogeneity in populations and treatments across RCTs included in the NMAs. For this reason, we stratified analyses by acne severity, using clear criteria and excluding RCTs with populations of all severity levels or with unclear acne severity. Treatments such as hormonal contraceptives are relevant only to females, and thus analyses were conducted separately for males and females where appropriate. Treatments were assigned to treatment classes using detailed definitions, considering differentiation in dosing (e.g. oral isotretinoin, chemical peels vs. topical acids) and excluding treatments administered using suboptimal dosing. As age is a potential effect modifier, we reviewed the study samples' age ranges in the included RCTs. Other effect modifiers might be present in the dataset, but these were either unknown or could not be explored as they were not consistently reported (e.g. socioeconomic factors).

Violations of the transitivity assumption may lead to inconsistency, i.e. conflict between the direct and indirect evidence estimates of the same treatment comparisons.[8] This was assessed statistically by undertaking global inconsistency[21] and node-split tests.[21] Details on inconsistency checking methods are provided in Appendix S4 (see Supporting Information).

Bias adjustment models

Bias adjustment models were fitted for all outcomes to downweight trials at high or unclear risk of bias (assessed using the Cochrane risk-of-bias tool)[16] on domains where sufficient variability in ratings was observed across studies. Additional bias adjustment models tested for bias associated with small sample size studies.[22–25] Analyses assumed possible bias in comparisons of active interventions vs. inactive control. In analyses where there was indication of the presence of such biases, results from bias-adjusted models were considered. Details on bias adjustment methods and respective codes are shown in Appendix S5 (see Supporting Information).

Threshold analysis

Threshold analysis was undertaken on the efficacy outcome to assess the robustness of NMA-based recommendations to potential biases or sampling variation in the included evidence.[26–28] Results of threshold analysis describe how much each data point would have to change (e.g. if adjusted for bias) before the conclusion changes and what the revised conclusion would be. Appendix S6 (see Supporting Information) reports threshold analysis methods.

Results

Studies and treatments

The systematic literature search identified 5586 potentially eligible publications, of which 173 publications reporting on 179 RCTs (112 for mild-to-moderate and 67 for moderate-to-severe acne) met eligibility criteria for the NMA (Figure 1). Appendix S7 (see Supporting Information) reports included study characteristics. Appendix S8 (see Supporting Information) provides the excluded studies list, with reasons for exclusion.

Appendix S9 (see Supporting Information) shows data utilized in each NMA. The NMAs of efficacy included 90 RCTs, 41 treatment classes and 17 260 observations for mild-to-moderate acne and 56 RCTs, 27 treatment classes and 16 493 observations for moderate-to-severe acne. Respective networks are shown in Figure 2. Figures S1 and S2 (see Supporting Information) show the networks of discontinuation for any reason and discontinuation owing to side-effects, respectively, for each acne severity level. Appendix S10 (see Supporting Information) provides, for each network, details on the number of RCTs, treatment classes, interventions and observations.

Assessment of model fit, inconsistency and bias

Model fit statistics suggested that there was insufficient information to differentiate effects across treatments within each class, therefore fixed class effects models were used across analyses (i.e. all treatments within each class were assumed to have equal effects). The selected study-specific treatment effects models (fixed or random) for each analysis are reported in Appendix S11 (see Supporting Information). Although there were no meaningful differences between the selected consistency and inconsistency models (Appendix S11), some evidence of local-level inconsistency was identified across all analyses (Appendix S12; see Supporting Information).

Of the 112 RCTs for mild-to-moderate acne, 52 were at high overall risk of bias, and for 60 RCTs there were some

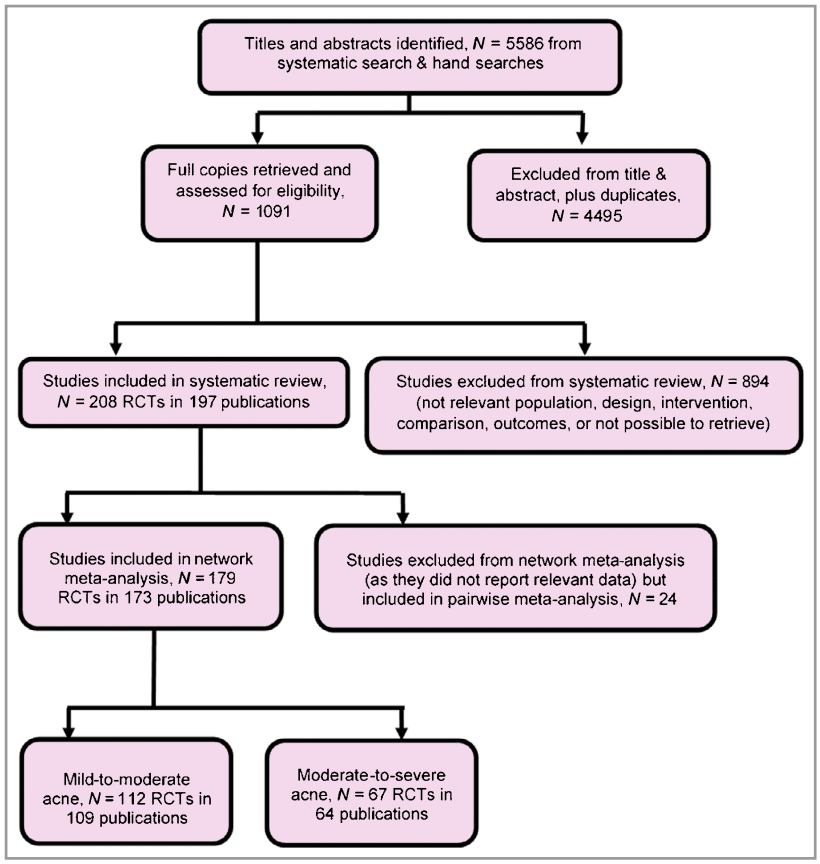

Fig 1 Flow diagram of study selection for the systematic review and the network meta-analysis.RCT, randomized controlled trial.

concerns about bias. Of the 67 RCTs for moderate-to-severe acne, 36 RCTs were at high overall risk of bias, and for 31 RCTs there were some concerns about bias (Appendix S13; see Supporting Information). Overall, the quality of included RCTs was judged to be moderate to very low.

Evidence of bias was identified in the following analyses (Appendix S14; see Supporting Information):

- Mild-to-moderate acne, efficacy (%CFB): evidence of small-study bias
- Moderate-to-severe acne, discontinuation owing to side-effects: evidence of bias in Domain 4 of the Cochrane risk-of-bias tool [outcome measurement (efficacy)].[16]

Thus, for these two analyses we considered results from bias-adjusted models.

Treatment outcomes

Efficacy of each treatment class relative to placebo is shown in Table 1 for mild-to-moderate acne and Table 2 for moderate-to-severe acne. In each analysis, treatment classes have been ordered from best to worst using their mean ranking for females. For mild-to-moderate acne, bias-adjusted results are presented, as there was indication of bias owing to small study size in this evidence; base-case results (before bias adjustment) are shown in Appendix S15 (see Supporting Information). Large uncertainty in the results for most treatments was indicated by wide 95% CrIs around mean effects and rankings.

No evidence of effect on treatment discontinuation for any reason was found for any treatment class compared with placebo at either acne severity level. In mild-to-moderate acne, topical retinoids, BPO and their combination showed higher discontinuation owing to side-effects compared with placebo; in moderate-to-severe acne (bias-adjusted analysis), topical retinoids alone or combined with an oral tetracycline, oral cocyprindiol alone or combined with an oral tetracycline, and oral tetracycline alone showed higher discontinuation owing to side-effects compared with placebo (Appendix S15).

Relative effects between all pairs of treatment classes (including results from indirect and available head-to-head comparisons) are reported in Appendix S16 (see Supporting Information).

Threshold analysis

After excluding antibiotic monotherapies, physical treatments and oral isotretinoin, which the committee considered unsuitable first-line treatments owing to associated potential harms or lack of routine availability and use, threshold analysis

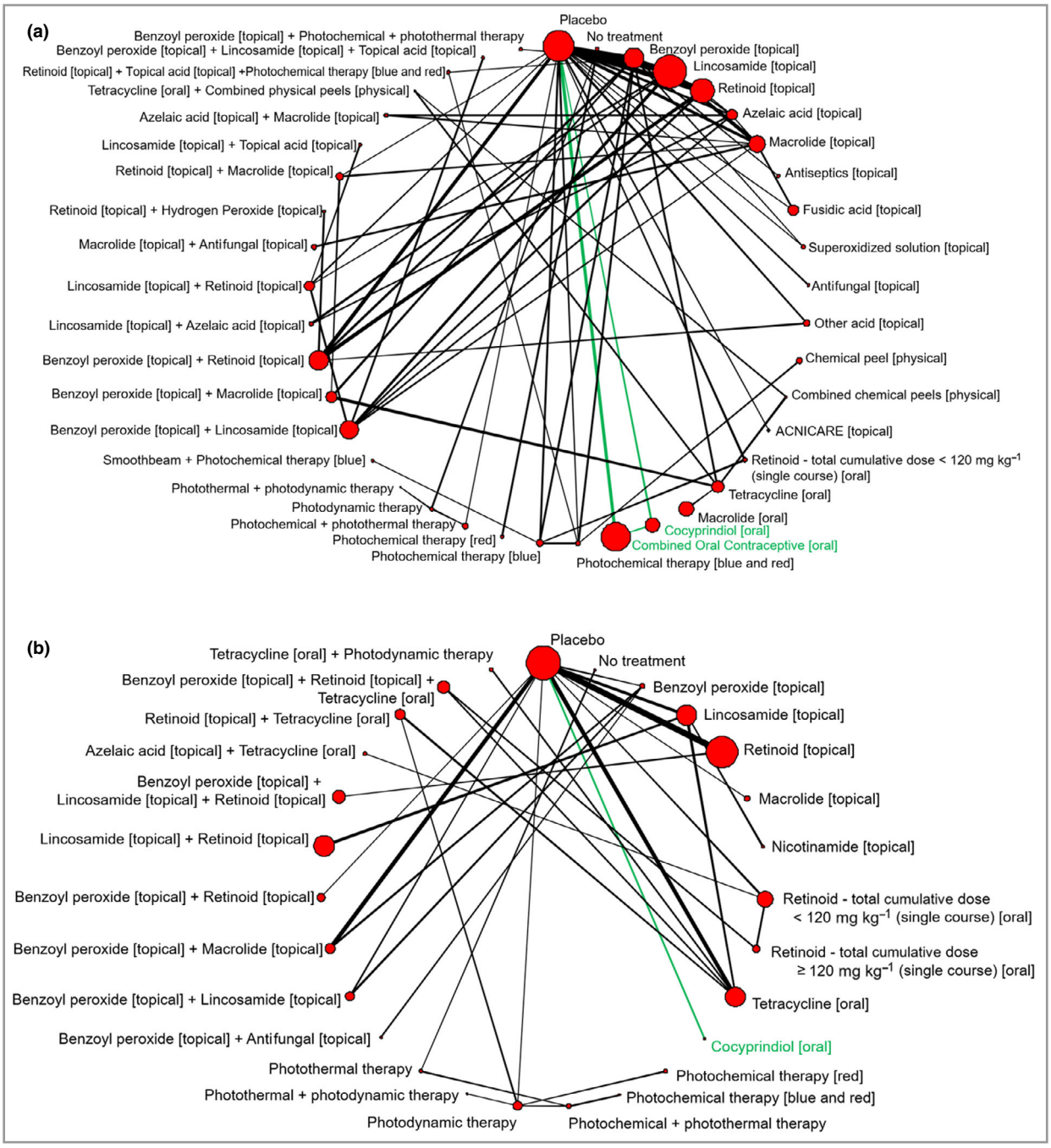

Fig 2 Network of treatment classes for people with (a) mild-to-moderate acne and (b) moderate-to-severe acne on the efficacy outcome (percentage change in total lesion count from baseline). The width of lines is proportional to the number of trials in which each direct comparison is made. The size of each circle (treatment node) is proportional to the number of observations made on each treatment class (which is the sum of the number of participants in parallel trials and number of observations in split-face/body trials). Treatment classes and lines in green indicate treatments and comparisons relevant only to females.

suggested that conclusions for mild-to-moderate acne were fairly robust to changes in the evidence. In moderate-to-severe acne, a moderate change in the evidence would lead to BPO entering the top four efficacious treatments that were eligible for a recommendation (Appendix S17; see Supporting Information).

Discussion

This study compared a wide range of treatments for acne vulgaris. For mild-to-moderate acne, topical and physical treatments (chemical peels and photochemical therapy) were shown to be effective compared with placebo. Among topical

Table 1 Network meta-analysis: treatment efficacy (percentage change in total acne lesion count from baseline) in mild-to-moderate acne: bias-adjusted treatment class effects vs. placebo and rankings

Class	N	Effect vs. placebo (mean, 95% CrI)	Rank, females (mean, 95% CrI)	Rank, males (mean, 95% CrI)
ACNICARE (topical)	20	81·57 (32·49–135·70)	2·73 (1–10)	2·72 (1–10)
Photothermal + photodynamic therapy	9	67·87 (16·51–118·00)	4·30 (1–22)	4·27 (1–22)
Photochemical therapy (red)	28	84·57 (3·34–163·80)	4·34 (1–35)	4·26 (1–33)
Smoothbeam + photochemical therapy (blue)	24	54·34 (19·99–88·78)	5·51 (1–20)	5·49 (1–20)
Chemical peels (physical)	**101**	**39·70 (12·54–66·78)**	9·23 (2–28)	9·18 (2–27)
Photochemical therapy (combined blue/red light)	**69**	**35·36 (17·75–53·08)**	10·05 (4–21)	10·03 (4–21)
Benzoyl peroxide (topical) + lincosamide (Clindamycin) (topical) + other acid (topical)	24	32·37 (11·97–52·76)	12·13 (4–28)	12·06 (4–28)
Retinoid (topical) + Hydrogen Peroxide (topical)	26	32·16 (11·94–52·16)	12·27 (4 to 29)	12·20 (4–28)
Azelaic acid (topical) + lincosamide (Clindamycin) (topical)	44	30·24 (10·97–49·54)	13·38 (4–29)	13·29 (4–29)
Superoxidized solution (topical)	39	31·07 (3·94–58·38)	13·93 (3–35)	13·76 (3–34)
Photodynamic therapy (physical)	36	33·95 (−9·34–75·64)	14·03 (3–39)	13·74 (3–37)
Photochemical therapy (blue) (physical)	**138**	**28·58 (12·55–44·72)**	14·14 (6–27)	14·06 (6–26)
Benzoyl peroxide (topical) + photochemical + photothermal therapy (physical)	29	29·37 (6·81–52·22)	14·38 (4–33)	14·24 (4–32)
Benzoyl peroxide (topical) + retinoid (topical)	**1057**	**26·16 (16·75–35·36)**	15·44 (8–24)	15·39 (8–24)
Azelaic acid (topical) + macrolide (topical)	40	25·92 (7·96–43·87)	16·31 (6–32)	16·16 (6–31)
Lincosamide (clindamycin) (topical) + retinoid (topical)	**276**	**24·23 (10·84–37·51)**	17·22 (8–29)	17·08 (8–28)
No treatment	39	29·88 (−36·27–93·56)	17·83 (2–41)	17·28 (2–39)
Macrolide (topical) + antifungal (topical)	**74**	**22·77 (0·74–44·65)**	19·18 (5–37)	18·85 (5–35)
Benzoyl peroxide (topical) + Macrolide (topical)	**351**	**20·14 (1·44–38·73)**	21·00 (8–35)	20·62 (8–34)
Retinoid (topical) + other acid (topical) + photochemical therapy (combined blue/red light) (physical)	35	20·26 (−5·28–45·98)	21·49 (6–39)	21·00 (6–38)
Lincosamide (clindamycin) (topical) + other acid (topical)	23	18·67 (−4·10–41·07)	22·61 (7–39)	22·09 (7–37)
Retinoid (topical)	**1623**	**18·27 (10·28–26·14)**	22·71 (15–31)	22·43 (15–30)
Photochemical + photothermal therapy [physical]	**107**	**18·42 (−21·39–56·29)**	23·02 (5–41)	22·34 (5–39)
Benzoyl peroxide (topical) + lincosamide (clindamycin) (topical)	**992**	**17·91 (8·01–27·73)**	23·14 (15–32)	22·80 (15–31)
Tetracycline (oral) + combined chemical peels (physical)	13	16·44 (−10·96–43·82)	24·17 (6–40)	23·49 (6–38)
Combined chemical peels (physical)	14	16·06 (−11·37–43·40)	24·49 (6–40)	23·78 (6–38)
Retinoid (topical) + macrolide (topical)	**135**	**16·19 (−3·65–35·89)**	24·67 (9–39)	24·05 (9–37)
Benzoyl peroxide (topical)	**1109**	**15·60 (6·02–25·11)**	25·53 (18–33)	25·04 (18–32)
Antiseptics (topical)	30	13·41 (−9·20–36·05)	26·94 (9–40)	26·12 (9–38)
Other acid (topical)	**106**	**12·28 (−3·38–28·30)**	28·27 (14–39)	27·42 (13–37)
Retinoid - total cumulative dose < 120 mg kg^{-1} (single course) (oral)	**54**	**11·40 (−12·13–34·87)**	28·50 (10–41)	27·56 (10–39)
Macrolide (topical)	**765**	**11·71 (1·50–21·87)**	29·19 (20–36)	28·34 (20–35)
Cocyprindiol (oral)	**584**	**10·49 (−5·10–26·01)**	29·65 (14–40)	Not relevant
Combined oral contraceptive (oral)	**2313**	**10·18 (−0·47–20·85)**	30·36 (19–38)	Not relevant
Tetracycline (oral)	**388**	**9·41 (−10·54–29·32)**	30·54 (15–40)	29·48 (15–38)
Azelaic acid (topical)	**301**	**9·54 (−1·83–20·59)**	31·15 (22–38)	30·08 (21–37)
Macrolide (oral)	**143**	**3·54 (−24·34–31·38)**	33·35 (13–41)	32·00 (13–39)
Lincosamide (clindamycin) (topical)	**3073**	**6·28 (−1·67–14·18)**	34·02 (27–39)	32·59 (26–37)
Antifungal (topical)	20	−7·12 (−51·55–37·13)	35·37 (8–41)	33·81 (8–39)
Fusidic acid (topical)	**310**	**0·34 (−15·84–16·89)**	36·65 (25–41)	34·97 (25–39)
Placebo	**2698**	**Reference**	37·80 (33–41)	35·93 (31–39)

CrI, credible interval; N, number of observations across trials included in the analysis. Classes ordered by mean rank for females (rank = 1 indicates highest efficacy). Treatment classes and values in bold indicate treatment classes with N ≥ 50 each across randomized controlled trials included in the analysis. Treatment classes and values in italics indicate treatment classes with 95% CrI crossing the 'no effect' line.

treatments, combinations of BPO with clindamycin, BPO with a retinoid, BPO with a macrolide, clindamycin with a retinoid, and a macrolide with an antifungal appeared to be the most effective. Overall, single topical agents (e.g. retinoids, BPO, macrolides) ranked lower than topical treatment combinations. Topical retinoids and BPO were less well tolerated than placebo.

For moderate-to-severe acne, the most effective treatments in ranking included oral isotretinoin, oral tetracyclines combined with topical treatments (azelaic acid, retinoid, or

Table 2 Network meta-analysis: treatment efficacy (percentage change in total acne lesion count from baseline) in moderate-to-severe acne: treatment class effects vs. placebo and rankings

Class	N	Effect vs. placebo (mean, 95% CrI)	Rank, females (mean, 95% CrI)	Rank, males (mean, 95% CrI)
Retinoid - total cumulative dose ≥ 120 mg kg^{-1} (single course) (oral)	**182**	**58·09 (36·99–79·29)**	3·39 (1–11)	3·35 (1–10)
Photothermal therapy (physical)	46	57·60 (23·38–91·34)	4·29 (1–17)	4·21 (1–16)
Nicotinamide (topical)	29	49·75 (22·74–76·82)	6·43 (1–19)	6·31 (1 to 19)
Retinoid - total cumulative dose < 120 mg kg^{-1} (single course) (oral)	**938**	**47·72 (19·76–75·65)**	7·10 (1–20)	6·96 (1 to 20)
Photothermal + photodynamic therapy [physical]	14	47·82 (17·10–77·78)	7·33 (1–22)	7·18 (1–21)
Lincosamide (clindamycin) (topical) + retinoid (topical)	**1548**	**44·43 (29·20–60·02)**	7·66 (2–15)	7·53 (2–15)
Tetracycline (oral) + photodynamic therapy (physical)	48	44·84 (26·19–63·58)	7·75 (2–17)	7·61 (2–17)
Benzoyl peroxide (topical) + retinoid (topical) + tetracycline (oral)	**556**	**43·53 (29·49–57·70)**	8·15 (3–16)	8·01 (3–15)
Photodynamic therapy (physical)	**298**	**40·45 (26·17–54·11)**	9·47 (4–16)	9·29 (4–16)
No treatment	25	39·44 (2·64–75·70)	11·02 (2–25)	10·74 (2–24)
Azelaic acid (topical) + tetracycline (oral)	**50**	**38·55 (7·31–69·87)**	11·48 (2–25)	11·20 (2–24)
Retinoid (topical) + tetracycline (oral)	**379**	**35·22 (23·55–46·75)**	12·50 (7–19)	12·22 (6–18)
Benzoyl peroxide (topical) + retinoid (topical)	**217**	**33·97 (12·04–55·53)**	13·14 (3–24)	12·81 (3–23)
Lincosamide (clindamycin) (topical)	**1479**	**34·08 (21·26–47·02)**	13·22 (6–21)	12·92 (6–20)
Photochemical therapy (red) (physical)	**53**	**29·72 (6·81–52·10)**	15·46 (5–25)	15·06 (5–24)
Benzoyl peroxide (topical)	**80**	**28·75 (12·08–45·65)**	15·62 (6–23)	15·20 (6–22)
Photochemical + photothermal therapy (physical)	**71**	**28·21 (−2·54–58·82)**	16·09 (4–26)	15·65 (4–25)
Cocyprindiol (oral)	12	25·25 (−5·24–55·96)	17·12 (3–27)	Not relevant
Tetracycline (oral)	**1386**	**24·23 (16·24–32·28)**	18·63 (14–23)	18·10 (13–22)
Benzoyl peroxide (topical) + lincosamide (clindamycin) (topical) + retinoid (topical)	**600**	**23·09 (8·21–37·97)**	18·82 (10–25)	18·27 (10–24)
Benzoyl peroxide (topical) + antifungal (topical)	25	21·98 (−2·11–46·13)	18·99 (6–26)	18·43 (6–25)
Benzoyl peroxide (topical) + lincosamide (clindamycin) (topical)	**276**	**22·64 (6·24–39·14)**	19·11 (10–25)	18·55 (10–24)
Benzoyl peroxide (topical) + macrolide (topical)	**365**	**22·14 (12·76–31·79)**	19·53 (13–24)	18·96 (13–23)
Photochemical therapy (combined blue/red light) (physical)	15	8·76 (−43·29–53·96)	21·88 (5–27)	21·17 (5–26)
Retinoid (topical)	**3570**	**13·15 (8·30–18·05)**	23·60 (20–26)	22·82 (19–25)
Macrolide (topical)	**109**	**10·91 (−3·66–25·39)**	23·80 (17–27)	23·00 (17–26)
Placebo	**4122**	**Reference**	26·43 (25–27)	25·48 (24–26)

CrI, credible interval; N, number of observations across trials included in the analysis. Classes ordered by mean rank for females (rank = 1 indicates highest efficacy). Treatment classes and values in bold indicate treatment classes with N ≥ 50 each across randomized controlled trials included in the analysis. Treatment classes and values in italics indicate treatment classes with 95% CrI crossing the 'no effect' line.

combined retinoid with BPO), and topical treatment combinations (e.g. retinoid with clindamycin or BPO, retinoid with clindamycin and BPO, BPO with clindamycin or with a macrolide). Overall, monotherapies of oral tetracyclines or topical treatments ranked lower than combined treatments. Photodynamic and photochemical therapies also appeared to be effective. Topical retinoids and oral tetracyclines were less well tolerated than placebo.

No evidence was identified for hormone-modifying agents (metformin, spironolactone). Hormonal contraceptives (combined oral contraceptives and cocyprindiol) showed evidence of a small effect in reducing acne lesions in mild-to-moderate acne in the base-case analysis, reflecting findings of individual RCTs; however, no such evidence was found after adjusting for bias (the presence of which was indicated by a bias adjustment model). It is noted that the systematic review and NMAs excluded RCTs recruiting specifically people with acne vulgaris and PCOS, for whom benefits of hormonal contraceptives may be different.

A previous NMA on topical treatments for mild-to-moderate acne vulgaris included 40 RCTs and found that adapalene combined with BPO was the most effective topical treatment, but had a slightly higher incidence of withdrawal than monotherapy.[11] Another NMA of topical, oral and physical treatments for acne vulgaris (which did not consider oral isotretinoin or hormonal agents) included 73 RCTs and reported that, for mild-to-moderate acne, combined topical retinoids with BPO were the best option, followed by topical antibiotics and BPO. Topical antibiotics combined with BPO and chemical peels, and topical antibiotics combined with topical retinoids, were another two good options for noninflammatory lesions, while light devices were good for inflammatory lesions. No results or conclusions for moderate-to-severe acne were reported.[12] Results of both studies are consistent with our findings.

A strength of our review and NMA was the inclusion of a wide range of acne treatments and, subsequently, a much larger number of RCTs (112 for mild-to-moderate and 67 for moderate-to-severe acne) than either of the two previously published NMAs. Furthermore, our NMA assessed treatments for moderate-to-severe acne. The NMA results informed national clinical guidance.[13] Our methodology enabled evidence synthesis from direct and indirect treatment comparisons and allowed simultaneous inference on all treatments.[7,10] Our NMA employed class models to gain precision on the effects of treatments within the same class and to connect networks disconnected at the treatment level, thus allowing consideration of a wider evidence base. We measured efficacy using the percentage change in total acne lesion count from baseline, as this is commonly reported across RCTs or can often be estimated using other available data, which allowed inclusion of a large evidence base in the respective analyses. Another validated efficacy measure, the Investigator Global Assessment scale, recommended by the American Food and Drug Administration (FDA) for the assessment of effectiveness of pharmacological treatments of acne vulgaris,[29] was used by fewer studies in our dataset; therefore, had we selected this outcome to measure efficacy, we would have limited our evidence base.

Dietary interventions (e.g. milk-free diet, low glycaemic load diet), which may have an effect on acne vulgaris and its response to treatment,[30] were not included in this review but were assessed in another review conducted to inform the NICE guideline.[13] Although we searched for treatments for acne vulgaris at any body site, the majority of the RCTs included in our review focused on facial acne. This is a limitation of the evidence base and not of the review per se. Another potential limitation of our review was its focus on evidence published in the English language, following NICE guidance.[31] On the other hand, evidence suggests that use of language restrictions in systematic review-based meta-analyses in conventional medicine does not introduce systematic bias.[32] Furthermore, as the purpose of our NMA was to inform national guidance in England, we focused on pharmacological treatments that are available in the UK. This resulted in the exclusion of a number of potentially effective drug treatments for acne from the NMA, as they were not licensed in the UK at the time of the analysis (e.g. topical dapsone, topical tetracyclines). Final searches for evidence were conducted in May 2020, and it is possible that new evidence (and new treatments) have emerged since.

All analyses showed some inconsistency between direct and indirect evidence, possibly reflecting heterogeneity in populations (e.g. regarding age or definition of acne severity), treatments (e.g. regarding treatment regime), or study design (e.g. parallel vs. split-face) across RCTs included in the NMAs. There was insufficient evidence to explore age as a potential effect modifier. We did not identify any imbalance in the study samples' age ranges in RCTs of moderate-to-severe acne, but some variation was observed in RCTs of mild-to-moderate acne and this may have affected the estimates for this population. To analyse discontinuation outcomes we used a continuity correction for studies with zero events in some – but not all – arms that performs well with 1 : 1 randomization, which was the case in the majority of studies; however, there may be a small bias for the few studies that were unbalanced. Our findings were based on evidence from RCTs of moderate to very low quality and were overall characterized by uncertainty. Results for some types of treatments (chemical peels, photochemical and photodynamic therapies) were based on rather limited evidence and informed through limited network connections. Nevertheless, threshold analysis on the efficacy outcome supported the robustness of our conclusions. For discontinuation outcomes, results suggested similar effects across the vast majority of treatment classes with largely overlapping 95% CrIs, suggesting a high degree of uncertainty in the optimal intervention. Therefore threshold analysis was not considered informative and was thus not attempted for discontinuation outcomes.

NMA results were interpreted in light of further clinical considerations when formulating recommendations, including practicality in use of fixed topical treatment combinations relative to nonfixed combinations, concerns about antibiotic resistance relating to antibiotic monotherapies, current regulations and safety concerns regarding oral isotretinoin,[33,34] limited availability and use of physical treatments and topical antifungals for acne management in the British National Health Service, and concerns about the long-term harms of chemical peel use outside of specialist settings (e.g. risk for significant skin damage from inappropriate strength or type of peel). Despite its more limited evidence base, azelaic acid combined with an oral tetracycline was considered a good alternative for people with moderate-to-severe acne who have irritation to topical retinoids; moreover, azelaic acid has a possible effect in reducing the risk of hyperpigmentation in people with darker skin and acne.[35]

Based on the NMA findings, the above considerations and cost-effectiveness findings[36] the NICE guideline on acne vulgaris management recommends, as first-line treatments, fixed topical treatment combinations (adapalene with BPO, clindamycin with BPO, or tretinoin with clindamycin) for mild-to-moderate acne, and fixed topical treatment combinations (adapalene with BPO, tretinoin with clindamycin) or oral tetracyclines (doxycycline or lymecycline) combined with topical treatments (fixed combination of adapalene with BPO; or azelaic acid) for moderate-to-severe acne. Where oral lymecycline or doxycycline are not tolerated or are contraindicated, alternative oral antibiotics such as trimethoprim or an oral macrolide (e.g. erythromycin) might be considered. Choice should be determined following shared decision making with the person with acne, taking into account their values and preferences on the benefits, risks and other characteristics of each treatment, their history of previous therapy and scarring, their risk of future scarring and the psychosocial burden imposed by acne. BPO alone may be considered as an option across all acne severity levels if other recommended first-line treatments are contraindicated (e.g. during pregnancy) or there is a patient preference against their use. Topical retinoids and BPO should be initiated with alternate-day or short-contact application because of their increased risk of discontinuation owing to side-effects. Photodynamic therapy may be considered as an option for

adults with moderate-to-severe acne if other treatments are ineffective, not tolerated or contraindicated.[13]

Recommendations should reduce variation in practice, as a number of commonly used treatments showed evidence of low or no efficacy after adjusting for potential bias (e.g. some topical pharmacological monotherapies, oral antibiotic monotherapies in mild-to-moderate acne, hormonal contraceptives) and were thus not recommended as first-line acne treatments. However, hormonal contraceptives were considered as options for people with acne vulgaris and PCOS, if their chosen first-line treatment was not effective, based on available evidence specific to this population.[13]

Further research was recommended for chemical peels, photochemical and photodynamic therapies (for which the evidence was promising but limited), for hormone-modifying agents, e.g. metformin and spironolactone (for which no evidence was identified), and for oral isotretinoin in reduced dosage ($< 0{\cdot}5$ mg kg^{-1} per day) or reduced-dose regime (e.g. weekly or biweekly), to explore whether it is an effective, safer and better-tolerated alternative to standard-dose oral isotretinoin ($0{\cdot}5$–1 mg kg^{-1} per day).

In conclusion, this NMA allowed evidence synthesis from a wide range of treatments for acne vulgaris stratified by severity level. Topical pharmacological treatment combinations, chemical peels and photochemical therapy appeared to be most effective for mild-to-moderate acne. Topical pharmacological treatment combinations, oral antibiotics combined with topical pharmacological treatments, oral isotretinoin, and photodynamic therapy appeared to be most effective for moderate-to-severe acne. Further research is warranted for chemical peels and for photochemical and photodynamic therapies for which evidence was more limited and uncertain.

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Conflicts of interest

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Data availability

The data that support the findings of this study are available in the Supporting Information.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Search strategy.
Appendix S2 Study protocol.
Appendix S3 Methods of the statistical analysis and codes for data synthesis.
Appendix S4 Methods of inconsistency checks and statistical codes.
Appendix S5 Methods of bias adjustment models and statistical codes.
Appendix S6 Methods of threshold analysis.
Appendix S7 Characteristics of studies included in the network meta-analysis, and full references.
Appendix S8 List of excluded studies with reasons for exclusion.
Appendix S9 Network meta-analysis data files.
Appendix S10 Treatment classes, interventions and numbers of observations made on each, for each outcome considered in the network meta-analysis.
Appendix S11 Model fit statistics.
Appendix S12 Inconsistency checks – results.
Appendix S13 Risk of bias of studies included in the network meta-analysis.
Appendix S14 Bias adjustment models – results.
Appendix S15 Network meta-analysis additional results.
Appendix S16 Relative effects between all pairs of treatment classes: results of direct (head-to-head), indirect and network meta-analysis comparisons.

Appendix S17 Threshold analysis on the efficacy outcome – results.

Figure S1 Network of treatment classes for people with (a) mild-to-moderate acne and (b) moderate-to-severe acne on discontinuation for any reason.

Figure S2 Network of treatment classes for people with (a) mild-to-moderate acne and (b) moderate-to-severe acne on discontinuation owing to side-effects.

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