National Institute for Health and Care Excellence

Final

Acne vulgaris: management

[E1] Management options for mild to moderate acne – network meta-analyses

NG198

Evidence review underpinning recommendations 1.5.1, 1.5.2 and 1.5.5 to 1.5.14 (excluding 1.5.6 which is underpinned by evidence review L, 1.5.10 and bullet points 2 and 3 of recommendation 1.5.12, underpinned by evidence review F1) and 3 research recommendations in the NICE guideline

June 2021

Final

These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:978-1-4731-4147-6

Contents

Summary of review questions covered in this chapter

A single review protocol and literature search was used to identify randomised trials of treatments for acne vulgaris to address 9 review questions covering topical or oral pharmacological treatments and physical treatments, shown below. Outcomes were prioritised for either pairwise or network meta-analysis (NMA) and the evidence was divided according to the severity of acne into mild to moderate and moderate to severe categories. NMA was employed to assess comparative efficacy, acceptability and tolerability of treatments, which are outcomes commonly reported in the literature for the majority of treatments. Pairwise meta-analysis was used to synthesise outcomes for which evidence was more limited across treatments or was treatment-specific. The evidence was then summarised in four separate reviews covering the treatment of:

- mild to moderate acne (NMA)
- mild to moderate acne (pairwise meta-analysis)
- moderate to severe acne (NMA)
- moderate to severe acne (pairwise meta-analysis)

This evidence report contains information on the NMAs conducted to assess treatments for people with mild to moderate acne vulgaris. Information on the pairwise meta-analyses conducted to assess treatments for people with mild to moderate acne vulgaris is contained in the evidence report E2. Information on the NMAs and pairwise meta-analyses conducted to assess treatments for people with moderate to severe acne vulgaris are contained in the evidence reports F1 and F2, respectively.

1. What is the effectiveness of topical treatments individually or in combination in the treatment of acne vulgaris, for example:
- benzoyl peroxide
- antibiotics
- antiseptics
- retinoids and retinoid-like agents (for example, tretinoin, adapalene, trifarotene)
- azelaic acid
- nicotinamide
- combination of antibiotic and retinoid or retinoid-like agent
- combination of benzoyl peroxide and retinoid or retinoid-like agent
- combination of antibiotic and benzoyl peroxide?

2. What is the effectiveness of oral antibiotic treatments in the treatment of acne vulgaris, for example:
- tetracyclines (for example oxytetracycline, doxycycline, minocycline, tetracycline, lymecycline)
- macrolide antibiotics (for example, erythromycin and azithromycin)
- trimethoprim?

3. What is the effectiveness of an oral antibiotic with a topical agent compared to oral antibiotic alone in the treatment of acne vulgaris?

4. What is the optimal duration of antibiotic treatments (topical and systemic) for acne vulgaris?

5. What is the effectiveness of hormonal contraceptives in the treatment of acne vulgaris?

6. What is the effectiveness of spironolactone in the treatment of acne vulgaris?

7. What is the effectiveness of metformin in the treatment of acne vulgaris?

8. What is the effectiveness of oral isotretinoin in the treatment of acne vulgaris?

9. What is the effectiveness of physical treatments for acne vulgaris, for example
- comedone extraction
- chemical peels (for example, glycolic acid, lactic acid, salicylic acid)
- intralesional steroids
- light devices (for example, intense pulsed light, photopneumatic therapy and photodynamic therapy)?

Management options for people with mild to moderate acne vulgaris - network meta-analyses

Review question

For people with mild to moderate acne vulgaris what are the most effective treatment options?

Introduction

Mild to moderate acne is very common with a wide range of treatment modalities available including over the counter products. Management options should be effective and acceptable to individual, taking into consideration potential side effects and contraindications. The identification of the most effective treatment options from this wide range is therefore the aim of this review.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review. The protocol for this topic was written to encompass both the NMA and pairwise analysis. To give the full context of this topic, the summary of the protocol and the full protocol in appendix A contain the details of both (this is also how the protocol is registered on PROSPERO).

Table 1: Summary of the protocol (PICO table)

Population	People with acne vulgaris, of all ages and levels of symptom severity. For all outcomes, separate analyses will be conducted for mild to moderate acne vulgaris and moderate to severe acne vulgaris.
Intervention	Interventions will be categorised into the following classes and, if relevant, subclasses (the list is non-exhaustive): ➢ **TOPICAL TREATMENTS** **Abrasive/cleaning agents** • Aluminium oxide [own class] **Anthelmintics** • Cysticide (praziquantel) [own class] • Class of avermectins: ivermectin **Antibacterials** • Class of triclocarban and triclozan **Antibiotics** • Class of sulphones (dapsone) • Fusidic acid (sodium fusidate) [own class] • Class of lincosamides (for example clindamycin) • Class of macrolides (for example clarithromycin, erythromycin with zinc acetate dihydrate) • Class of nitroimidazoles (metronidazole) • Class of carboxylic acids (mupirocin) • Class of penicillins ○ Sub-class of natural (for example almecillin) ○ Sub-class of aminopenicillins (for example ampicillin) ○ Sub-class of β-lactamase-resistant (for example methicillin) ○ Sub-class of carboxypenicillins (for example ticarcillin) ○ Sub-class of ureidopenicillins (for example azlocillin)

	○ Sub-class of other penicillins (mecillinam, pivmecillinam hydrochloride) • Class of pleuromutilins (for example retapamulin) **Antiseptics** • Benzoyl peroxide (trade: Acnecide, Brevoxyl, Panoxyl) [own class] • Chlorhexidine gluconate (trade: Acnemed, Cepton) or digluconate [own class] **Dicarboxylic acids** • Azelaic acid [own class] **Vitamin B3** • Nicotinamide (niacinamide) [own class] **Retinoids or retinoid-like agents** • Class of retinoids or retinoid-like agents (adapalene, isotretinoin, retinol, tazarotene, tretinoin, trifarotene) **Combined interventions** • Benzoyl peroxide & potassium hydroxyguinoline sulfate [own class] • Class of benzoyl peroxide & retinoid (benzoyl peroxide + adapalene) • Class of benzoyl peroxide & lincosamide (benzoyl peroxide + clindamycin) • Class of lincosamides & retinoid (clindamycin + tretinoin) • Class of macrolides & retinoid (erythomycin + retinoid) [topical] • Germolene (phenol 1.2% + chlorhexidine diculconate [own class] ➢ **ORAL ANTIBIOTICS** • Class of carbapenems (for example imipenem, meropenem) • Class of carbapenems with cilastatin (imipenem with cilastatin) • Class of carbapenems with b lactamase inhibitor (meropenem with vaborbactam) • Class of cephamycins/cephalosporins ○ Sub-class of 1st-generation (for example cefadroxil) ○ Sub-class of 2nd-generation (for example cefaclore) ○ Sub-class of 3rd-generation (for example cefdinir) ○ Sub-class of 4th-generation (for example cefozopran) ○ Sub-class of 5th-generation (for example ceftolozane) • Class of cephamycins/cephalosporins with β-lactamase inhibitor (for example ceftraroline or ceftazidime with avibactam, cefoperazone with sulbactam, ceftolozane with tazobactam) • Class of sulphones (dapsone) • Fusidic acid (sodium fusidate) [own class] • Class of lincosamides (for example clindamycin) • Class of macrolides (for example clarithromycin, erythromycin) • Class of monobactams (aztreonam) • Class of monobactams with β-lactamase inhibitor (aztreonam with avibactam) • Class of penicillins ○ Sub-class of natural (for example almecillin) ○ Sub-class of aminopenicillins (for example ampicillin) ○ Sub-class of β-lactamase-resistant (for example methicillin) ○ Sub-class of carboxypenicillins (for example ticarcillin) ○ Sub-class of ureidopenicillins (for example azlocillin) ○ Sub-class of other penicillins (mecillinam, pivmecillinam hydrochloride) • Class of penicillin with β-lactamase inhibitor (for example co-amoxiclav [amoxicillin with clavulanic acid], piperacillin with tazobactam, ticaricillin with clavulanic acid, sultamicillin [ampicillin with sulbactam]) • Class of penicillin with flucloxacilin (co-fluampicil [ampicillin + flucloxacilin]) • Class of pleuromutilins (for example retapamulin) • Class of quinolones ○ Sub-class of 1st-generation (for example rosoxacin) ○ Sub-class of 2nd-generation (for example ofloxacin) ○ Sub-class of 3rd-generation (for example temafloxacin) ○ Sub-class of 4th-generation (for example sitafloxacin) • Class of tetracyclines (for example doxycycline, oxytetracycline) • Trimethoprim [own class] • Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMX) [own class]

➢ **TOPICAL TREATMENTS COMBINED WITH ORAL ANTIBIOTICS**

➢ **ORAL HORMONAL CONTRACEPTIVES AND HORMONE-MODIFYING AGENTS**

- Co-cyprindiol (ethinylestradiol + cyproterone acetate) [own class of combined oral contraceptive]
- Class of combined oral contraceptives
  - Sub-class of 2nd generation (oestrogen, for example ethinylestradiol or estradiol or mestranol combined with levonorgestrel or norethisterone)
  - Sub-class of 3rd generation (oestrogen, for example ethinylestradiol combined with desogestrel or gestodene or norgestimate)
  - Sub-class of 4th generation (oestrogen, for example ethinylestradiol or estradiol combined with dienogest or drospirenone or nomegestrol acetate)

Monophasic and phasic combined oral contraceptives containing the same hormones will be analysed as separate interventions within their sub-class.

- Class of progestogen-only oral contraceptives
  - Sub-class of 1st generation (for example medroxyprogesterone acetate)
  - Sub-class of 2nd generation (for example levonorgestrel, norethisterone/ norethindrone)
  - Sub-class of 3rd generation (for example desogestrel, norgestimate, gestodene)
  - Sub-class of 4th generation (for example dienogest, drospirenone, nomegestrol acetate)
- Class of selective aldosterone receptor antagonists (for example spironolactone alone or combined with furosemide or hydroflumethiazide [co-flumactone], eplerenone, canrenone)
- Class of 5α-reductase inhibitors (dutasteride, finasteride, tamsulosin with dutasteride)
- Class of other non-steroidal anti-androgens (for example abiraterone acetate, apalutamide, bicalutamide, cyproterone acetate, clormadinone acetate, enzalutamide, flutamide)
- Metformin [own class]

➢ **ORAL ISOTRETINOIN**

- Class of oral retinoid and total cumulative dose ≥ 120mg/kg (single course)
  - Sub-class of daily dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
  - Sub-class of alternate day dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
  - Sub-class of less frequent or other dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
- Class of oral retinoid and total cumulative dose < 120mg/kg (single course)
  - Sub-class of daily dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
  - Sub-class of alternate day dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)
  - Sub-class of less frequent or other dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day)

➢ **PHYSICAL TREATMENTS**

- Class of chemical peels
  - Sub-class of superficial peels
  - Sub-class of moderate peels
  - Sub-class of deep peels

  for example amino fruit acid, glycolic acid, Jessner's peel, lactic acid, salicylic acid, trichloroacetic acid [TCA]; these will be categorised into different sub-classes as reported in the included studies, according to the concentration of their active ingredient and treatment duration.
- Comedone extraction [own class]
- Class of photothermal therapy (for example fractional erbium glass laser)
- Class of photochemical therapy (for example blue or red light and their combination)

	• Class of photochemical and photothermal therapy (for example potassium titanyul phosphate laser, Intense Pulsed Light [IPL], Pulsed Dye Laser) • Class of photodynamic therapy (for example 5-aminolevuliniv acid [ALA], liposomal methylene blue gel, methylaminolevulinate [MAL]) • Smoothbeam™ laser [own class] • Photopneumatic therapy (for example intense pulsed light + vacuum) • Radiofrequency (for example fractional microneedling, bipolar)
Comparison	• No treatment • Waiting list • Pill placebo • Other active intervention • Sham physical treatment
Outcomes (for NMA)	**Critical** • Efficacy ○ Clinician-rated improvement at treatment endpoint - % change in acne lesion count from baseline - change or final score on a validated acne severity scale ○ Participant-reported improvement at treatment endpoint - Change in acne severity or symptoms (e.g. assessed using global acne score) ○ Prevention of scarring at any follow-up - Final / change in number of scars from baseline - Incidence of scarring **Important** • Acceptability ○ Treatment discontinuation for any reason • Tolerability ○ Treatment discontinuation due to side-effects

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplement 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Clinical evidence

Overview of method of synthesis

Network meta-analysis (NMA) is a generalisation of standard pairwise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials (see supplement 1). A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from an A versus B trial, is the same with the relative effect between A and B estimated indirectly from A versus C and B versus C trials. NMA techniques include both direct and indirect comparisons across treatments, and allow simultaneous inference on the relative effect of all treatments that participate in a single 'network of evidence', where every treatment is linked to at least one of the other treatments under assessment through direct or indirect comparisons. NMA was employed to assess comparative treatment efficacy (expressed as the change in the number of total acne lesion counts following treatment),

treatment acceptability (expressed as treatment discontinuation for any reason) and treatment tolerability (expressed as treatment discontinuation due to side effects).

Included studies

This review included 107 randomised controlled trials (RCTs). For brevity we have not listed the references of the included studies in this section, but they are summarised in Table 2.

According to the treatments assessed and the types of outcomes reported in each RCT, the included RCTs have contributed data to one ore more networks of evidence and respective NMAs. Below, the terminology 'observations' rather than 'participants' has been used because the evidence includes split-face RCTs where parts of the face are randomised.

For the outcome of efficacy, the network of evidence (and the respective NMA) included 76 RCTs, 41 treatment classes and 17,735 observations relevant to females; of these, 39 treatment classes were relevant also to males, assessed in 67 RCTs and 14,145 observations.

For details of the interventions that have been included in this analysis see Figure 1.

For the outcome of discontinuation for any reason, the network of evidence (and the respective NMA) included 85 RCTs, 40 treatment classes and 18,606 observations relevant to females; of these, 38 treatment classes were relevant also to males, assessed in 77 RCTs and 15,147 observations.

For details of the interventions that have been included in this analysis see Figure 2.

For the outcome of discontinuation due to side effects, the network of evidence (and the respective NMA) included 48 RCTs, 24 treatment classes and 15,213 observations relevant to females; of these, 22 treatment classes were relevant also to males, assessed in 42 RCTs and 12,134 observations.

For details of the interventions that have been included in this analysis see Figure 3.

For the outcome of participant-reported improvement there were very limited data to allow conducting a meaningful NMA, therefore these have been analysed in pairwise meta-analysis (see evidence report E2).

For the outcome of prevention of scarring there were no data, therefore no analysis was conducted.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population*	Interventions	Outcomes
Abels 2011b **Country**: Europe	N=120 **Sex**: mixed **Number randomised: arm 1**: 59 **Number randomised: arm 2**: 61	**Intervention: arm 1**: GLY 10% lotion topical **Intervention: arm 2**: PLC-topical	• Treatment discontinuation for any reason

Study	Population*	Interventions	Outcomes
Study type: RCT	**Inclusion details**: Aged 12 years or older with mild facial acne (Leeds score 0.25; 0.5; 0.75; 1.00)		
Akarsu 2012 **Country**: Turkey **Study type**: RCT	N=50 **Sex**: mixed **Number randomised: arm 1**: 25 **Number randomised: arm 2**: 25 **Inclusion details**: Mild to moderate AV, between the ages of 18 and 35 years, and with between 10–50 IL and 10–100 NIL above the mandibular line at baseline.	**Intervention: arm 1**: SAL 3% + CLIND-topical 1% + BPO-topical 5% **Intervention: arm 2**: CLIND-topical 1% + BPO-topical 5%	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Alba 2017 **Country**: Brazil **Study type**: RCT	N=22 **Sex**: mixed **Number randomised: arm 1**: 11 **Number randomised: arm 2**: 11 **Inclusion details**: Adolescents aged between 12 and 18 years old, with grades I and II comedonal and papulopustular acne, and who sought help at the clinic in the trial period.	**Intervention: arm 1**: SAL 10% **Intervention: arm 2**: BLUE + RED LIGHT (Spectra G3 machine, Tonederm)	• Clinician rated improvement in acne
Alirezai 2005 **Country**: Europe **Study type**: RCT	N=592 **Sex**: mixed **Number randomised: arm 1**: 265 **Number randomised: arm 2**: 261 **Number randomised: arm 3**: 66 **Inclusion details**: At least age 12, acne vulgaris on face (severity grade of 2 to 5 on the Leeds revised scale), and 15-50 inflammatory facial lesions.	**Intervention: arm 1**: CLIND-topical 1% gel **Intervention: arm 2**: CLIND-topical 1% topical solution **Intervention: arm 3**: Vehicle gel	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Alora Palli 2013 **Country**: United States **Study type**: RCT	N=30 **Sex**: female **Number randomised: arm 1**: 16 **Number randomised: arm 2**: 14 **Inclusion details**: Female, age 18 to 45 years, who achieved spontaneous menarche, desired contraception and had a diagnosis of truncal acne of 10 to 50 inflammatory lesions on the back and chest combined with not more than 5 nodules	**Intervention: arm 1**: EE-oral 0.02 mg + DROS-oral 3mg od **Intervention: arm 2**: PLC-oral	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Babaeinejad 2013 **Country**: Iran **Study type**: RCT	N=60 **Sex**: mixed **Number randomised: arm 1**: 30 **Number randomised: arm 2**: 30 **Inclusion details**: Mild acne vulgaris (Evaluator Global Severity Score, EGSS, of 2)	**Intervention: arm 1**: BPO 2.5% gel **Intervention: arm 2**: ADAP 0.1% gel	• Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
Babayeva 2011 **Country**: Turkey **Study type**: RCT	N=46 **Sex**: mixed **Number randomised: arm 1**: 23 **Number randomised: arm 2**: 23 **Inclusion details**: 18 and 35 years of age, with 10–50 inflammatory lesions and 10–100 non-Inflammatory lesions above the mandibular line at baseline	**Intervention: arm 1**: SAL 3% + CLIND-topical 1% **Intervention: arm 2**: TRET-topical 0.05% + CLIND-topical 1%	• Clinician rated improvement in acne
Barbareschi 1991 **Country**: Italy **Study type**: RCT	N=30 **Sex**: mixed **Number randomised: arm 1**: 10 **Number randomised: arm 2**: 10 **Number randomised: arm 3**: 10 **Inclusion details**: Comedonic acne.	**Intervention: arm 1**: AZE-topical 20% twice daily **Intervention: arm 2**: TRET-topical 0.05% **Intervention: arm 3**: PLC-topical	• Clinician rated improvement in acne
Barolet 2010 **Country**: Canada **Study type**: RCT (split face design)	N=20 (observations) **Sex**: mixed **Number randomised: arm 1**: 10 **Number randomised: arm 2**: 10 **Inclusion details**: Mild to moderate acne based on the Combined Acne Severity Classification with a lesion count of at least 10 and skin type I to III according to the Fitzpatrick Classification System	**Intervention: arm 1**: IRL and then 5ALA-RED-PDT **Intervention: arm 2**: 5ALA-RED-PDT	• Clinician rated improvement in acne
Becker 1981 **Country**: United States **Study type**: RCT	N=238 **Sex**: mixed **Number randomised: arm 1**: 124 **Number randomised: arm 2**: 114 **Inclusion details**: Age 12 to 30 with a minimum of 12 and a maximum of 70 inflammatory papules on the face.	**Intervention: arm 1**: CLIND-topical 1% (clindamycin phosphate) **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Bernhardt 2016 **Country**: United States **Study type**: RCT	N=68 **Sex**: mixed **Number randomised: arm 1**: 35 **Number randomised: arm 2**: 33 **Inclusion details**: Older than 12 years old with more than 1-inflammatory lesions	**Intervention: arm 1**: Topical salicylic acid in "Next Science Acne" gel **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Bleeker 1983 **Country**: Sweden **Study type**: RCT	N=40 **Sex**: mixed **Number randomised: arm 1**: 20 **Number randomised: arm 2**: 20 **Inclusion details**: Mild to moderate papulopustular acne	**Intervention: arm 1**: Erythromycin stearate capsules 500mg b.d. **Intervention: arm 2**: Erythromycin base capsules 500mg b.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Boutli 2003	N=37 **Sex**: mixed	**Intervention: arm 1**: Topical benzoil peroxide 5% gel	• Treatment discontinuation for any reason

Study	Population*	Interventions	Outcomes
Country: Greece **Study type**: RCT	**Number randomised: arm 1**: 19 **Number randomised: arm 2**: 18 **Inclusion details**: Age 13-25, moderate acne (grade 11, Pilsbury and Kligman), 20-50 comedones and 20-40 papulopustules	**Intervention: arm 2**: Topical Nisal cream (chloroxylenol 0.5% + salicylic acid 2%)	• Treatment discontinuation due to side effects
Callender 2012b **Country**: United States **Study type**: RCT	N=33 **Sex**: mixed **Number randomised: arm 1**: 17 **Number randomised: arm 2**: 16 **Inclusion details**: 12 years of age or older with skin types IV to VI and exhibited mild-to-moderate facial acne and mild-to-moderate PIH	**Intervention: arm 1**: Topical clindamycin 1.2% + topical tretinoin 0.025% **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Capizzi 2004 **Country**: Italy **Study type**: RCT	N=52 **Sex**: mixed **Number randomised: arm 1**: 26 **Number randomised: arm 2**: 26 **Inclusion details**: Aged 15– 35 years with mild to moderate AV defined as: at least 10 and <50 inflammatory lesions (IL), at least 10 and <100 noninflammatory lesions (NL) and no more than two nodulocystic lesions	**Intervention: arm 1**: Adapalene topical gel 0.1% + HPS-topical cream 1% **Intervention: arm 2**: Adapalene topical gel 0.1% + BPO-topical cream 4%	• Clinician rated improvement in acne
Carey 1996 **Country**: Canada **Study type**: RCT	N=499 **Sex**: mixed **Number randomised: arm 1**: 249 **Number randomised: arm 2**: 250 **Inclusion details**: Under 25 years, 15 - 75 inflammed lesions on the face	**Intervention: arm 1**: Topical fusidic acid 2% **Intervention: arm 2**: Topical erythromycin 2%	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Charakida 2007 **Country**: United Kingdom **Study type**: RCT	N=40 **Sex**: mixed **Number randomised: arm 1**: 20 **Number randomised: arm 2**: 20 **Inclusion details**: Patients aged between 16 and 45 years with mild to moderate facial inflammatory acne defined as the presence of at least 10 acne papules or pustules between the brow and jaw line and an acne severity score of between 2 and 7 on the Leeds revised acne grading system.	**Intervention: arm 1**: ACNICARE (triethyl citrate + ethyl linoleate) topical b.d. **Intervention: arm 2**: Vehicle topical b.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Cheema 2018 **Country**: Pakistan **Study type**: RCT	N=140 **Sex**: mixed **Number randomised: arm 1**: 70 **Number randomised: arm 2**: 70 **Inclusion details**: Mild to moderate acne	**Intervention: arm 1**: blue light (Soret Blue Light) 407-420nm high intensity light	• Treatment discontinuation for any reason • Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
		Intervention: arm 2: BPO 4% topical cream o.d.	
Choi 2010 **Country**: Korea, Republic of **Study type**: RCT (split face design)	N=40 (observations) **Sex**: mixed **Number randomised: arm 1**: 20 **Number randomised: arm 2**: 20 **Inclusion details**: Age >15 years, general good health, the ability to comply with the study protocol and an acne severity grade of 2–4, as defined by Cunliffe's grading system	**Intervention: arm 1**: INTENSE PULSED LIGHT [IPL] Ellipse Flex System **Intervention: arm 2**: PULSED DYE LASER 585-nm (Cynergy; system)	• Clinician rated improvement in acne
Chottawornsak 2019 **Country**: Thailand **Study type**: RCT	N=41 **Sex**: female **Number randomised: arm 1**: 20 **Number randomised: arm 2**: 21 **Inclusion details**: Participants were women aged above 25 years.Mild acne with an AFA score of 2 on the face based on the Global Acne Severity Scale	**Intervention: arm 1**: Topical 2% ketoconazole cream **Intervention: arm 2**: Placebo	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Cunliffe 2002b **Country**: United Kingdom **Study type**: RCT	N=79 **Sex**: mixed **Number randomised: arm 1**: 40 **Number randomised: arm 2**: 39 **Inclusion details**: Acne vulgaris, aged 13 to 30. Baseline or screening P acnes counts on facial skin (cheek or forehead) had to be at least 104 colony-forming units (CFUs) per square centimeter, of which no more than 104 CFU/cm 2 could be erythromycin or clindamycin resistant. Eligible patients also had to have 15 to 100 inflammatory lesions, 15 to 100 comedones, and <2 nodules/cysts on the face. Sexually active female patients were required to use contraception for 28 days before the start and for the duration of the study.	**Intervention: arm 1**: topical clindamycin 1% / BPO 5% gel b.d. **Intervention: arm 2**: topical clindamycin 1%	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Cunliffe 2005 **Country**: Europe **Study type**: RCT	N=246 **Sex**: mixed **Number randomised: arm 1**: 83 **Number randomised: arm 2**: 80 **Number randomised: arm 3**: 83 **Inclusion details**: Age between 12 and 40 years with mild to moderate acne graded between 2 and 7 with at least 15 inflammatory and 10 non-inflammatory lesions, but fewer than 75 lesions of either type	**Intervention: arm 1**: topical clindamycin 1% / zinc gel b.d. **Intervention: arm 2**: topical clindamycin 1% / zinc gel q.d. **Intervention: arm 3**: topical clindamycin 1% b.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
Darrah 1996 **Country**: United Kingdom **Study type**: RCT	N=188 **Sex**: mixed **Number randomised: arm 1**: 95 **Number randomised: arm 2**: 93 **Inclusion details**: Aged 12 to 25 with diagnosis of mild-to-moderate acne vulgaris of the face, and history of acne for at least 3 months. Mild acne was defined as the presence of 5 to 20 papules and/or pustules, and moderate acne was defined as the presence of 21 to 50 papules and/or pustules on the right side of the face.	**Intervention: arm 1**: topical fusidic acid 2% lotion b.d. **Intervention: arm 2**: oral minocycline 50mg b.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects
Dayal 2017 **Country**: India **Study type**: RCT	N=40 **Sex**: mixed **Number randomised: arm 1**: 20 **Number randomised: arm 2**: 20 **Inclusion details**: Mild-to-moderate (grade I and grade II) facial acne vulgaris, graded using a system taking into account the predominant lesions present: Grade 1 (mild): comedones, occasional papules. Grade 2 (moderate): papules, comedones, few pustules. Grade 3 (severe): predominant pustules, nodules, abscesses. Grade 4 (cystic): mainly cysts, abscesses, widespread scarring.	**Intervention: arm 1**: salicylic acid 30% **Intervention: arm 2**: Jessner's peel	• Clinician rated improvement in acne
Dayal 2020 **Country**: India **Study type**: RCT	N=50 **Sex**: mixed **Number randomised: arm 1**: 25 **Number randomised: arm 2**: 25 **Inclusion details**: Mild-to-moderate (grade I and grade II) facial acne vulgaris on the Vaishampayan grading system.	**Intervention: arm 1**: 30% salicylic acid peel **Intervention: arm 2**: 45% mandelic acid peel	• Clinician rated improvement in acne
Draelos 2002 **Country**: United States **Study type**: RCT	N=440 **Sex**: mixed **Number randomised: arm 1**: 89 **Number randomised: arm 2**: 85 **Number randomised: arm 3**: 89 **Number randomised: arm 4**: 90 **Number randomised: arm 5**: 87 **Inclusion details**: At least 12 years of age, had mild-to-moderate facial acne vulgaris, and had not used any topical anti-acne medication in the 14 days preceding study entry, any oral anti-acne medication in the 28 days preceding study entry, or any	**Intervention: arm 1**: topical tazarotene 0.1% o.d. **Intervention: arm 2**: topical clindamycin b.d. **Intervention: arm 3**: topical tazarotene 0.1% o.d. plus BPO 4% b.d. **Intervention: arm 4**: topical tazarotene 0.1% o.d. plus topical erythromycin 3%/BPO 5% gel b.d. **Intervention: arm 5**: topical tazarotene 0.1%	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects

Study	Population*	Interventions	Outcomes
	investigational drug or device in the 30 days preceding study entry.	o.d. plus topical clindamycin b.d.	
Dubey 2016 **Country**: India **Study type**: RCT	N=100 **Sex**: mixed **Number randomised: arm 1**: 50 **Number randomised: arm 2**: 50 **Inclusion details**: Male and non-pregnant participants aged between 12 and 30 years. Participants with mild to moderate acne vulgaris; based on simple acne grading scale (grade 1 to grade 4).Participants with only comedones as noninflammatory lesions, and papules and pustules as inflammatory lesions were included in the study (mild to moderate acne vulgaris- grades 1 and 2).	**Intervention: arm 1**: adapalene (0.1%) o.d. **Intervention: arm 2**: benzoyl peroxide (2.5%) clindamycin (1%) combination o.d.	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Eichenfield 2013a **Country**: north america **Study type**: RCT	N=285 **Sex**: mixed **Number randomised: arm 1**: 142 **Number randomised: arm 2**: 143 **Inclusion details**: 9 to 11 years of age, with a score of 3 (moderate) on the Investigator's Global Assessment (IGA) scale and 20-100 total lesions (non-inflammatory and/or inflammatory) on the face, including the nose	**Intervention: arm 1**: ADAP 0.1%/BPO 2.5% gel o.d. **Intervention: arm 2**: Vehicle o.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Elgendy 2015 **Country**: Egypt **Study type**: RCT	N=60 **Sex**: mixed **Number randomised: arm 1**: 30 **Number randomised: arm 2**: 30 **Inclusion details**: Age at least 12 years, mild to moderate facial acne vulgaris which failed to respond to standard topical treatment	**Intervention: arm 1**: Blue light: high intensity, enhanced, narrowband, blue, light source (cure light, Iclear XL) **Intervention: arm 2**: isotretinoin 0.3 mg/kg/d in divided doses for six months	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Glass 1999 **Country**: United Kingdom **Study type**: RCT	N=160 **Sex**: mixed **Number randomised: arm 1**: 40 **Number randomised: arm 2**: 41 **Number randomised: arm 3**: 40 **Number randomised: arm 4**: 39 **Inclusion details**: Between 15 and 100 inflammatory lesions and/or between 15 and 100 non-inflammatory lesions and no more than 3 nodules	**Intervention: arm 1**: Topical ISO 0.05% + ERYTH 2% gel b.d. **Intervention: arm 2**: Topical placebo gel **Intervention: arm 3**: Topical ISO 0.05% gel b.d. **Intervention: arm 4**: Topical ERYTH 2% gel b.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Gollnick 2009 **Country**: North	N=1670 **Sex**: mixed **Number randomised: arm 1**: 419 **Number randomised: arm 2**: 418 **Number randomised: arm 3**: 415	**Intervention: arm 1**: Adapalene 0.1%–BPO 2.5% fixed combination topical gel o.d.	• Treatment discontinuation for any reason

Study	Population*	Interventions	Outcomes
America/Europe **Study type**: RCT	**Number randomised: arm 4**: 418 **Inclusion details**: 12 years of age or older with acne vulgaris, having on the face 20–50 inflammatory lesions, 30–100 noninflammatory lesions and an Investigator's Global Assessment (IGA) score of 3, corresponding to moderate acne.	**Intervention: arm 2**: Adapalene 0.1% topical gel o.d. **Intervention: arm 3**: BPO 2.5% topical gel o.d. **Intervention: arm 4**: Vehicle topical o.d.	• Treatment discontinuation due to side effects • Clinician rated improvement in acne
Guerra-Tapia 2012 **Country**: Spain **Study type**: RCT	N=168 **Sex**: mixed **Number randomised: arm 1**: 83 **Number randomised: arm 2**: 85 **Inclusion details**: Aged 12 to 39 years, with = 15 inflammatory lesions and/ or non-inflammatory lesions but = 3 nodulocystic lesions and an acne grade of = 2.0 and < 7.0 on the Leeds Revised Acne Grading System.	**Intervention: arm 1**: topical BPO % + CLIND 1% o.d. **Intervention: arm 2**: Adapalene 0.1% topical gel o.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects
Gupta 2003 **Country**: Canada **Study type**: RCT	N=112 **Sex**: mixed **Number randomised: arm 1**: 53 **Number randomised: arm 2**: 59 **Inclusion details**: 13-40 years of age, with moderate acne vulgaris of the face. This was grade II-III with more than12 inflammatory lesions.	**Intervention: arm 1**: Topical 3% Erythromycin/5% Benzoyl Peroxide b.d. **Intervention: arm 2**: Topical 0.025% Tretinoin/Erythromycin 4% b.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects
Hajheydari 2011 **Country**: Iran **Study type**: RCT	N=96 **Sex**: mixed **Number randomised: arm 1**: 32 **Number randomised: arm 2**: 32 **Number randomised: arm 3**: 32 **Inclusion details**: Aged 12-28 years with mild to moderate acne vulgaris	**Intervention: arm 1**: Topical azithromycin 2% b.d. **Intervention: arm 2**: Topical erythromycin 2% b.d. **Intervention: arm 3**: Topical clindamycin 2% b.d.	• Clinician rated improvement in acne
Hansted 1985 **Country**: Denmark **Study type**: RCT	N=79 **Sex**: mixed **Number randomised: arm 1**: 40 **Number randomised: arm 2**: 39 **Inclusion details**: Mild to moderate acne vulgaris	**Intervention: arm 1**: Topical fucidin cream 2% **Intervention: arm 2**: Topical placebo cream	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Henderson 1995 **Country**: United States **Study type**: RCT	N=120 **Sex**: mixed **Number randomised: arm 1**: 59 **Number randomised: arm 2**: 61 **Inclusion details**: 10-50 inflammatory facial lesions and no more than 2 cysts.	**Intervention: arm 1**: Clindamycin phosphate 1% topical solution o.d. **Intervention: arm 2**: Erythromycin 2% topical pledgets o.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
Hughes 1992 **Country**: United Kingdom **Study type**: RCT	N=77 **Sex**: mixed **Number randomised: arm 1**: 25 **Number randomised: arm 2**: 26 **Number randomised: arm 3**: 26 **Inclusion details**: 15-100 inflamed and/or 15-100 non-inflamed lesions but no more than three nodulocystic lesions on the face	**Intervention: arm 1**: Topical isotretinoin 0.05% b.d. **Intervention: arm 2**: Topical BPO 5% b.d. **Intervention: arm 3**: Vehicle b.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects
Hunt 1992 **Country**: Australia **Study type**: RCT	N=150 **Sex**: mixed **Number randomised: arm 1**: 50 **Number randomised: arm 2**: 50 **Number randomised: arm 3**: 50 **Inclusion details**: Mild to moderate acne, older than 12 years, free from intercurrent disease	**Intervention: arm 1**: Topical gluconolactone lotion 14% **Intervention: arm 2**: Topical BPO 5% lotion **Intervention: arm 3**: Topical vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects
Ianosi 2013 **Country**: Romania **Study type**: RCT	N=180 **Sex**: mixed **Number randomised: arm 1**: 60 **Number randomised: arm 2**: 60 **Number randomised: arm 3**: 60 **Inclusion details**: Mild to moderate comedonal and inflammatory acne vulgaris, with one or more inflammatory lesions, over 18 years with Fitzpatrick skin phototypes I – IV	**Intervention: arm 1**: IPL+Vacuum **Intervention: arm 2**: IPL **Intervention: arm 3**: Sebium H2O Micellaire solution	• Treatment discontinuation for any reason
Iraji 2007 **Country**: Iran **Study type**: RCT	N=60 **Sex**: mixed **Number randomised: arm 1**: 30 (c) **Number randomised: arm 2**: 30 (c) **Inclusion details**: Age 15-35 years with mild to moderate acne	**Intervention: arm 1**: 20% azelaic acid gel b.d. **Intervention: arm 2**: vehicle gel (contains carbapol 934 (1%), glycerin (5%) and triethanolamine (0.2-0.5%) b.d.	• Clinician rated improvement in acne
Jaisamran 2014 **Country**: Thailand **Study type**: RCT	N=201 **Sex**: female **Number randomised: arm 1**: 100 **Number randomised: arm 2**: 101 **Inclusion details**: Healthy females aged between 18 and 45 years with mild to moderate acne vulgaris - defined as having no more than 5 comedones or papules and no pustule while moderate acne vulgaris was defined as 6–15 comedones or papules and/or a maximum of three pustules.	**Intervention: arm 1**: triphasic EE/NGM treatment at the dosage of 0.035/0.18, 0.035/0.215 and 0.035/0.25mg on days 1–7, 8–14 and 15–21, respectively, and took inactive tablets for 7 days before starting the next treatment cycle **Intervention: arm 2**: biphasic EE/DSG treatment at the dosage of 0.04/0.025 and 0.03/0.125mg on days 1–7 and 8–22 of each cycle,	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
		respectively, and discontinued treatment for 6 days before starting the next treatment cycle	
Jung 2009 **Country**: Korea **Study type**: RCT (split face design)	N=36 (observations) **Sex**: mixed **Number randomised: arm 1**: 18 **Number randomised: arm 2**: 18 **Inclusion details**: Mild to moderate facial acne (acne severity grade of 2–5, as defined using the Cunliffe grading system), that hadn't improved for more than a year.	**Intervention: arm 1**: combined 585-nm PDL + 1,064-nm Nd:YAG lasers **Intervention: arm 2**: 585-nm PDL laser	• Clinician rated improvement in acne
Katsambas 1989 **Country**: Greece **Study type**: RCT	N=92 **Sex**: mixed **Number randomised: arm 1**: 43 **Number randomised: arm 2**: 49 **Inclusion details**: Papulo-pustular acne (degree II/III of Plewig-Kligmann)	**Intervention: arm 1**: 20% azelaic acid cream **Intervention: arm 2**: vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Kaur 2015 **Country**: India **Study type**: RCT	N=66 **Sex**: mixed **Number randomised: arm 1**: 33 **Number randomised: arm 2**: 33 **Inclusion details**: Age range of 15–35 years having =2 and =30 inflammatory and/or noninflammatory lesions with Investigator's Global Assessment score (IGA) 2 or 3.	**Intervention: arm 1**: benzoyl peroxide 2.5% gel and clindamycin 1% gel **Intervention: arm 2**: tretinoin 0.025% and clindamycin 1% gel	• Clinician rated improvement in acne
Korkut 2005 **Country**: Turkey **Study type**: RCT	N=105 **Sex**: Mixed **Number randomised: arm 1**: 35 **Number randomised: arm 2**: 35 **Number randomised: arm 3**: 35 **Inclusion details**: Diagnosis of acne vulgaris	**Intervention: arm 1**: 0.1% adapalene gel, **Intervention: arm 2**: 5% benzoyl peroxide lotion **Intervention: arm 3**: combination of 0.1% adapalene gel +5% benzoyl peroxide	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Kwon 2019 **Country**: Korea **Study type**: RCT (split face design)	N=50 (observations) **Sex**: Mixed **Number randomised: arm 1**: 25 **Number randomised: arm 2**: 25 **Inclusion details**: Mild-to-moderate acne vulgaris as defined by revised Leeds score 2-8	**Intervention: arm 1**: sequential application of both nonablative 1,450-nm diode laser (Smoothbeam) and 450-nm blue light; For the DL mode treatment, each half of the facial area received 2 passes of the stamp mode, which comprised 4 micropulses lasting a total of 280 ms with 5 cryogen spurts interspersed lasting a	• Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
		total of 35 to 40 ms. The spot size was 6 mm. Laser energies ranged from 5 to 7 J/cm2. **Intervention: arm 2**: 450-nm visible blue light; With the BL mode, treatment hand piece delivered symmetrical peak wavelengths; 450 nm for the BL. The irradiance range was 3.5 to 7.0 mW/cm2 for the BL, with the radiant fluencies during a single treatment being 0.6 to 1.2 J/cm2.	
Langner 2007 **Country**: Europe **Study type**: RCT	N=148 **Sex**: Mixed **Number randomised: arm 1**: 73 **Number randomised: arm 2**: 75 **Inclusion details**: Patients aged 12–39 years with mild to moderate acne vulgaris of the face, with at least 15 inflammatory and/or non-inflammatory lesions but no more than three nodulocystic lesions and an acne grade of less than 7	**Intervention: arm 1**: a ready mixed, once daily gel containing clindamycin phosphate (1%) plus benzoyl peroxide (5%) **Intervention: arm 2**: a twice daily solution of erythromycin (4%) plus zinc acetate (1.2%)	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Langner 2008 **Country**: Europe **Study type**: RCT	N=130 **Sex**: Mixed **Number randomised: arm 1**: 65 **Number randomised: arm 2**: 65 **Inclusion details**: Patients aged 12–39 years with mild to moderate acne vulgaris of the face, with at least 15 inflammatory and/or non-inflammatory lesions but no more than three nodulocystic lesions and an acne grade of 2 or more, but less than 7	**Intervention: arm 1**: a ready-mixed once daily gel containing clindamycin phosphate 10 mg mL-1 + benzoyl peroxide 50 mg mL-1 (Duac; also known as Clindoxyl and Indoxyl **Intervention: arm 2**: a once-daily gel containing adapalene 0.1% (Differin)	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Leheta 2009 **Country**: Egypt **Study type**: RCT	N=45 **Sex**: Mixed **Number randomised: arm 1**: 15 **Number randomised: arm 2**: 15 **Number randomised: arm 3**: 15 **Inclusion details**: Age of 18 years or older, general good health, mild to moderately severe facial acne vulgaris.	**Intervention: arm 1**: non-purpuric PDL treatment with the RegenLite laser, using the following laser parameters: wavelength of 585 nm, pulse duration of 350, spot size of 7 mm, and fluence of 3 J/cm2 **Intervention: arm 2**: 0.1% tretinoin cream each evening and 5% benzoyl peroxide gel each morning. **Intervention: arm 3**: retinoic acid cream (0.025%) at bedtime for 2	• Treatment discontinuation for any reason

Study	Population*	Interventions	Outcomes
		weeks prior to TCA peeling.	
Leyden 1987 **Country**: United States **Study type**: RCT	N=109 **Sex**: Mixed **Number randomised: arm 1**: 55 **Number randomised: arm 2**: 54 **Inclusion details**: At least 14 years of age and had to have a minimum of ten but no more than sixty facial papules and pustules, and no more than six facial nodular cystic lesions	**Intervention: arm 1**: 2% erythromycin gel **Intervention: arm 2**: clindamycin phosphate 1% solution	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Leyden 2001 **Country**: United States **Study type**: RCT	N=164 **Sex**: Mixed **Number randomised: arm 1**: 82 **Number randomised: arm 2**: 82 **Inclusion details**: 12 years or older with mild to moderate facial acne vulgaris (10 - 60 inflammatory lesions, 10-200 facial noninflammatory lesions, no more than 2 facial nodular cystic lesions - no more than 5mm in diameter)	**Intervention: arm 1**: tazarotene 1% gel on alternate evenings with vehicle gel on intervening evenings **Intervention: arm 2**: adapalene 0.1% gel each evening	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects
Leyden 2002 **Country**: United States **Study type**: RCT	N=371 **Sex**: Female **Number randomised: arm 1**: 185 **Number randomised: arm 2**: 186 **Inclusion details**: Healthy women, at least 14 years of age, with regular menstrual cycles and moderate facial acne. Moderate facial acne was defined as a total facial count of 6 to 200 noninflammatory comedones, 10 to 75 inflammatory lesions (papules and pustules), and 5 or fewer nodules. Also required a normal Papanicolaou test result within the past 6 months or a low-grade abnormal Papanicolaou test result under medical evaluation, a negative pregnancy test result, and agreement to use a nonhormonal method of contraception if at risk for pregnancy.	**Intervention: arm 1**: tablets containing 20 g of EE and 100 g of LNG in a 28-day blister pack with 21 days of active medication followed by 7 days of placebo **Intervention: arm 2**: Placebo oral	• Clinician rated improvement in acne
Lucky 2001 **Country**: United States **Study type**: RCT	N=237 **Sex**: Mixed **Number randomised: arm 1**: 119 **Number randomised: arm 2**: 118 **Inclusion details**: 12 to 30 years of age, with grade 2 or 3 acne vulgaris (using the Cunliffe acne grade 1-5: 30 or more noninflammatory comedones and	**Intervention: arm 1**: adapalene cream 0.1% **Intervention: arm 2**: vehicle	• Treatment discontinuation for any reason • Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
	10 or more inflammatory lesions), who observed a washout period of 2 weeks of other treatments.		
Maleszka 2011 **Country**: Poland **Study type**: RCT	N=240 **Sex**: mixed **Number randomised: arm 1**: 120 **Number randomised: arm 2**: 120 **Inclusion details**: 14 years or older with a clinical diagnosis of moderate acne vulgaris.	**Intervention: arm 1**: Azithromycin 500mg o.d. for 3 days in the first week, followed by 500-mg tablets weekly to complete 10 weeks of treatment. **Intervention: arm 2**: Doxycycline (Hiramicin) 100-mg capsules twice a day on the first day of the treatment, followed by doxycycline 100-mg capsules once a day during 12 weeks of treatment	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Marazzi 2002a **Country**: United Kingdom **Study type**: RCT	N=188 **Sex**: Mixed **Number randomised: arm 1**: 95 **Number randomised: arm 2**: 93 **Inclusion details**: Facial acne vulgaris having 15–100 inflammatory lesions and/or 15–100 non-inflammatory lesions, but not more than three nodulocystic lesions.	**Intervention: arm 1**: gel containing isotretinoin 0.1%w/w and erythromycin 4.0%w/w in a vehicle of butylated hydroxytoluene, hydroxypropylcellulose and ethanol **Intervention: arm 2**: comparator gel contained benzoyl peroxide 5.0%w/w and erythromycin 3.0%w/w	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Milani 2003 **Country**: Italy **Study type**: RCT	N=60 **Sex**: Mixed **Number randomised: arm 1**: 30 **Number randomised: arm 2**: 30 **Inclusion details**: 15-35 years with mild to moderate acne vulgaris, defined as at least 10 inflammatory lesions and 10 non-inflamatory lesions, and no more than two nodulo-cystic lesions.	**Intervention: arm 1**: Hydrogen peroxide gel (Crystacide 1%) **Intervention: arm 2**: Benzoyl peroxide gel (PanOxyl 4%)	• Clinician rated improvement in acne
Mills 1986 **Country**: United States **Study type**: RCT	N=50 **Sex**: Mixed **Number randomised: arm 1**: 25 **Number randomised: arm 2**: 25 **Inclusion details**: Mild to moderately severe inflammatory acne vulgaris of the face (minimum of 10 inflammatory lesions)	**Intervention: arm 1**: 2.5% BPO gel **Intervention: arm 2**: vehicle	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Mills 1992 **Country**: United States	N=116 **Sex**: mixed **Number randomised: arm 1**: 59 (c)	**Intervention: arm 1**: Clindamycin phosphate 1% topical solution b.d. **Intervention: arm 2**: Erythromycin 2% topical pledgets b.d.	• Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
Study type: RCT	**Number randomised: arm 2**:57 (c) **Inclusion details**: Good health, 18-30 years, and with 10 to 50 lesions consisting of comedones, papules and pustules.		
Mohammadi 2019 **Country**: Iran **Study type**: RCT	N=110 **Sex**: mixed **Number randomised: arm 1**: 55 **Number randomised: arm 2**: 55 **Inclusion details**: Participants ranging from 12 to 30 years	**Intervention: arm 1**: niosomal CL 1% **Intervention: arm 2**: niosomal combination of BPO 1% and CL 1%	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Mokhtari 2017 **Country**: Iran **Study type**: RCT	N=72 **Sex**: Mixed **Number randomised: arm 1**: 32 **Number randomised: arm 2**: 40 **Inclusion details**: Mild-to-moderate acne and Fitzpatrick skin phototype III and IV, patient preference to experience laser therapy, having no acne scar, no pregnancy or breast feeding, not receiving topical or systemic antibiotic in the last 2 weeks, not receiving systemic steroid and retinoid in the last 6 months, photosensitivity, no tendency to developing hypertrophic and keloid scars.	**Intervention: arm 1**: benzoyl peroxide 5% with concomitant intense-pulsed light **Intervention: arm 2**: BPO only	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Na 2007 **Country**: Korea **Study type**: RCT (split face design)	N=60 (observations) **Sex**: Mixed **Number randomised: arm 1**: 30 **Number randomised: arm 2**: 30 **Inclusion details**: Mild to moderate acne	**Intervention: arm 1**: The irradiation source was a portable red light–emitting device, which had a wavelength of 635 to 670nm and an irradiance of 6mW. **Intervention: arm 2**: No treatment	• Clinician rated improvement in acne
Nestor 2016 **Country**: United States **Study type**: RCT	N=105 **Sex**: Mixed **Number randomised: arm 1**: 35 **Number randomised: arm 2**: 35 **Number randomised: arm 3**: 35 **Inclusion details**: Healthy male and female subjects 12 to 35 years old with Fitzpatrick Skin Types I to VI. Mild to moderate facial acne vulgaris, defined as 20 to 140 total lesions, with 10 to 90 noninflammatory and 10 to 50 inflammatory facial lesions, but no nodules or cysts (Investigator's Global Assessment Score of 2,	**Intervention: arm 1**: 445nm blue/630nm red light therapy mask (MASK) **Intervention: arm 2**: Neutrogena® Complete Acne Therapy System Overnight Acne Control Lotion (2.5% benzoyl peroxide) **Intervention: arm 3**: Neutrogena® All-in-1 Acne Control Facial Treatment (1% salicylic acid plus retinol) and the MASK treatment	• Treatment discontinuation for any reason • Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
	2.5, 3, or 3.5 using the Modified Cook's Scale)		
Ozolins 2004 **Country**: United Kingdom **Study type**: RCT	N=649 **Sex**: mixed **Number randomised: arm 1**: 131 **Number randomised: arm 2**: 130 **Number randomised: arm 3**: 130 **Number randomised: arm 4**: 127 **Number randomised: arm 5**: 131 **Inclusion details**: Mild to moderate acne vulgaris (acne grade 3·0 or less) and at least 15 inflamed and 15 non-inflamed lesions on the face	**Intervention: arm 1**: OXYTETRA-oral 500mg b.d. + PLC-topical **Intervention: arm 2**: MINO-oral 100mg + PLC-topical **Intervention: arm 3**: BPO- topical 5% + PLC-oral **Intervention: arm 4**: Combined formulation of BPO- topical 5%/ERYTH-topical 3%+ PLC-oral **Intervention: arm 5**: BPO-topical 5% + ERYTH-topical 2% + PLC-oral	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Palombo-Kinne 2009 **Country**: Europe **Study type**: RCT	N=1338 **Sex**: female **Number randomised: arm 1**: 530 **Number randomised: arm 2**: 541 **Number randomised: arm 3**: 267 **Inclusion details**: Female patients between 16 and 45 years old with mild to moderate papulopustular acne and without contraindications to COC use. Mild to moderate facial papulopustular acne was defined as 10–50 comedones (non-inflammatory lesions), 10–50 papules and pustules together (inflammatory lesions) and not more than three small nodules (inflammatory lesions); a normal Papanicolaou test result within the past 6 months; use of a non-hormonal method of contraception for sexually active patients	**Intervention: arm 1**: EE-oral 0.030mg + DNG-oral 2mg **Intervention: arm 2**: CPA-oral (2mg) + EE-oral (0.035mg) **Intervention: arm 3**: PLC-oral	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Papageorgiou 2000a **Country**: United Kingdom **Study type**: RCT	N=107 **Sex**: mixed **Number randomised: arm 1**: 27 **Number randomised: arm 2**: 30 **Number randomised: arm 3**: 25 **Number randomised: arm 4**: 25 **Inclusion details**: Mild to moderate acne, age ranging from 14 to 50 years, otherwise healthy	**Intervention: arm 1**: BLU-PT 415nm **Intervention: arm 2**: BR-LED 415 and 660nm **Intervention: arm 3**: White light control **Intervention: arm 4**: BPO-topical 5%	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Papageorgiou 2000b **Country**: United Kingdom	N=45 **Sex**: mixed **Number randomised: arm 1:** 15 **Number randomised: arm 2:** 15 **Number randomised: arm 3:** 15	**Intervention: arm 1**: Nels Cream (chloroxylenol + zinc oxide) b.d. **Intervention: arm 2**: Vehicle b.d.	• Treatment discontinuation for any reason

Study	Population*	Interventions	Outcomes
Study type: RCT	**Inclusion details:** Age ranging from 14 to 50 years, with grade I acne severity and a minimum of five inflammatory lesions on the face.	**Intervention: arm 3**: BPO-topical 5% b.d.	
Pazoki-Toroudi 2010 **Country**: Iran **Study type**: RCT	N=126 **Sex**: mixed **Number randomised: arm 1**: 35 (c) **Number randomised: arm 2**: 31 (c) **Number randomised: arm 3**: 40 (c) **Number randomised: arm 4**: 20 (c) **Inclusion details**: Age between 14 and 40 years, mild-to-moderate forms of acne vulgaris with at least 10 inflammatory lesions on the face (with a maximum of three nodules)	**Intervention: arm 1**: Azelaic acid 5% gel **Intervention: arm 2**: Erythromycin 2% gel **Intervention: arm 3**: Azelaic acid 5% + Erythromycin 2% gel **Intervention: arm 4**: Placebo	• Clinician rated improvement in acne
Pazoki-Toroudi 2011 **Country**: Iran **Study type**: RCT	N=150 **Sex**: mixed **Number randomised: arm 1**: 50 **Number randomised: arm 2**: 50 **Number randomised: arm 3**: 50 **Inclusion details**: Age between 14 and 40 years, mild-to-moderate forms of acne vulgaris with at least 10 inflammatory lesions on the face.	**Intervention: arm 1**: Azelaic acid 5% gel **Intervention: arm 2**: Clindamycin 2% gel **Intervention: arm 3**: Azelaic acid + Clindamycin gel	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Poli 2005 **Country**: France **Study type**: RCT	N=79 **Sex**: mixed **Number randomised: arm 1**: 42 **Number randomised: arm 2**: 39 **Inclusion details**: Greasy or normal or combination skin type, with phototypes II–IV, presenting with inflammatory (7–15 lesions) and retentional (15–30 lesions) mild to moderate acne vulgaris	**Intervention: arm 1**: Diacneal (0.1% retinaldehyde and 6% glycolic acid) **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Rademaker 2014 **Country**: New Zealand **Study type**: RCT	N=58 **Sex**: mixed **Number randomised: arm 1**: 29 **Number randomised: arm 2**: 29 **Inclusion details**: 25–55 years of age, with low-grade adult acne - defined as three or more acne lesions/ month on the face, for at least the last 3 months	**Intervention: arm 1**: 5mg isotretinoin once daily **Intervention: arm 2**: No treatment for 16 weeks	• Clinician rated improvement in acne
Ragab 2014 **Country**: Egypt	N=25 **Sex**: mixed **Number randomised: arm 1**: 15 **Number randomised: arm 2**: 10	**Intervention: arm 1**: PDT using 5-aminolevulinic acid (ALA) with intense pulsed light (IPL)	• Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
Study type: RCT	**Inclusion details**: Participants aged 14 years or over. Participants with mild to moderate acne vulgaris; determined by Evaluator Global Severity score. Score of 2 or 3 on scale before treatment	**Intervention: arm 2**: IPL alone	
Rao 2009 **Country**: India **Study type**: RCT	N=175 **Sex**: mixed **Number randomised: arm 1**: 88 **Number randomised: arm 2**: 87 **Inclusion details**: Aged between 12–40 years were with mild to moderate facial acne vulgaris - a minimum of 20 inflammatory (mean range at baseline 20–50) and 20 noninflammatory (mean range at baseline 20–100) lesions, otherwise in good health. Female patients had to be post-menopausal for 1 year, sterile or using birth control for > 6 months. Patients with any skin phototype were included in the study provided the degree of skin pigmentation did not interfere with the test site evaluation.	**Intervention: arm 1**: microsphere adapalene 0.1% gel O.D. **Intervention: arm 2**: adapalene 0.1% gel o.d.	• Clinician rated improvement in acne
Redmond 1997 **Country**: United States **Study type**: RCT	N=227 **Sex**: women **Number randomised: arm 1**: 114 **Number randomised: arm 2**: 113 **Inclusion details**: Female with 6 to 100 comedones, ten to 50 inflammatory lesions (papules or pustules), and fewer than five nodules	**Intervention: arm 1**: Ethinyl estradiol 0.035mg+norgestimate 0.18mg (week 1), 0.215mg (week 2), 0.250mg (week 3) **Intervention: arm 2**: Placebo	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Rizer 2001 **Country**: United States **Study type**: RCT	N=667 **Sex**: mixed **Number randomised: arm 1**: 168 **Number randomised: arm 2**: 84 **Number randomised: arm 3**: 166 **Number randomised: arm 4**: 84 **Number randomised: arm 5**: 165 **Inclusion details**: Acne Vulgaris	**Intervention: arm 1**: 1% Clindagel QD (water based formulation) **Intervention: arm 2**: Vehicle QD **Intervention: arm 3**: Clindagel BID **Intervention: arm 4**: Vehicle BID **Intervention: arm 5**: Cleocin T BID (gel based formulation)	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Rosen 2003 **Country**: United States **Study type**: RCT	N=34 **Sex**: female **Number randomised: arm 1**: 17 **Number randomised: arm 2**: 17 **Inclusion details**: Premenopausal women aged 18 to 46 years. Facial acne evidence by clinical examination.	**Intervention: arm 1**: 0.3 mg of ethinyl estradiol (EE)/0.15 mg of levonorgestrel **Intervention: arm 2**: 0.3 mg of EE/0.15 mg of desogestrel	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects

Study	Population*	Interventions	Outcomes
			• Clinician rated improvement in acne
Sadick 2010b **Country**: Israel **Study type**: RCT	N=63 **Sex**: mixed **Number randomised: arm 1**: 31 **Number randomised: arm 2**: 32 **Inclusion details**: At least 14 years old, at least four inflamed, facial, acne lesions	**Intervention: arm 1**: no!no! Skin device (broad spectrum light of 450-2000nm, 6 J/cm-2) **Intervention: arm 2**: Placebo	• Treatment discontinuation for any reason
Sagi 2000 **Country**: Israel **Study type**: RCT	N=207 **Sex**: mixed **Number randomised: arm 1**: 106 **Number randomised: arm 2**: 101 **Inclusion details**: Aged 16–25 years, suffering from mild to moderate facial acne, Cook's grade > 3, with 10–30 inflamed papules and pustules (but no cysts) aged 16–25 years, suffering from mild to moderate facial acne, Cook's grade > 3, with 10–30 inflamed papules and pustules (but no cysts)	**Intervention: arm 1**: 2.3% erythromycin (w/v) **Intervention: arm 2**: 2.3% erythromycin (w/v) + 1% bifonazole	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Schaller 2016 **Country**: Germany **Study type**: RCT	N=217 **Sex**: mixed **Number randomised: arm 1**: 108 **Number randomised: arm 2**: 109 **Inclusion details**: 12–45 years old, having facial acne vulgaris (defined as having 17–60 inflammatory lesions [papules and pustules], =1 facial nodular cystic lesion, 20–125 non-inflammatory facial lesions and an Investigator's Static Global Assessment [ISGA] score of 'mild' or 'moderate').	**Intervention: arm 1**: Benzoyl peroxide 3% + clindamycin 1% QD **Intervention: arm 2**: Azelaic acid 20% BID	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Seaton 2003 **Country**: United Kingdom **Study type**: RCT	N=41 **Sex**: mixed **Number randomised: arm 1**: 31 **Number randomised: arm 2**: 10 **Inclusion details**: Aged between 18 and 45 years with mild-to-moderate facial inflammatory acne defined as the presence of at least ten acne papules or pustules between the brow and jawline and an acne severity score of between 2 and 7 on the Leeds revised acne grading system.	**Intervention: arm 1**: Pulsed dye laser **Intervention: arm 2**: Sham laser	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Shalita 1984 **Country**: United States	N=178 **Sex**: mixed **Number randomised: arm 1**: 88 **Number randomised: arm 2**: 90	**Intervention: arm 1**: topical 1.5% erythromycin solution	• Treatment discontinuation for any reason

Study	Population*	Interventions	Outcomes
Study type: RCT	**Inclusion details**: Moderate acne vulgaris of the face,defined as at least ten papules or pustules and at least five open or closed comedones.	**Intervention: arm 2**: topical 1% clindamycin phosphate solution	• Treatment discontinuation due to side effects • Clinician rated improvement in acne
Shalita 1999 **Country**: United States **Study type**: RCT	N=446 **Sex**: mixed **Number randomised: arm 1**: 150 **Number randomised: arm 2**: 148 **Number randomised: arm 3**: 148 **Inclusion details**: 14 years or older with mild to moderate facial acne vulgaris defined as 10 to 60 inflammatory lesions, 25 to 200 noninflammatory lesions, and six or less nodular cystic lesions.	**Intervention: arm 1**: Topical tazarotene 0.1% o.d. **Intervention: arm 2**: Topical tazarotene 0.05% o.d. **Intervention: arm 3**: Topical vehicle o.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Shalita 2005 **Country**: United States **Study type**: RCT	N=1026 **Sex**: mixed **Number randomised: arm 1**: 386 **Number randomised: arm 2**: 127 **Number randomised: arm 3**: 385 **Number randomised: arm 4**: 128 **Inclusion details**: 12 years of age or older with mild to moderate facial acne vulgaris and an Investigator's Static Global Assessment (ISGA) score of 2 or greater at baseline. Also a minimum of 17 but no more than 40 facial inflammatory lesions, including nasal lesions, and a minimum of 20, but no more than 150 facial non-inflammatory lesions, excluding nasal lesions.	**Intervention: arm 1**: Clindamycin foam o.d. **Intervention: arm 2**: Vehicle foam o.d. **Intervention: arm 3**: Clindamycin gel 1% o.d. **Intervention: arm 4**: Vehicle gel o.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Shwetha 2014 **Country**: India **Study type**: RCT	N=120 **Sex**: mixed **Number randomised: arm 1**: 60 **Number randomised: arm 2**: 60 **Inclusion details**: Mild to moderate acne on face as per Indian Acne Alliance Grading for Severity of acne, aged between 12 to 25 years	**Intervention: arm 1**: topical 1% clindamycin + 0.1% adapalene **Intervention: arm 2**: topical 1% clindamycin + 2.5% benzoyl peroxide	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Smith 1980b **Country**: United States **Study type**: RCT	N=59 **Sex**: mixed **Number randomised: arm 1**: 29 **Number randomised: arm 2**: 30 **Inclusion details**: At least ten inflammatory papules and/or pustules and no more than three nodulocystic lesions on the face, otherwise in good health	**Intervention: arm 1**: 20% Benzoyl-peroxide b.d. **Intervention: arm 2**: Vehicle b.d.	• Treatment discontinuation for any reason

Study	Population*	Interventions	Outcomes
Smith 2006 **Country**: United States **Study type**: RCT	N=48 **Sex**: mixed **Number randomised: arm 1**: 24 **Number randomised: arm 2**: 24 **Inclusion details**: Mild to moderate facial acne vulgaris, 12 years of age or older, had 20 to 50 papules and pustules, 20 to 60 open and closed comedones (excluding those on the nose), and no more than 1 nodule in the facial treatment area	**Intervention: arm 1**: NeoBenz (5.5% benzoyl peroxide microsphere cream) b.d. **Intervention: arm 2**: Triaz (6% benzoyl peroxide gel) b.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects
Sommer 1997 **Country**: United Kingdom **Study type**: RCT	N=56 **Sex**: mixed **Number randomised: arm 1**: 28 **Number randomised: arm 2**: 28 **Inclusion details**: Aged 12-25 years with predominantly mild to moderate facial acne vulgaris, and between 15 and 75 inflamed papules and pustules, and off of anti-acne treatment for one month	**Intervention: arm 1**: Fucidin lotion (fusidic acid) **Intervention: arm 2**: Vehicle (Fucidin base)	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Stinco 2007 **Country**: Italy **Study type**: RCT	N=65 **Sex**: mixed **Number randomised: arm 1**: 25 **Number randomised: arm 2**: 20 **Number randomised: arm 3**: 20 **Inclusion details**: Mild or moderate comedonic or papulopustular acne, localized on the face. each patients had a minimum of 20 facial non-inflammatory lesions (open and closed comedones) and 10 inflamed lesions. Also required to be in good health and have not received any oral or topical anti-acne therapy in the 8 weeks prior the study.	**Intervention: arm 1**: Azelaic acid o.d. **Intervention: arm 2**: Benzoyl peroxide o.d. **Intervention: arm 3**: Adapalene o.d.	• Treatment discontinuation for any reason
Stoughton 1987 **Country**: United States **Study type**: RCT	N=50 **Sex**: mixed **Number randomised: arm 1**: 25 **Number randomised: arm 2**: 25 **Inclusion details**: Patients between the ages of twelve and thirty-five with acne and a minimum of ten erythematous facial papules and pustules	**Intervention: arm 1**: Benzoyl peroxide b.d. **Intervention: arm 2**: Chlorhexidine gluconate b.d.	• Treatment discontinuation for any reason
Strauss 1984b **Country**: United States **Study type**: RCT	N=22 **Sex**: mixed **Number randomised: arm 1**: 12 **Number randomised: arm 2**: 10 **Inclusion details**: Aged between 13 and 35 years of age with mild-to-moderate ache vulgaris. Each	**Intervention: arm 1**: 4% erythromycin solution containing 1.2% zinc acetate **Intervention: arm 2**: Vehicle	• Treatment discontinuation for any reason

Study	Population*	Interventions	Outcomes
	volunteer had to have P. acnes bacterial counts greater than 10 and free fatty acids greater than 8% of the skin surface lipids in two baseline determinations.		
Swinyer 1988 **Country**: United States **Study type**: RCT	N=60 **Sex**: mixed **Number randomised: arm 1**: 30 **Number randomised: arm 2**: 30 **Inclusion details**: Aged 16 to 25 with acne vulgaris grades I and II. More than 20 total facial lesions but no nodular-cystic lesions	**Intervention: arm 1**: Benzac W5 (5% benzoyl peroxide gel) b.d. **Intervention: arm 2**: Cleocin T (1% clindamycin phosphate solution) b.d.	• Clinician rated improvement in acne
Tan 2018 **Country**: Canada **Study type**: RCT	N=123 **Sex**: mixed **Number randomised: arm 1**: 32 **Number randomised: arm 2**: 29 **Number randomised: arm 3**: 32 **Number randomised: arm 4**: 30 **Inclusion details**: Aged between 12 and 35 years of age with mildto- moderate facial acne vulgaris, assessed using the Investigator Global Assessment Scale (IGA of 2 or 3 on a scale from 0=clear to 5=very severe) with a minimum of 10 inflammatory lesions, 10 to 100 non-inflammatory lesions, and no more than one nodule or cyst on the face, as well as Phototype of I to IV on the Fitzpatrick scale	**Intervention: arm 1**: A/BPO-3h: adapalene 0.1% + benzoyl peroxide 2.5% - daily for 3h **Intervention: arm 2**: A/BPO-moisturizer: adapalene 0.1% + benzoyl peroxide 2.5%- daily overnight with moisturizer **Intervention: arm 3**: A/BPO-EoN: adapalene 0.1% + benzoyl peroxide 2.5%- every other night **Intervention: arm 4**: A/BPO-EN: adapalene 0.1% + benzoyl peroxide 2.5%- - daily overnight	• Treatment discontinuation due to side effects
Thiboutot 2001a **Country**: United States **Study type**: RCT	N=168 **Sex**: mixed **Number randomised: arm 1**: 84 **Number randomised: arm 2**: 84 **Inclusion details**: Between 12 and 35 years of age, with mild or moderate facial acne vulgaris (global facial grades 1-5, according to Cunliffe acne grades7), inflammatory lesion counts (papules and pustules) between 10 and 40 inclusive, and a minimum of 20 and a maximum of 125 noninflammatory lesions (open and closed comedones).	**Intervention: arm 1**: Adapalene gel 0.1% **Intervention: arm 2**: Tretinoin gel 0.025%	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Thiboutot 2006 **Country**: North America **Study type**: RCT	N=653 **Sex**: mixed **Number randomised: arm 1**: 258 **Number randomised: arm 2**: 261 **Number randomised: arm 3**: 134 **Inclusion details**: 12 years or older, with 20 to 100 noninflammatory facial lesions, 20	**Intervention: arm 1**: ADAP 0.3% gel **Intervention: arm 2**: ADAP 0.1% gel **Intervention: arm 3**: Vehicle gel	• Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
	to 50 inflammatory facial lesions, and no nodules or cysts		
Thiboutot 2007 **Country**: United States **Study type**: RCT	N=512 **Sex**: mixed **Number randomised: arm 1**: 149 **Number randomised: arm 2**: 148 **Number randomised: arm 3**: 149 **Number randomised: arm 4**: 71 **Inclusion details**: 12 years of age or older, with 30 to 100 noninflammatory facial lesions, 20 to 50 inflammatory facial lesions, and no nodules or cysts	**Intervention: arm 1**: ADAP 0.1%/BPO 2.5% gel **Intervention: arm 2**: ADAP 0.1% gel **Intervention: arm 3**: BPO 2.5% gel **Intervention: arm 4**: Vehicle gel	• Treatment discontinuation due to side effects • Clinician rated improvement in acne
Thiboutot 2009 **Country**: United States **Study type**: RCT	N=139 **Sex**: mixed **Number randomised: arm 1**: 69 **Number randomised: arm 2**: 70 **Inclusion details**: Aged 12 to 45 years with mild to moderate facial acne vulgaris (10–100 noninflammatory lesions; 17–60 inflammatory lesions; =2 nodulocystic lesions on the face, excluding the nose). Females of childbearing potential were required to have a negative urine pregnancy test result and to use an acceptable method of contraception throughout the study.	**Intervention: arm 1**: Salicylic acid cleanser 2% BID + salicylic acid toner 2% QD + solubilized BPO gel 5% BID **Intervention: arm 2**: Control cleanser BID + Clindamycin 1%-benzoyl peroxide gel 5% BID	• Treatment discontinuation for any reason
Thielitz 2015 **Country**: Germany **Study type**: RCT	N=55 **Sex**: female **Number randomised: arm 1**: 17 **Number randomised: arm 2**: 19 **Number randomised: arm 3**: 19 **Inclusion details**: Female patients with mild-to-moderate acne including 'late-type acne', aged 18–45 years. Acne global severity grades 2–4 (mild – moderate – moderately severe), according to a modified Investigator's Static Global Assessment (ISGA) and 2–7, according to the Leeds Revised Acne Grading Scale (LRAGS, a pictorial acne grading system) corresponding to mild (2–3) and moderate (4–7) forms.	**Intervention: arm 1**: Azelaic acid 15% for 9 months (results reported for treatment phase only, 12 weeks) **Intervention: arm 2**: Azelaic acid 15% for 3 months, followed by 6 months observation (results reported for treatment phase only, 12 weeks) **Intervention: arm 3**: Adapalene gel 0.1% for 9 months (results reported for treatment phase only, 12 weeks)	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Thorneycroft 2004 **Country**: Germany **Study type**: RCT	N=1154 **Sex**: female **Number randomised: arm 1**: 568 **Number randomised: arm 2**: 586 **Inclusion details**: Otherwise healthy female subjects ranging in age from 15 to 40 years without	**Intervention: arm 1**: 30micrograms ethinyl estradiol + 3milligrams drospirenone **Intervention: arm 2**: 35micrograms ethinyl	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects

Study	Population*	Interventions	Outcomes
	contraindications for combined oral contraceptive use with mild to moderate acne vulgaris, having 6 to 100 comedones (noninflammatory lesions), 10 to 50 papules or pustules together, and not more than 5 nodules on the face (inflammatory lesions). Normal gynaecologic examination and cervical smear within the last 6 months; negative pregnancy test; 3 spontaneous withdrawal bleedings following delivery, abortion, or lactation; and avoidance of comedogenic cosmetics or sunscreens, sex hormone preparations, and antiacne therapy	estradiol + 0.18, 0.215, 0.25mg norgestimate	• Clinician rated improvement in acne
Tirado-Sanchez 2009 **Country**: Mexico **Study type**: RCT	N=87 **Sex**: mixed **Number randomised: arm 1**: 39 **Number randomised: arm 2**: 24 **Number randomised: arm 3**: 24 **Inclusion details**: Mild to moderate inflammatory acne, meaning 10–50 inflammatory lesions (papules and pustules) with an absence of nodulocystic lesions	**Intervention: arm 1**: Superoxidised solution (an electrochemically processed aqueous solution manufactured from pure water and sodium chloride) **Intervention: arm 2**: Benzoyl peroxide 5% gel **Intervention: arm 3**: Placebo	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Tirado-Sanchez 2013 **Country**: Mexico **Study type**: RCT	N=131 **Sex**: mixed **Number randomised: arm 1**: 43 **Number randomised: arm 2**: 43 **Number randomised: arm 3**: 45 **Number randomised: arm 4**: 40 **Inclusion details**: 18 years or older with at least ten non-inflammatory acne lesions and <30 inflammatory lesions on the entire face. Patients with childbearing potential were required to use birth control and to have a negative pregnancy test result at the beginning of the study	**Intervention: arm 1**: Adapalene 0.1% gel **Intervention: arm 2**: Adapalene 0,3% gel **Intervention: arm 3**: Tretinoin 0.05% gel **Intervention: arm 4**: Placebo gel	• Treatment discontinuation for any reason • Clinician rated improvement in acne
Tong 1994 **Country**: Australia **Study type**: RCT	N=96 **Sex**: mixed **Number randomised: arm 1**: 48 **Number randomised: arm 2**: 48 **Inclusion details**: Healthy, non-institutionalized patients free of intercurrent disease and over 12 years old, with a minimum of six and maximum of 50 inflammatory papules, and no more than six nodulocystic lesions.	**Intervention: arm 1**: Metronizadole 0.75% **Intervention: arm 2**: Placebo	• Treatment discontinuation for any reason

Study	Population*	Interventions	Outcomes
van Vloten 2002 **Country**: Europe **Study type**: RCT	N=125 **Sex**: female **Number randomised: arm 1**: 82 **Number randomised: arm 2**: 43 **Inclusion details**: Women aged 16 to 35 years (30 years for smokers), otherwise healthy with mild-to-moderate facial acne (comedones, papules, pustules, nodules <0.5 cm), who had minor occurrence of seborrhea and/or hair growth on the upper lip, chin and chest. At least 8 papulopustular lesions on the face.	**Intervention: arm 1**: 30 micrograms EE and 3 mg DRSP (Yasmin) **Intervention: arm 2**: 35 micrograms EE and 2 mg CPA (Diane 35)	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Wiegell 2006b **Country**: Denmark **Study type**: RCT	N=36 **Sex**: mixed **Number randomised: arm 1**: 21 **Number randomised: arm 2**: 15 **Inclusion details**: 18 years or older with general good health and more than 12 inflammatory acne lesions in the face	**Intervention: arm 1**: MAL 2g RED-PDT **Intervention: arm 2**: No treatment	• Clinician rated improvement in acne
Wolf 2003 **Country**: United States **Study type**: RCT	N=249 **Sex**: Mixed **Number randomised: arm 1**: 125 **Number randomised: arm 2**: 124 **Inclusion details**: Patients with mild to moderate acne vulgaris, at least 12 years of age, and had a global severity grade ranging from 2 to 8, according to the Leeds Revised Acne Grading System. They had 10 to 50 inflammatory facial lesions (no more than 3 nodules or cysts) and 20 to 150 non-inflammatory facial lesions.	**Intervention: arm 1**: adapalene gel 0.1% plus clindamycin phosphate lotion 1% b.d. **Intervention: arm 2**: clindamycin plus vehicle b.d.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Xu 2016 **Country**: China **Study type**: RCT	N=1016 **Sex**: Mixed **Number randomised: arm 1**: 500 **Number randomised: arm 2**: 516 **Inclusion details**: Aged 12–45 years (inclusive) diagnosed with mild to moderate acne, with at least 17, but not more than 60 facial inflammatory lesions (papules plus pustules), at least 20 but not more than 125 facial non-inflammatory lesions (open and closed comedones), no more than 1 facial nodular lesion with no cystic lesions, and who had a baseline Investigator's Static Global Assessment (ISGA) score of 2 or 3	**Intervention: arm 1**: topical clindamycin 1%/benzoyl peroxide 5% once-daily gel **Intervention: arm 2**: clindamycin 1% twice-daily gel	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne

Study	Population*	Interventions	Outcomes
Yentzer 2010 **Country**: United States **Study type**: RCT	N=26 **Sex**: Mixed **Number randomised: arm 1**: 13 **Number randomised: arm 2**: 13 **Inclusion details**: 12 years and older with an investigator global assessment (IGA) of mild to moderate acne vulgaris (score of 2 or 3)	**Intervention: arm 1**: once daily application of clindamycin phosphate 1.2%–tretinoin 0.025% gel combination product **Intervention: arm 2**: separate daily applications of clindamycin phosphate gel 1% and tretinoin cream 0.025% (C gel 1 T cream) for a total of 2 applications daily.	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Zayed 2019 **Country**: Egypt **Study type**: RCT	N=45 **Sex**: female **Number randomised: arm 1**: 15 **Number randomised: arm 2**: 15 **Number randomised: arm 3**: 15 **Inclusion details**: Mild to moderate acne vulgaris (active lesions). Skin phototypes III and IV. No topical or systemic treatment for the preceding 1 month. Having realistic expectations	**Intervention: arm 1**: Sequential peeling sessions with 70% Glycolic Acid kept for 3 minutes followed by 20% Salicylic Acid once every 2 weeks for 3 months **Intervention: arm 2**: A combination of sequential peeling sessions and oral doxycycline, 100 mg twice/day for 1 month and then 100 mg/day for 2 months. **Intervention: arm 3**: Oral doxycycline for 3 months	• Treatment discontinuation for any reason • Treatment discontinuation due to side effects • Clinician rated improvement in acne
Zheng 2019 **Country**: China **Study type**: RCT (split-face)	N=68 (observations) **Sex**: Mixed **Number randomised: arm 1**: 34 **Number randomised: arm 2**: 34 **Inclusion details**: Mild to moderate acne, age range of 18–35 years. The severity of acne was classified as mild (grade I), moderate (grade II and III), and severe (grade IV) according to the Pillsbury grading system. Patients with grade I–III acne were enrolled in this clinical trial.	**Intervention: arm 1**: 0.01% adapalene plus 5% benzoyl peroxide **Intervention: arm 2**: 2% supramolecular salicylic acid	• Clinician rated improvement in acne

**Population most often refers to people randomised. However, sometimes these could be observations, such as when parts of the body are randomised as in split face designs (this is indicated in brackets). For some studies only numbers who completed the trial were reported rather than numbers randomised and this is indicated by (c) behind the total N.*

Abbreviations: AZE + SAL peel: azelaic acid and salicylic acid peel; 1319-LSR: 1319 nm laser photochemical therapy; 589-LSR: 589 nm laser photochemical therapy; 5ALA: 5-aminolevulinic acid with unspecified light source; 5ALA-IPL-PDT: 5 aminolevulinic acid using intense pulsed light; 5ALA-KTP-PDT: 5-aminolevulinic acid using KTP (potassium titanyl phosphate) laser; 5ALA-PDL-PDT: 5-aminolevulinic acid using pulsed dye laser; 5ALA-RED-PDT: 5-aminolevulinic acid using red light; 5ARI: 5-alpha-reductase inhibitors; ACTINAC: Actinac (4% chloramphenicol, 4% hydrocortisone acetate, 2.4% butoxyethyl nicotinate, 2.4% allantoin, 32% precipitated sulphur); ADAP + BPO: adapalene + benzoyl peroxide; ADAP: adapalene; AFA peel: amino fruit acid (available in creams, pads, lotions); AZE: azelaic acid; AZITH: azithromycin; BIFON: bifonazole; BiRF: bipolar radiofrequency; BLU-PT: blue light emitting diode therapy (LED) photochemical therapy; BPO + CLIND: benzoyl peroxide 5%/clindamycin 1%; BPO: benzoyl peroxide; BR-LED: blue + red light; BUTEN: butenifine; CD271: CD 271 alcoholic gel; CHLOR: chlorhexidine gluconate/digluconate; CIPRO: ciprofloxacine; CLIND: clindamycin; CLIND + TRET: clindamycin 1% + tretioin 0.025%; CLIND+ ZINC: clindamycin with zinc acetatedihydrate; CMA:

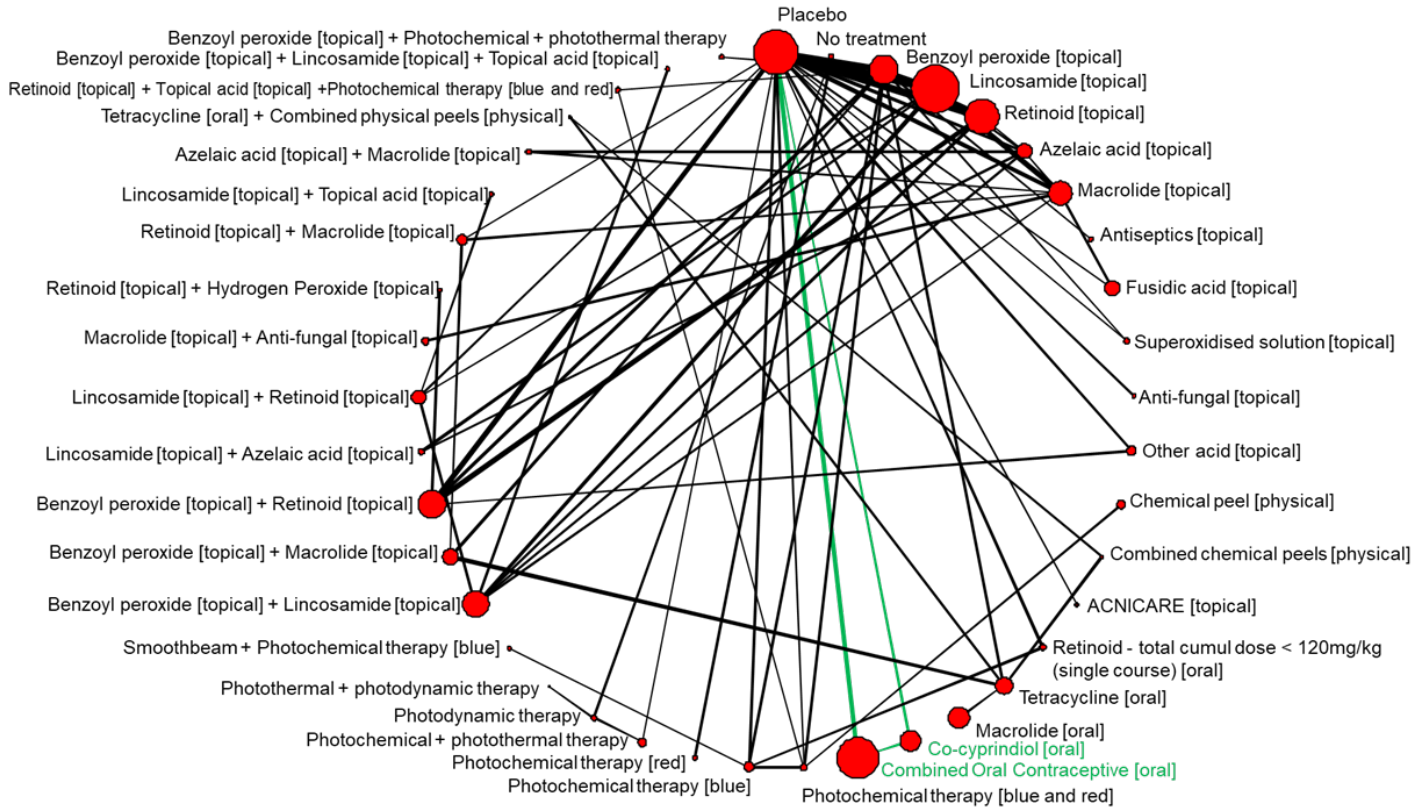
chlormadinone acetate; CO2: fractional CO2 laser; CPA + EE: co-cyprindiol (ethinylestradiol with cyproterone acetate); CPA: cyproterone acetate; DAPS: dapsone; DEM: demeclocycline; DOXY: doxycycline; DRSP: drospirenone; EE + DNG: estradiol (valerate) + dienogest; EE + DROS: ethinylestradiol + drospirenone; EE + LNG: ethinylestradiol+levonorgestrel; EE: ethinylestradiol; EE+DSGethinylestradiol+ desogestrel; EE+NGM: ethinylestradiol+norgestimate; ERYTH + ZINC: erythromycin with zinc acetate dihydrate; ERYTH:erythromycin; FCA: fusidic acid (sodium fusidate); FMR: fractional microneedling radiofrequency; GLY peel: glycolic acid; GOLDMP: gold microparticles; HPS: hydrogen peroxide; IPL: intense pulsed light; IPL+VAC: intense pulsed light + vacuum; IRL: near infrared light; ISO<120.Alt<0.5: isotretinoin ≥0.5mg/kg/every other day total cumulative dose < 120mg/kg; ISO<120.Alt≥0.5: isotretinoin <0.5mg/kg/every other day total cumulative dose < 120mg/kg; ISO<120.Daily<0.5: isotretinoin ≥0.5mg/kg/day total cumulative dose < 120mg/kg; ISO<120.Daily≥0.5: isotretinoin<0.5mg/kg/day total cumulative dose < 120mg/kg; ISO<120.Other<0.5: isotretinoin≥0.5mg/kg/less frequently total cumulative dose < 120mg/kg; ISO<120.Other≥0.5: isotretinoin<0.5mg/kg/less frequently total cumulative dose < 120mg/kg; ISO≥120.Alt<0.5: isotretinoin≥0.5mg/kg/every other day total cumulative dose ≥ 120mg/kg; ISO≥120.Alt≥0.5: isotretinoin<0.5mg/kg/every other day total cumulative dose ≥ 120mg/kg; ISO≥120.Daily<0.5: ISOisotretinoin ≥0.5mg/kg/day total cumulative dose ≥ 120mg/kg; ISO≥120.Daily≥0.5: isotretinoin<0.5mg/kg/day total cumulative dose ≥ 120mg/kg; ISO≥120.Other<0.5: isotretinoin≥0.5mg/kg/less frequently total cumulative dose ≥ 120mg/kg; ISO≥120.Other≥0.5: isotretinoin<0.5mg/kg/less frequently total cumulative dose ≥ 120mg/kg; ISO: isotretinoin; JES peel: Jessner's peel; KTP: potassium titanyl phosphate laser; LEVA: levamisole; LNG: levonorgestrel; LYME: lymecycline; MAL with occlusion: methyl aminolevulinate ; MAL without occlusion: methylaminolevulinate ; MAL-DL-PDT: methyl aminolevulinate using daylight; MAL-IPL-PDT: methyl aminolevulinate using intense pulsed light; MAL-KTP-PDT: methyl aminolevulinate using potassium titanyl phosphate (KTP) laser; MAL-RED-PDT: methyl aminolevulinate using red light; MD: microdermabrasion; METF: metformin; MET: metronidazole; MICO: miconazole nitrate; MINO: minocycline; MOT:motretinide; n: number of participants randomised/completed to/in each trial arm; NAD: nadifloxacin; NAFL: fractional erbiumglass laser; NBUVB: nearband ultraviolet light; Nd:YAG: long-pulse neodymium-doped yttrium aluminum garnet laser; NELS: Nels Cream (chloroxylenol + zinc oxide); NICO: nicotinamide (NIACINAMID); no!no!: no!no! skin device (broad spectrum light of 450-2000nm, 6 J/cm-2); NOR + EE: norethisterone + ethinylestradiol; OXYTETRA: oxytetracycline; PBBL: pneumatic broadband light therapy; PDL: pulsed dye laser; PLC: placebo; PLC-physical: sham physical treatment; PRED: prednisolone; PYA peel: pyruvic acid; RED: red light; RETINOL: retinol (vitamin A); ROXI: roxithromycin; SAL peel: salicylic acid; SARE: sarecyclin; SOS: superoxidised solution (an electrochemically processed aqueous solution manufactured from pure water and sodium chloride); SPIRO: spironolactone; TAZ: tazarotene; TCA peel: trichloroacetic acid; TETRA: tetracycline; TRET: tretinoin (retin A, all-trans reinoic acid); TRIC: triclozan; ZINCG: zinc gluconate

The network plots of treatment classes for efficacy (% change in total lesion count from baseline), discontinuation for any reason, and discontinuation due to side effects analysed in NMA are shown in Figure 1, Figure 2, and Figure 3, for each outcome respectively. In each network plot, the width of lines is proportional to the number of trials that make each direct comparison; 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 trials). In addition, the numbers of observations on each treatment class, and on each intervention within class, are shown in Table 3, Table 4 and Table 5, for the outcomes of efficacy, discontinuation for any reason, and discontinuation due to side effects, respectively.

See the full evidence tables in appendix D and the NMA results including forest plots, effects versus placebo and ranking tables in appendix E. Where bias models suggested evidence of bias, bias-adjusted effects versus placebo and corresponding ranking tables are also shown. Full NMA methods including NMA models, inconsistency checks, bias-adjusted models, as well as NMA results are provided in appendix M.

Efficacy (% change in total lesion from baseline)

Figure 1. Efficacy network of treatment classes for people with mild to moderate acne.



Treatment classes and lines in green indicate treatments and comparisons relevant to females only.

Table 3. Treatment classes, interventions and numbers of observations made on each, in the efficacy network of treatments for people with mild to moderate acne.

Class	n	Treatment	n	Duration	n
Placebo	2698F 2005M	Placebo [oral]	722F 29M	12 to <24 weeks	39F 29M
				24+ weeks	683F
		Placebo [topical]	1945	6 to <12 weeks	231
				12 to <24 weeks	1714
		Placebo [physical]	31	12 to <24 weeks	31
No treatment	39	No treatment	39	NA	39
Benzoyl peroxide [topical]	1109	Benzoyl peroxide [topical]	1109	6 to <12 weeks	246
				12 to <24 weeks	834
				24+ weeks	29
Lincosamide [topical]	3073	Clindamycin [topical]	2910	6 to <12 weeks	236
				12 to <24 weeks	2674
		Clindamycin [topical] with Zinc Acetate Dihydrate	163	12 to <24 weeks	163
Retinoid [topical]	1623	Adapalene [topical]	1377	6 to <12 weeks	30
				12 to <24 weeks	1315
				24+ weeks	32
		Tazarotene [topical]	246	12 to <24 weeks	246
Azelaic acid [topical]	301	Azelaic Acid [topical]	301	6 to <12 weeks	30
				12 to <24 weeks	271
Macrolide [topical]	765	Erythromycin [topical]	669	6 to <12 weeks	108
				12 to <24 weeks	561
		Erythromycin [topical] with Zinc Acetate Dihydrate	96	6 to <12 weeks	11
				12 to <24 weeks	85
Antiseptics [topical]	30	Hydrogen Peroxide [topical]	30	6 to <12 weeks	30
Fusidic acid [topical]	310	Fusidic acid (Sodium Fusidate) [topical]	310	6 to <12 weeks	36
				12 to <24 weeks	274
Superoxidised solution [topical]	39	Superoxidised solution [topical]	39	12 to <24 weeks	39
Anti-fungal [topical]	20	Ketoconazole [topical]	20	6 to <12 weeks	20
Other acid [topical]	106	Salicylic Acid [topical]	64	6 to <12 weeks	31
				12 to <24 weeks	33
		Diacneal (0.1% retinaldehyde and 6% glycolic acid) [topical]	42	12 to <24 weeks	42
Chemical peel [physical]	101	Jessner's Peel [physical]	20	12 to <24 weeks	20

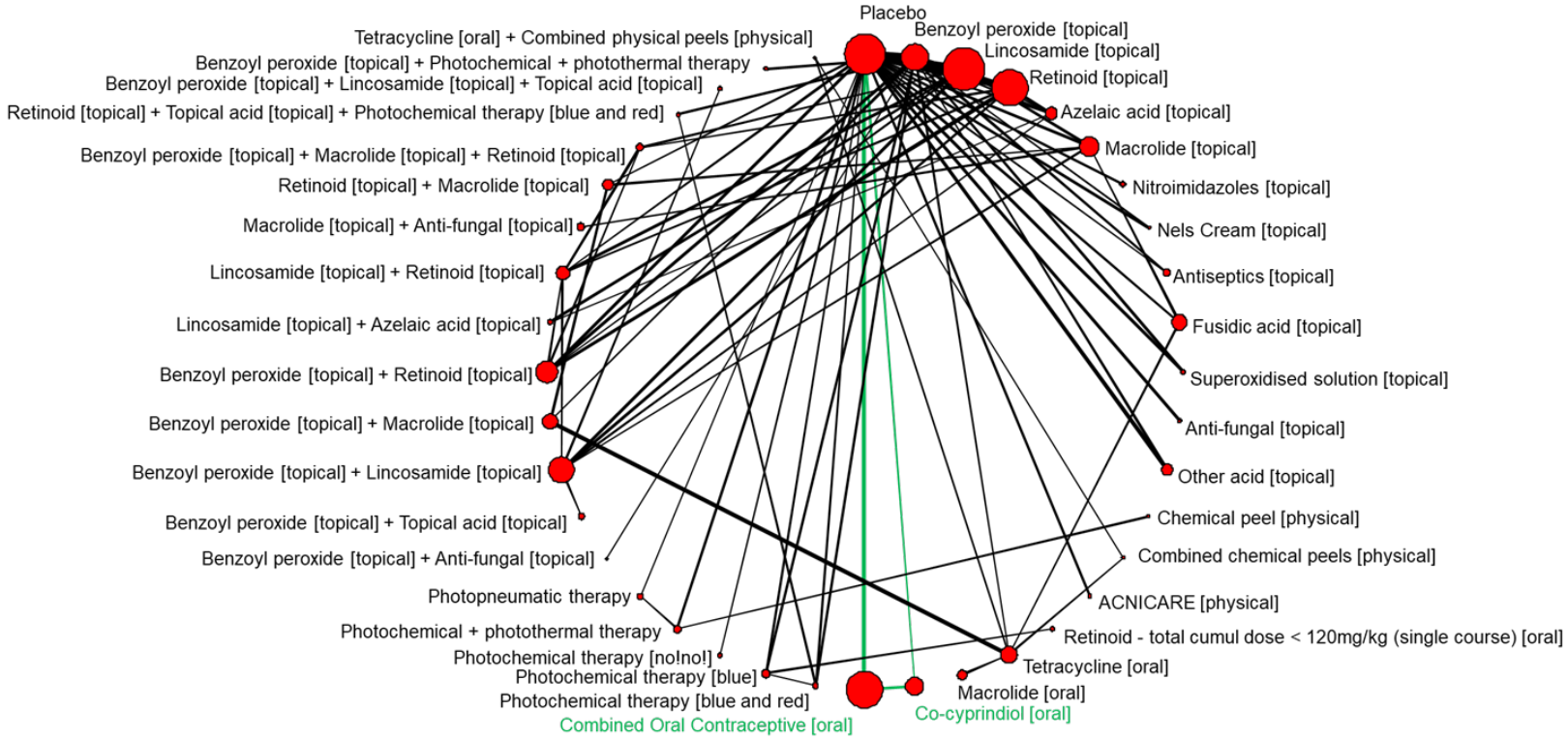
Class	n	Treatment	n	Duration	n
		Mandelic Acid	25	12 to <24 weeks	25
		Salicylic Acid [physical]	56	6 to <12 weeks	11
				12 to <24 weeks	45
Combined chemical peels [physical]	14	Salicylic Acid [physical] + Glycolic Acid [physical]	14	12 to <24 weeks	14
ACNICARE [topical]	20	ACNICARE (triethyl citrate + ethyl linoleate) [topical]	20	12 to <24 weeks	20
Retinoid - total cumulative dose < 120mg/kg (single course) [oral]	54	Isotretinoin < 120. Daily< 0.5 [oral]	54	6 to <12 weeks	25
				12 to <24 weeks	29
Tetracycline [oral]	388	Doxycycline [oral]	127	12 to <24 weeks	127
		Minocycline [oral]	130	12 to <24 weeks	130
		Oxytetracycline [oral]	131	12 to <24 weeks	131
Macrolide [oral]	618	Azithromycin [oral]	109	12 to <24 weeks	109
		Erythromycin [oral]	34	0 to <6 weeks	34
Co-cyprindiol [oral]	584	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	584	24+ weeks	584
Combined Oral Contraceptive [oral]	2313	Estradiol (valerate) [oral] + Dienogest [oral]	530	24+ weeks	530
		Ethinylestradiol [oral] + Desogestrel [oral]	102	24+ weeks	102
		Ethinylestradiol [oral] + Drospirenone [oral]	626	12 to <24 weeks	11
				24+ weeks	615
		Ethinylestradiol [oral] + Levonorgestrel [oral]	303	24+ weeks	303
		Ethinylestradiol [oral] + Norgestimate [oral]	752	24+ weeks	752
Photochemical therapy [blue and red]	69	Blue + Red light	69	NA	69
Photochemical therapy [blue]	138	Blue Light LED	138	NA	138
Photochemical therapy [red]	28	Red light	28	NA	28
Photochemical + photothermal therapy	107	Intense Pulsed Light (IPL)	27	NA	27
		Pulsed Dye Laser	64		64
		Pulsed Dye Laser + Long-pulse neodymium-doped yttrium aluminum garnet (Nd:YAG) laser	16		16
Photodynamic therapy	36	5-Aminolevulinic Acid (ALA) using red light	9	NA	9
		PDT using 5-aminolevulinic acid (ALA) with intense pulsed light (IPL)	15		15
		Methyl Aminolevulinate (MAL) using red light	12		12
Photothermal + photodynamic therapy	9	Near infrared light + 5-Aminolevulinic Acid (ALA) using red light	9	NA	9
Smoothbeam + Photochemical therapy [blue]	24	Smoothbeam + Blue Light LED	24	NA	24
Benzoyl peroxide [topical] + Lincosamide [topical]	992	Benzoyl peroxide [topical] + Clindamycin [topical]	992	12 to <24 weeks	992
Benzoyl peroxide [topical] + Macrolide [topical]	351	Benzoyl peroxide [topical] + Erythromycin [topical]	351	12 to <24 weeks	351
Benzoyl peroxide [topical] + Retinoid [topical]	1057	Benzoyl peroxide [topical] + Adapalene [topical]	1057	6 to <12 weeks	57
				12 to <24 weeks	968
				24+ weeks	32

Class	n	Treatment	n	Duration	n
Lincosamide [topical] + Azelaic acid [topical]	44	Clindamycin [topical] + Azelaic Acid [topical]	44	12 to <24 weeks	44
Lincosamide [topical] + Retinoid [topical]	276	Clindamycin [topical] + Adapalene [topical]	184	12 to <24 weeks	184
		Clindamycin [topical] + Tretinoin [topical]	92	12 to <24 weeks	92
Macrolide [topical] + Anti-fungal [topical]	74	Erythromycin [topical] + Bifonazole [topical]	74	12 to <24 weeks	74
Retinoid [topical] + Hydrogen Peroxide [topical]	26	Adapalene [topical] + Hydrogen Peroxide [topical]	26	6 to <12 weeks	26
Retinoid [topical] + Macrolide [topical]	135	Isotretinoin [topical] + Erythromycin [topical]	135	12 to <24 weeks	135
Lincosamide [topical] + Other acid [topical]	23	Clindamycin [topical] + Salicylic Acid [topical]	23	12 to <24 weeks	23
Azelaic acid [topical] + Macrolide [topical]	40	Azelaic acid [topical] + Erythromycin [topical]	40	12 to <24 weeks	40
Tetracycline [oral] + Combined chemical peels [physical]	13	Doxycycline [oral] + Salicylic Acid [physical] + Glycolic Acid [physical]	13	12 to <24 weeks	13
Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red]	35	Retinol (Vitamin A) [topical] + Salicylic Acid [topical] + Blue + Red light	35	12 to <24 weeks	35
Benzoyl peroxide [topical] + Lincosamide [topical] + Other acid [topical]	24	Benzoyl peroxide [topical] + Clindamycin [topical] + Salicylic Acid [topical]	24	12 to <24 weeks	24
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	29	Benzoyl peroxide [topical] + Intense Pulsed Light (IPL)	29	12 to <24 weeks	29

In green, classes and numbers of observations from RCTs assessing treatments relevant to females; in blue, numbers of observations from RCTs assessing treatments also relevant to males.

Discontinuation for any reason

Figure 2. Discontinuation for any reason network of treatment classes for people with mild to moderate acne.



Treatment classes and lines in green indicate treatments and comparisons relevant to females only.

Table 4. Treatment classes, interventions and numbers of observations made on each, in the discontinuation for any reason network of treatments for people with mild to moderate acne.

Class	n	Treatment	n	Duration	n
Placebo	2893F 2323M	Placebo [oral]	570F	24+ weeks	570F
		Placebo [topical]	2256	0 to <6 weeks	60
				6 to <12 weeks	199
				12 to <24 weeks	1997
		Placebo [physical]	67	0 to <6 weeks	32
				12 to <24 weeks	35
Benzoyl peroxide [topical]	1270	Benzoyl peroxide [topical]	1270	6 to <12 weeks	220
				12 to <24 weeks	1015
				24+ weeks	35
Lincosamide [topical]	3073	Clindamycin [topical]	2910	6 to <12 weeks	183
				12 to <24 weeks	2727
		Clindamycin [topical] with Zinc Acetate Dihydrate	163	12 to <24 weeks	163
Retinoid [topical]	2290	Adapalene [topical]	1821	6 to <12 weeks	20
				12 to <24 weeks	1766
				24+ weeks	35
		Tazarotene [topical]	469	12 to <24 weeks	469
Azelaic acid [topical]	263	Azelaic Acid [topical]	263	6 to <12 weeks	25
				12 to <24 weeks	238
Macrolide [topical]	686	Erythromycin [topical]	599	6 to <12 weeks	61
				12 to <24 weeks	538
		Erythromycin [topical] with Zinc Acetate Dihydrate	87	6 to <12 weeks	12
				12 to <24 weeks	75
Nitroimidazoles [topical]	48	Metronidazole [topical]	48	12 to <24 weeks	48
Nels Cream [topical]	15	Nels Cream (chloroxylenol + zinc oxide) [topical]	15	6 to <12 weeks	15
Antiseptics [topical]	80	Chlorhexidine Gluconate/Digluconate [topical]	80	12 to <24 weeks	80
Fusidic acid [topical]	412	Fusidic acid (Sodium Fusidate) [topical]	412	6 to <12 weeks	135
				12 to <24 weeks	277
Superoxidised solution [topical]	39	Superoxidised solution	39	12 to <24 weeks	39
Anti-fungal [topical]	20	Ketoconazole [topical]	20	6 to <12 weeks	20
Other acid [topical]	204	Glycolic Acid [topical]	59	12 to <24 weeks	59
		Salicylic Acid [topical]	35	12 to <24 weeks	35
		Nisal Cream (chloroxylenol + salicylic acid) [topical]	18	12 to <24 weeks	18

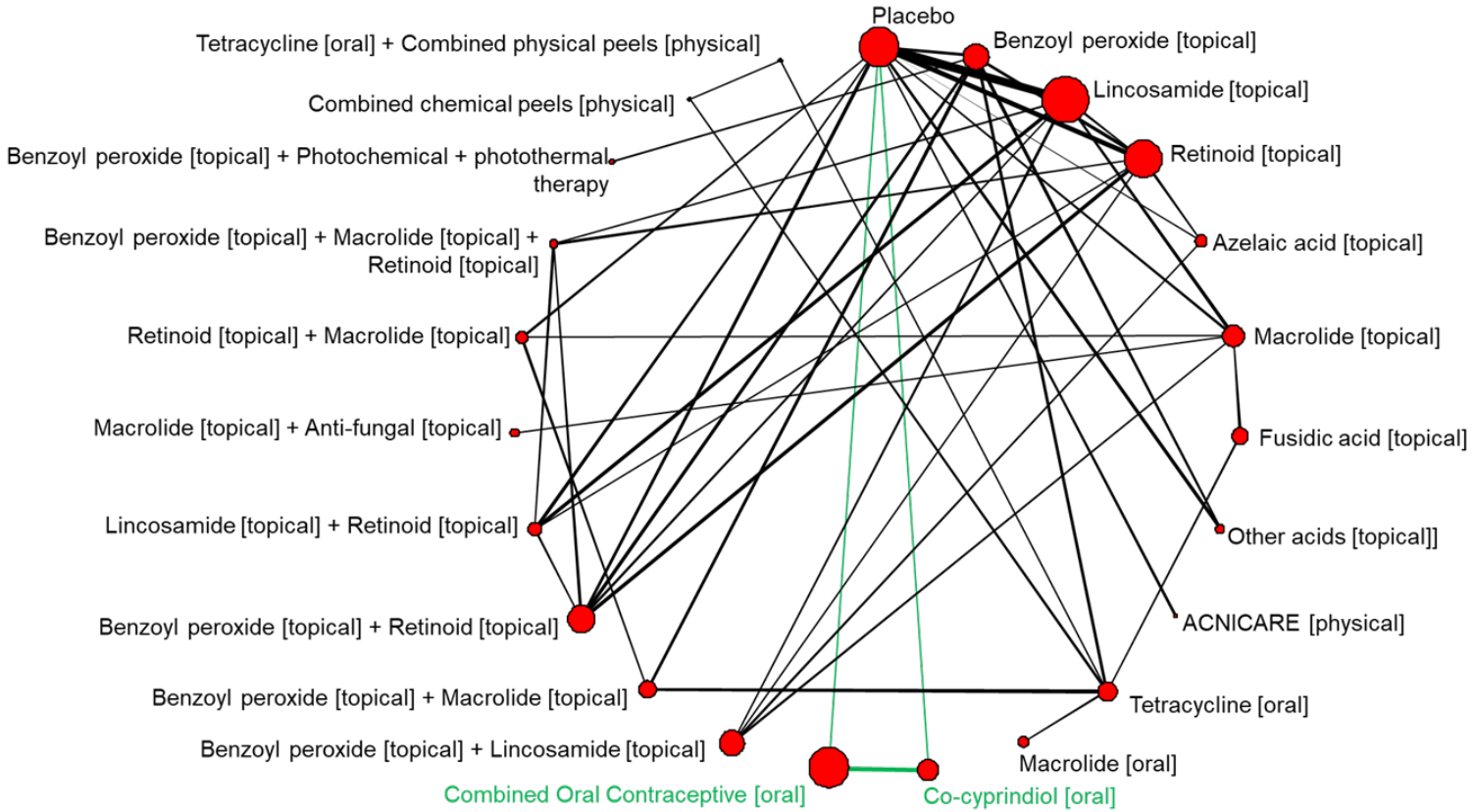
Class	n	Treatment	n	Duration	n
		Gluconolactone [topical]	50	12 to <24 weeks	50
		Diacneal (0.1% retinaldehyde and 6% glycolic acid)	42	12 to <24 weeks	42
Chemical peel [physical]	15	Trichloroaecetic Acid [physical]	15		15
Combined chemical peels [physical]	15	Salicylic Acid [physical] + Glycolic Acid [physical]	15	12 to <24 weeks	15
ACNICARE [physical]	20	ACNICARE (triethyl citrate + ethyl linoleate) [physical]	20	12 to <24 weeks	20
Retinoid - total cumulative dose < 120mg/kg (single course) [oral]	30	Isotretinoin < 120. Daily < 0.5 [oral]	30	6 to <12 weeks	30
Tetracycline [oral]	489	Doxycycline [oral]	135	12 to <24 weeks	135
		Minocycline [oral]	223	6 to <12 weeks	93
				12 to <24 weeks	130
		Oxytetracycline [oral]	131	12 to <24 weeks	131
Macrolide [oral]	160	Azithromycin [oral]	120	12 to <24 weeks	120
		Erythromycin [oral]	40	0 to <6 weeks	40
Co-cyprindiol [oral]	584	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	584	24+ weeks	584
Combined Oral Contraceptive [oral]	2305	Estradiol (valerate) [oral] + Dienogest [oral]	530	24+ weeks	530
		Ethinylestradiol [oral] + Desogestrel [oral]	118	24+ weeks	118
		Ethinylestradiol [oral] + Drospirenone [oral]	666	24+ weeks	666
		Ethinylestradiol [oral] + Levonorgestrel [oral]	191	24+ weeks	191
		Ethinylestradiol [oral] + Norgestimate [oral]	800	24+ weeks	800
Photochemical therapy [blue and red]	65	Blue + Red light	65	12 to <24 weeks	65
Photochemical therapy [blue]	127	Blue Light LED	127		127
Photochemical therapy [no!no!]	31	no!no! skin device	31		31
Photochemical + photothermal therapy	106	Intense Pulsed Light (IPL)	60		60
		Pulsed Dye Laser	46		46
Photopneumatic therapy	60	Intense Pulsed Light (IPL) + Vacuum	60		60
Benzoyl peroxide [topical] + Anti-fungal [topical]	13	Benzoyl peroxide [topical] + Butenifine [topical]	13	6 to <12 weeks	13
Benzoyl peroxide [topical] + Topical acid [topical]	69	Benzoyl peroxide [topical] + Salicylic Acid [topical]	69	6 to <12 weeks	69
Benzoyl peroxide [topical] + Lincosamide [topical]	1129	Benzoyl peroxide [topical] + Clindamycin [topical]	1129	6 to <12 weeks	70
				12 to <24 weeks	1059
Benzoyl peroxide [topical] + Macrolide [topical]	404	Benzoyl peroxide [topical] + Erythromycin [topical]	404	12 to <24 weeks	404
Benzoyl peroxide [topical] + Retinoid [topical]	834	Benzoyl peroxide [topical] + Adapalene [topical]	745	12 to <24 weeks	710
				24+ weeks	35
		Benzoyl peroxide [topical] + Tazarotene [topical]	89	12 to <24 weeks	89
Lincosamide [topical] + Azelaic acid [topical]	50	Clindamycin [topical] + Azelaic Acid [topical]	50	12 to <24 weeks	50
Lincosamide [topical] + Retinoid [topical]	315	Clindamycin [topical] + Adapalene [topical]	185	12 to <24 weeks	185
		Clindamycin [topical] + Tazarotene [topical]	87	12 to <24 weeks	87

Class	n	Treatment	n	Duration	n
		Clindamycin [topical] + Tretinoin (RETIN A, All-trans reinoic acid) [topical]	43	12 to <24 weeks	43
Macrolide [topical] + Anti-fungal [topical]	101	Erythromycin [topical] + Bifonazole [topical]	101	12 to <24 weeks	101
Retinoid [topical] + Macrolide [topical]	194	Isotretinoin [topical] + Erythromycin [topical]	135	12 to <24 weeks	135
		Tretinoin (RETIN A, All-trans reinoic acid) [topical] + Erythromycin [topical]	59	12 to <24 weeks	59
Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical]	90	Benzoyl peroxide [topical] + Erythromycin [topical] + Tazarotene [topical]	90	12 to <24 weeks	90
Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red]	35	Retinol (Vitamin A) [topical] + Salicylic Acid [topical] + Blue + Red light	35	12 to <24 weeks	35
Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical]	25	Benzoyl peroxide [topical] + Clindamycin [topical] + Salicylic Acid [topical]	25	12 to <24 weeks	25
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	32	Benzoyl peroxide [topical] + Intense Pulsed Light (IPL)	32		32
Tetracycline [oral] + Combined chemical peels [physical]	15	Doxycycline [oral] + Salicylic Acid [physical] + Glycolic Acid [physical]	15	12 to <24 weeks	15

In green, classes and numbers of observations from RCTs assessing treatments relevant to females; in blue, numbers of observations from RCTs assessing treatments also relevant to males.

Discontinuation due to side effects

Figure 3. Discontinuation due to side effects network of treatment classes for people with mild to moderate acne.



Treatment classes and lines in green indicate treatments and comparisons relevant to females only.

Table 5. Treatment classes, interventions and numbers of observations made on each, in the discontinuation due to side effects network of treatments for people with mild to moderate acne.

Class	n	Treatment	n	Duration	n
Placebo	2024F 1644M	Placebo [oral]	380F	24+ weeks	380F
		Placebo [topical]	1644	12 to <24 weeks	1644
Benzoyl peroxide [topical]	912	Benzoyl peroxide [topical]	912	12 to <24 weeks	877
				24+ weeks	35
Lincosamide [topical]	2916	Clindamycin [topical]	2753	6 to <12 weeks	59
				12 to <24 weeks	2694
		Clindamycin [topical] with Zinc Acetate Dihydrate	163	12 to <24 weeks	163
Retinoid [topical]	1840	Adapalene [topical]	1371	12 to <24 weeks	1336
				24+ weeks	35
		Tazarotene [topical]	469	12 to <24 weeks	469
Azelaic acid [topical]	188	Azelaic Acid [topical]	188	12 to <24 weeks	188
Macrolide [topical]	619	Erythromycin [topical]	544	6 to <12 weeks	61
				12 to <24 weeks	483
		Erythromycin [topical] with Zinc Acetate Dihydrate	75	12 to <24 weeks	75
Fusidic acid [topical]	344	Fusidic acid (Sodium Fusidate) [topical]	344	6 to <12 weeks	95
				12 to <24 weeks	249
Other acid [topical]	110	Gluconolactone [topical]	50	12 to <24 weeks	50
		Diacneal (0.1% retinaldehyde and 6% glycolic acid) [topical]	42	12 to <24 weeks	42
		Nisal Cream (chloroxylenol + salicylic acid) [topical]	18	12 to <24 weeks	18
ACNICARE [topical]	20	ACNICARE (triethyl citrate + ethyl linoleate) [topical]	20	12 to <24 weeks	20
Combined chemical peels [physical]	15	Salicylic Acid [physical] + Glycolic Acid [physical]	15	12 to <24 weeks	15
Tetracycline [oral]	489	Doxycycline [oral]	135	12 to <24 weeks	135
		Minocycline [oral]	223	6 to <12 weeks	93
				12 to <24 weeks	130
		Oxytetracycline [oral]	131	12 to <24 weeks	131
Macrolide [oral]	160	Azithromycin [oral]	120	12 to <24 weeks	120
		Erythromycin [oral]	40	0 to <6 weeks	40
Co-cyprindiol [oral]	584	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	584	24+ weeks	584
Combined Oral Contraceptive [oral]	2115	Estradiol (valerate) [oral] + Dienogest [oral]	530	24+ weeks	530
		Ethinylestradiol [oral] + Desogestrel [oral]	118	24+ weeks	118
		Ethinylestradiol [oral] + Drospirenone [oral]	650	24+ weeks	650
		Ethinylestradiol [oral] + Levonorgestrel [oral]	17	24+ weeks	17

Class	n	Treatment	n	Duration	n
		Ethinylestradiol [oral] + Norgestimate [oral]	800	24+ weeks	80
Benzoyl peroxide [topical] + Lincosamide [topical]	829	Benzoyl peroxide [topical] + Clindamycin [topical]	829	12 to <24 weeks	829
Benzoyl peroxide [topical] + Macrolide [topical]	404	Benzoyl peroxide [topical] + Erythromycin [topical]	404	12 to <24 weeks	404
Benzoyl peroxide [topical] + Retinoid [topical]	957	Benzoyl peroxide [topical] + Adapalene [topical]	868	12 to <24 weeks	833
				24+ weeks	35
		Benzoyl peroxide [topical] + Tazarotene [topical]	89	12 to <24 weeks	89
Lincosamide [topical] + Retinoid [topical]	255	Clindamycin [topical] + Adapalene [topical]	125	12 to <24 weeks	125
		Clindamycin [topical] + Tazarotene [topical]	87	12 to <24 weeks	87
		Clindamycin [topical] + Tretinoin [topical]	43	12 to <24 weeks	43
Macrolide [topical] + Anti-fungal [topical]	101	Erythromycin [topical] + Bifonazole [topical]	101	12 to <24 weeks	101
Retinoid [topical] + Macrolide [topical]	194	Isotretinoin [topical] + Erythromycin [topical]	135	12 to <24 weeks	135
		Tretinoin [topical] + Erythromycin [topical]	59	12 to <24 weeks	59
Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical]	90	Benzoyl peroxide [topical] + Erythromycin [topical] + Tazarotene [topical]	90	12 to <24 weeks	90
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	32	Benzoyl peroxide [topical] + Intense Pulsed Light (IPL)	32	12 to <24 weeks	32
Tetracycline [oral] + Combined chemical peels [physical]	15	Doxycycline [oral] + Salicylic Acid [physical] + Glycolic Acid [physical]	15	12 to <24 weeks	15

In green, classes and numbers of observations from RCTs assessing treatments relevant to females; in blue, numbers of observations from RCTs assessing treatments also relevant to males.

Quality assessment of studies included in the evidence review

The Cochrane Risk of Bias tool version 2.0 (RoB 2, 2019) for RCTs was used to assess potential bias in each study. For each domain on the Cochrane Risk of Bias tool that had sufficient variability in the ratings, bias adjustment NMA models were fitted to down-weight trials at high or unclear risk of bias. NMA models that adjusted for small study bias were also fitted. Bias-adjusted NMA models and results are shown in appendix M.

Threshold analysis was undertaken to test the robustness of treatment recommendations based on the NMA, to potential biases or sampling variation in the included evidence. Threshold analysis has been developed as an alternative to GRADE for assessing confidence in guideline recommendations based on network meta-analysis (Phillippo 2018). Full methods and results of threshold analysis are presented in appendix N.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Economic model

A decision-analytic model was developed to assess the relative cost effectiveness of treatments for people with mild to moderate acne. The objective of economic modelling, the methodology adopted, the results and the conclusions from this economic analysis are described in detail in appendix J. The respective economic evidence profile is shown in Appendix I. This section provides a summary of the methods employed and the results of the economic analysis.

Overview of economic modelling methods

A decision-analytic model comprising a decision-tree was constructed to evaluate the relative cost effectiveness of a range of topical, oral and physical treatments for people with mild to moderate acne who present to primary care services, although they may be subsequently referred to a specialist dermatology setting. The measure of outcome of the economic analysis was the number of QALYs gained. The perspective of the analysis was that of the NHS and personal social services. The time horizon of the analysis was 1 year. The range of interventions assessed in the economic analysis was determined by the availability of relevant clinical data included in the guideline NMA on the efficacy outcome.

Based on the advice of the committee, only treatment classes with evidence of effect versus placebo with at least 40 observations each across the RCTs included in the NMA of efficacy were considered in the economic analysis, as this was deemed as the minimum amount of evidence that could suggest that a treatment may be effective and potentially cost-effective. A treatment class demonstrated evidence of effect if the 95% credible intervals [CrI] of its effect versus placebo did not cross the line of no effect.

One intervention was selected as a representative from each treatment class; this was necessary only for costing purposes, as there was no adequate evidence to estimate individual treatment effects within each treatment class. The criteria for selecting interventions to represent each treatment class were the intervention availability and usage in the UK and other practicalities of use (e.g. a combination of topical treatments available in a single formulation was preferred to combinations that are only available as separate formulations); the evidence base for each intervention within class; the risk of side effects of individual interventions within a class; and, for pharmacological treatments, the drug acquisition cost (drugs with lower acquisition costs were preferred).

A bias-adjusted NMA on the efficacy outcome suggested evidence of bias for small study size; following bias-adjustment, a number of treatment classes did not show evidence of effect versus placebo anymore (although they had shown evidence of effect in the base-case analysis). Therefore, a bias-adjusted economic analysis was conducted, which utilised efficacy data from the respective bias-adjusted NMA. Based on the above criteria, the bias-adjusted economic analysis included the following treatment classes and interventions that retained evidence of effect versus placebo following bias-adjustment:

- Topical retinoids: adapalene
- Benzoyl peroxide (topical treatment, own class)
- Topical macrolides: topical erythromycin
- Benzoyl peroxide + topical retinoid (adapalene)
- Benzoyl peroxide + topical lincosamide (clindamycin)
- Benzoyl peroxide + topical macrolide (erythromycin)
- Topical retinoid (tretinoin) + topical lincosamide (clindamycin)
- Azelaic acid + topical lincosamide (clindamycin)
- Azelaic acid + topical macrolide (erythromycin)
- Topical macrolide (erythromycin) + topical anti-fungal (bifonazole)
- Chemical peels: salicylic acid peel
- Photochemical therapy (blue light)
- GP care, comprising GP consultations without provision of any pharmacological or physical treatment, reflecting the placebo arm of the network.

According to the model structure, hypothetical cohorts of people with mild to moderate acne were initiated on each of the treatment options assessed, including GP care, and followed for one year (52 weeks). People within each cohort might receive a full course of treatment, or they might discontinue treatment due to intolerable side effects or any other reason. Following treatment, people might experience ‘excellent’, ‘good’, ‘moderate’ or no improvement. People with excellent and good improvement and some people with moderate improvement received maintenance therapy, as appropriate. People who discontinued treatment, people with no improvement and some of those with moderate improvement received ‘average acne care’, comprising a mixture of care that is anticipated to be currently received by people with acne in the NHS. By the end of one year, those who experienced excellent, good or moderate improvement might relapse and return to their initial state of mild to moderate acne, otherwise they remained at the same level of improvement. Those who experienced no improvement remained in the state of no improvement until the model endpoint.

Efficacy and discontinuation data were derived from the respective guideline NMAs. Other clinical input parameters (baseline efficacy and risk of discontinuation, relationship between efficacy and perceived improvement, risk of relapse,) were derived from RCTs, other published literature and the committee’s expert opinion where evidence was lacking. Utility data were estimated based on limited available evidence, identified from a systematic literature review, and the committee’s expert opinion. Resource use was based on RCT

relevant information and other published literature supplemented with the committee's expert opinion. National UK unit costs were used. The cost year was 2019. Model input parameters were synthesised in a probabilistic analysis. This approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. A number of one-way deterministic sensitivity analyses were also carried out.

Results were expressed in the form of Net Monetary Benefits (NMBs). Incremental mean costs and effects (QALYs) of each treatment option versus GP care were presented in the form of cost effectiveness planes. The cost effectiveness acceptability frontier (CEAF) was also plotted, showing the treatment option with the highest mean NMB over different cost effectiveness thresholds, and the probability that the option with the highest NMB is the most cost-effective among those assessed.

Overview of economic modelling results and conclusions

The results of the bias-adjusted economic analysis suggest that all assessed topical, oral and physical treatments are more cost-effective for people with mild to moderate acne compared with GP care. Topical combinations such as azelaic acid with lincosamide or macrolide, adapalene with benzoyl peroxide, or tretinoin with clindamycin, as well as photochemical therapy [blue & red] are likely to comprise the most cost-effective treatment options for this population. Topical treatments such as benzoyl peroxide, erythromycin and photochemical therapy [blue] appear to be less cost-effective, although more cost-effective than GP care alone. In-between, there is another group of treatments (topical erythromycin and bifonazole, topical benzoyl peroxide with clindamycin, topical benzoyl peroxide and erythromycin, adapalene, and chemical peels) that occupied middle cost effectiveness rankings in the guideline economic analysis.

Results of the economic analysis were overall robust to changes in input parameters tested in deterministic sensitivity analysis.

The guideline economic analysis was based on the best quality data derived from the guideline NMA. However, the NMAs were overall characterised by inconsistency between direct and indirect evidence, high between-study heterogeneity, as well as large effects and considerably wide 95% credible intervals for some treatments, and this was taken into account when interpreting the results of the analysis.

The committee's discussion of the evidence

This section includes the committee's discussion of evidence from both the NMA (covered in this evidence report) and the pairwise meta-analysis (covered in evidence report E2) because evidence from all of these analyses was used to draft recommendations.

Interpreting the evidence

The outcomes that matter most

NMA

Clinician-rated improvement at treatment endpoint (measured by percentage change in total acne lesion count and/or change in score or final score on a validated acne severity scale) as well as prevention of scarring at any follow-up (measured by final number or change in the number of scars from baseline and/or by incidence of scarring at follow up) were considered critical outcomes by the committee as they both reflected primary aims of treatment.

No data were identified on prevention of scarring, and therefore no NMA was conducted on this outcome.

Treatment discontinuation for any reason and due to side effects were considered as important outcomes that reflected acceptability and tolerability of treatments, respectively.

Generally, changes in numbers of acne lesion counts, number of scars and symptom scores from baseline were favoured over final (post-treatment or follow up) outcomes, because although in theory randomisation should balance out any differences at baseline, this assumption can be violated by small sample sizes. The committee also expressed a general preference for clinician-rated improvement over participant-reported improvement as the former, but not the latter, can be blinded. Furthermore, percentage change in acne lesion counts was preferred over either clinician-rated or patient-reported scale scores as it can be more objectively measured.

Pairwise meta-analysis

The committee selected side effects and participant reported improvement of acne as important outcomes. Side effects indicate whether the intervention is safe. Participant reported improvement of acne indicates whether the person with acne vulgaris perceives an improvement in acne symptoms.

The quality of the evidence

NMA

The quality of the individual studies ranged from very low to moderate. This was predominately due to serious risk of bias of individual studies included in the NMA. This impacted on the quality of the NMAs.

The NMAs allowed estimation of relative effects between all pairs of treatments for people with mild to moderate acne for which RCT evidence was available, via direct and indirect comparisons, without breaking the rules of randomisation.

All networks were disconnected at the intervention level, which was resolved by fitting class effects models. In principle, these models still allow estimation of individual intervention effects within the class, but the available evidence was inadequate to suggest different intervention effects within classes.

Ideally, the committee wanted to look at the effects of different treatment durations of the same intervention, but looking at these would result in sparse, disconnected networks for each duration category, since included RCTs did not compare directly different durations of the same intervention. This was also resolved by fitting class effects models, where duration was only considered at intervention level. Nevertheless, also in this case there was inadequate evidence to suggest that the treatment relative effects differed by treatment duration.

All 3 NMAs (clinician improvement as reflected in % change in total acne lesion count, discontinuation for any reason, discontinuation due to side effects) showed some evidence of inconsistency between direct and indirect evidence. For discontinuation due to side effects, inconsistency was identified at the intervention level only, as at the class level there were no loops with three independent sources of direct evidence (so inconsistency was not possible at this level). Heterogeneity across all NMAs was found to be rather high. Some relative effects versus placebo were characterised by considerably wide 95% credible intervals. The committee attributed the inconsistency and high heterogeneity identified across the NMAs to the heterogeneity in the populations included in the trials, as there was a range of definitions of mild to moderate acne across the RCTs included in the NMAs. Following consideration of the inconsistency and heterogeneity in the evidence, the committee did not make recommendations by strictly following a hierarchy of treatments according to their ranking in the NMA and the guideline economic analysis that was informed by the NMA, but instead considered treatments with small differences in clinical and cost-effectiveness as broadly similar. For this reason, recommendations for first line treatment included a range of

interventions that were considered to have broadly similar clinical and cost-effectiveness, with the final choice being determined by the values and preferences of the person with acne on the benefits, risks and other related characteristics of recommended treatment options.

Effects for several treatments in the NMA were informed by limited evidence: topical superoxidised solution, antiseptics, anti-fungals, Acnicare, azelaic acid combined with topical lincosamide or macrolide, topical retinoid combined with hydrogen peroxide, topical lincosamide combined with topical acids, benzoyl peroxide combined with topical lincosamide and topical acids, benzoyl peroxide combined with photochemical and photothermal therapy, topical retinoid combined with topical acids and photochemical therapy (blue and red), photodynamic therapy, photochemical therapy (red or blue), photothermal and photodynamic therapy, smoothbeam and photochemical therapy (blue), and also combined chemical peels alone or combined with oral tetracycline, had fewer than 50 observations available each on the efficacy outcome. The committee noted that single or combined topical treatments as well as oral hormonal treatments had overall larger evidence base compared with physical treatments.

Bias adjustment analyses suggested evidence of bias due to small sample size in the NMA of efficacy (clinician-rated improvement). A bias-adjusted NMA on this outcome was thus run and considered by the committee when making recommendations. No potential bias was identified in the NMAs of discontinuation for any reason and of discontinuation due to side effects.

The committee noted that there was a higher number of direct comparisons (and a wider evidence base) between different single or combined topical treatments compared with oral and physical treatments.

Threshold analysis suggested that conclusions of the NMA on efficacy were sensitive to plausible changes in the evidence. This issue, which affected recommendations, has been discussed in detail in the next section, under ‘benefits and harms’.

The committee noted the strengths and limitations of the NMA when interpreting the results. However, the committee agreed to make strong recommendations despite the uncertainty and limitations in the evidence, as the clinical evidence was strong for some treatments and supported by economic evidence and the committee’s clinical experience. The committee decided to make weaker (‘consider’) recommendations on interventions that were supported by a more limited evidence base.

Pairwise meta-analysis

The quality of the evidence ranged from very low to moderate, with most of the evidence being of a very low quality. This was predominately due to serious risk of bias of individual studies and imprecision around the effect estimate

Benefits and harms

The committee discussed the results of the NMA and noted the total size of the evidence base and the relative size of the evidence base of each treatment versus the other treatment classes in the network. Although they had decided to include in economic analysis treatments with evidence of effect versus placebo and with at least 40 observations each across the RCTs included in the NMA of efficacy, after looking at the relative size of the evidence base of each treatment in the network they decided to consider as candidates for practice recommendations only treatments that had at least 50 observations (rather than participants, as some data were derived from split-face trials) each, across trials included in the NMA of efficacy, as this was considered the minimum adequate evidence base that would allow drawing more robust conclusions on a treatment’s effectiveness; for treatments with a small (as deemed by the committee) number of observations across trials (roughly 50-

200), the committee used also their clinical experience in drawing conclusions on treatments' effectiveness.

According to the results of the bias-adjusted NMA of efficacy, among treatments with at least 50 observations across RCTs, the treatments that showed evidence of effect versus placebo, ranked by effectiveness (from highest to lowest), were: chemical peels, photochemical therapy (blue and red), photochemical therapy (blue), combined benzoyl peroxide with a topical retinoid, combined topical retinoid with a topical lincosamide, combined topical macrolide with a topical anti-fungal, combined benzoyl peroxide with a topical macrolide, topical retinoids, combined benzoyl peroxide with a topical lincosamide, benzoyl peroxide, and topical macrolides.

The following treatments with at least 50 observations across RCTs showed no evidence of effect versus placebo, as their 95% CrI crossed the line of no effect: azelaic acid, fusidic acid, topical lincosamides, combined topical retinoid with a topical macrolide, topical acids, oral tetracyclines, oral macrolides, oral co-cyprindiol, combined oral contraceptive pills, photochemical and photothermal therapy, and oral isotretinoin in a total cumulative dose of <120 mg/kg (single course).

First-line treatment

The committee noted that, in the bias-adjusted NMA, among pharmacological treatments with at least 50 observations each on the efficacy outcome that were available as single formulations, combined topical lincosamide (class of antibiotics with only clindamycin being available in the UK) with a topical retinoid, and combined benzoyl peroxide with a topical retinoid were the two most effective treatment options. The committee agreed that the findings of the NMA were consistent with their clinical experience. Based on their clinical judgment and after taking into account the inconsistency and uncertainty characterising the NMA, the committee expressed the opinion that there were no substantial differences in clinical effectiveness between these treatments. The committee also noted the conclusions of threshold analysis, according to which plausible changes in the evidence could lead to the fixed combination of benzoyl peroxide with a topical lincosamide becoming one of the most effective classes, and decided to make a recommendation for this treatment too, to increase choice. When making recommendations for specific interventions from each treatment class, the committee expressed a clear preference for single, fixed formulations of combined topical treatments for practicality and cost issues, as discussed under section 'Other factors the committee took into account'. Therefore, the committee recommended 3 alternative first-line treatment options for people with mild to moderate acne: a fixed combination of topical tretinoin with clindamycin; a fixed combination of topical adapalene with benzoyl peroxide; and a fixed combination of topical benzoyl peroxide with clindamycin. The choice should be determined following shared decision-making with the person with acne, after taking into account their values and preferences on the benefits, risks and other related characteristics of each of the 3 treatment options (some of these considerations were summarised in a table in the guideline to help shared decision making).

The committee selected tretinoin as the topical retinoid recommended for combination with clindamycin, and adapalene as the topical retinoid recommended for combination with benzoyl peroxide, because tretinoin with clindamycin, and adapalene with benzoyl peroxide are available in single, fixed formulations.

The committee agreed that azelaic acid tends to cause less irritancy compared with topical retinoids and topical benzoyl peroxide; this view was supported by the results of the NMA on discontinuation due to side effects. It may also help to reduce the risk of hyperpigmentation in acne with consideration in individuals with darker skin. However, azelaic acid as a monotherapy was not considered as a first-line treatment recommendation because, according to the bias-adjusted NMA on the efficacy outcome, azelaic acid was not shown to be effective compared with placebo in people with mild-to-moderate acne. Similarly, the combination of topical retinoid with topical macrolide (which is available as a fixed

combination of topical tretinoin with erythromycin) was not considered for a practice recommendation because it was not effective compared with placebo in the bias-adjusted NMA of efficacy.

The committee did not make recommendations for topical combinations of azelaic acid with lincosamide or macrolides, despite of their apparently high effectiveness, because they had a very limited evidence base (fewer than 50 observations, which the committee considered as the smallest evidence base that could lead to a practice recommendation). The committee decided not to make a recommendation for combined topical macrolide with antifungal, which appeared to be very effective compared with other treatments, because this evidence was based on 74 observations, which was considered a relatively limited evidence base, and the committee had no clinical experience on this treatment that could support this evidence. The committee also noted that all 3 treatments were not available as single fixed combinations which would mean that they would have to be separately prescribed and separately applied to the skin which would make the combination treatment more expensive to prescribe and less convenient in its use. For the same reason (unavailability as a single fixed combination), the committee decided not to make a recommendation for the topical combination of benzoyl peroxide with macrolide, despite its relatively high clinical effectiveness compared with other treatments.

The committee noted that the evidence showed that combinations of topical treatments that included benzoyl peroxide, lincosamide and/or a retinoid were overall more effective than these interventions being used as topical monotherapies. The committee agreed that this was consistent with their clinical experience.

The committee noted that monotherapy with benzoyl peroxide was clinically effective, albeit less effective compared with other recommended pharmacological options and decided to make a weaker ('consider') recommendation for benzoyl peroxide, for people with acne who do not want topical retinoids or topical or oral antibiotics or for whom these are contra-indicated (for example during pregnancy).

For people who have contraindications or do not wish to use the recommended treatment options, the committee agreed that other treatments may be suitable based on individual circumstances and clinical expertise.

Factors to take into account during consultations

There was a lack of evidence on the comparative effectiveness of different durations of treatments (including antibiotics). The committee discussed that usually, the positive effects of topical treatments only become noticeable after 6 to 8 weeks, so agreed it was important to encourage adherence and discuss the need for continued treatment with the person. The committee noted that the NICE guideline on medicine adherence was also relevant in this context and cross-referred to this for further information.

Factors to take into account when choosing a treatment option

The committee reviewed the results of the NMA on discontinuation due to side effects, which suggested that topical retinoids, benzoyl peroxide and their combination are associated with an increased risk of discontinuation due to side effects; moreover, evidence from pairwise meta-analysis indicated that topical agents such as benzoyl peroxide and retinoids often cause skin irritation. The committee confirmed that these findings were consistent with their clinical experience and, therefore, recommended that topical treatments associated with skin irritation, such as benzoyl peroxide or retinoids, be initiated with alternate-day or short-contact application.

Since some of the recommended options include a topical retinoid the committee highlighted, based on expertise, that these are contraindicated during pregnancy or planning a pregnancy. Therefore, effective contraceptive methods should be discussed.

According to the bias-adjusted NMA on efficacy, the combined oral contraceptive pill showed no effectiveness compared with placebo, as 95% CrI crossed the line of no effect. However, based on their clinical experience, the committee decided that females who need contraceptives could be given the combined oral contraceptive pill in addition to a first-line treatment option. This would be preferable to the progesterone-only pill, which is known to potentially cause acne (the committee noted that general information about combined hormonal contraception is outside the scope of this guideline but can be accessed from guidance by the Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists). The committee also recognised that making recommendations about contraceptive methods is outside the scope of this guideline, and that the most reliable contraceptive is the one which the women would prefer to use after shared decision making looking at all options. The committee also noted that co-cyprindiol showed no effectiveness versus placebo. In addition, the committee noted the lack of evidence on hormone-modifying agents in the treatment of people with mild to moderate acne and made a research recommendation for hormone-modifying agents for all levels of severity of acne.

The committee agreed that a topical or an oral antibiotic as a monotherapy or in combination should not be used due to an increased risk for the development of antibiotic resistance; they also noted the lack of effectiveness of oral tetracyclines (doxycycline, minocycline, oxytetracycline), oral macrolides (azithromycin, erythromycin) and topical lincosamides (clindamycin) as monotherapies compared with placebo and the lower effectiveness of topical macrolides (erythromycin) as monotherapy compared with other treatments in people with mild to moderate acne. The committee therefore decided to make a strong recommendation against the use of topical or oral antibiotics as monotherapies or a combination of a topical antibiotic with an oral antibiotic.

Factors to take into account at review

The committee agreed that all options should be given as a 12-week course, as this allows treatment to reach a sufficient effect. This is consistent with current practice and also the most common course length in the evidence; treatment should be reviewed at 12 weeks to determine if it is effective and tolerable.

The committee used their knowledge and experience to recommend that treatments including topical antibiotics be continued for longer than 6 months only in exceptional circumstances, because of the increased risk of developing antibiotic resistance. By using the term ‘exceptional’ the committee noted, based on experience, that this would only happen in rare and complex clinical situations. Clinicians would make the decision to use longer-term antibiotics after considering all the factors and discussions with the person with acne. The committee acknowledged that ‘exceptional’ would lack a definition but wanted to highlight that longer-term antibiotic use should be discouraged. Providing further detail on what would represent exceptional circumstances for one person as an example might not help clinicians decide if another person’s circumstances are exceptional. Rather than give fixed scenarios, the committee chose to highlight that continuing to give antibiotics past 6 months should not be routine, and for the cases where this does happen emphasised the importance of regular review and a prompt end to antibiotic treatment. Where treatments including topical antibiotics are continued beyond 6 months, the committee recommended that the antibiotic use be reviewed every 3 months and stopped at the earliest opportunity.The committee did not make a recommendation on length of treatment for other topical agents, as they expressed the view that it was safe for these to be continued for longer, when appropriate.

The committee took into account the principles of antimicrobial guidance and policy, as outlined in the NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use, as well as the Global action plan on antibiotic resistance from the World Health Organization. All of these antibiotic treatments increase the risk of

antimicrobial resistance and noted that people should be aware of the principles of antimicrobial stewardship when considering treatments for acne.

Physical treatments

The committee noticed that a number of physical treatments (light therapies and chemical peels) ranked in a high position in the NMA of efficacy, but they decided not to make any recommendations because these treatments had a rather limited evidence base (<200 observations each) compared with pharmacological treatments and the clinical experience with light therapies in particular for the treatment of acne is very limited within the NHS context. Instead, they made research recommendations for both light therapies and chemical peels. The committee also noted that, based on the pairwise meta-analysis, the majority of the evidence showed that there appears to be no clinically important difference between the different types of chemical peels or energy devices in terms of skin irritation, redness or pigmentation.

Pairwise meta-analysis

Evidence showed that topical treatments, such as benzoyl peroxide or retinoids, were associated with skin irritation which can be reduced by using a lower dose. For this reason, the committee recommended when beginning topical treatments to start with alternate-day or short contact application. Evidence about relative rates of specific side effects within other treatment classes was not informative and evidence was lacking about relapse.

Cost effectiveness and resource use

No published economic evidence was identified. The committee considered the results of the guideline economic analysis when making recommendations, which was informed by the NMAs conducted for the guideline. Therefore, the strengths and limitations of the NMA characterise the guideline economic analysis as well. Results of the guideline economic analysis were partially applicable to the NICE decision-making context, as the QALY estimates were based on the committee's expert opinion due to lack of relevant data of adequate quality. On the other hand, resource use and costs were directly relevant to the NHS context as they reflected clinical practice in England. The guideline base-case economic analysis was overall characterised by minor methodological limitations, so the committee were confident to use its findings to support recommendations. The committee was aware that discontinuation data were not available for a number of treatments, so other treatments served as proxies (based on committee's expert opinion) to inform discontinuation where relevant data were not available. Nevertheless, they noted that the impact of discontinuation data on the results of the economic model was relatively small as it affected only costs associated with discontinuation and not outcomes; this is because efficacy data used in the economic analysis were taken from intention-to-treat rather than completer analysis, where possible, and therefore they reflected effects on both those completing treatment and those discontinuing treatment early.

For costing purposes, the economic analysis selected one intervention as a representative from each treatment class modelled. The criteria for selecting interventions to represent each treatment class were the intervention availability and usage in the UK and other practicalities of use (e.g. a combination of topical treatments available in a single formulation was preferred to combinations that are only available as separate formulations); the evidence base for each intervention within class; the risk of side effects of individual interventions within a class; and, for pharmacological treatments, the drug acquisition cost (drugs with lower acquisition costs were preferred). The committee agreed that these were important factors to take into account and recommended specific interventions that were considered in economic modelling.

The results of the economic analysis suggested that all assessed topical, oral and physical treatments are more cost-effective for people with moderate to severe acne compared with

GP care. Among pharmacological treatments with an adequate evidence base (that is, with at least 50 observations each) for people with mild to moderate acne that are available as single formulations, combined topical adapalene with benzoyl peroxide and combined topical tretinoin with clindamycin were among the most cost-effective treatment options, without considerable differences in their relative cost-effectiveness. Combined topical benzoyl peroxide with clindamycin was less cost-effective than these two options, but the committee noted that, with the exception of topical adapalene, it was the next most cost-effective pharmacological treatment option that was available as a single formulation. These findings supported a recommendation for these 3 alternative options as first-line treatments for this population, with the final choice being determined following shared decision-making with the person with acne, after taking into account their values and preferences on the benefits, risks and other related characteristics of each of the 3 treatment options.

The combination of topical erythromycin with bifonazole as well as the combination of topical erythromycin with benzoyl peroxide were more cost-effective than combined topical benzoyl peroxide with clindamycin but these are not available as single formulations and were thus not considered any further due to their impracticality in use.

The committee noted that benzoyl peroxide was a cost-effective treatment option, albeit less cost-effective compared with other recommended first-line treatments; this finding supported a recommendation for use of benzoyl peroxide for people with acne who do not want topical retinoids or topical or oral antibiotics or for whom these are contra-indicated.

The committee noted the relatively high cost-effectiveness of light therapies and chemical peels, however, due to their limited evidence base, they decided to make a research recommendation.

The committee advised that the recommendations for first-line treatments largely reflect current practice, but discussions on the advantages and disadvantages of each option with the person may mean additional resource use (for example, if longer or more consultations are needed). This will, however, likely to lead to later benefits and reductions in resource use from better understanding and compliance with medication. The recommendation against oral or topical antibiotics used as monotherapy or in combination may lead to a significant change in current clinical practice, as topical and oral antibiotics are often used as a monotherapy or in combination for the treatment of acne vulgaris, although this is more prevalent in moderate to severe forms of acne.

Other factors the committee took into account

The committee recommended fixed formulations of combined topical treatments for practicality and cost issues. They advised that combined topical treatments that are not available as fixed combinations need to be applied separately and thus are impractical to use, but also impractical and potentially costly for pharmacists to prepare on an individual basis.

The committee noted that because physical treatments for acne are mainly available in the private sector, access to them differs across the country and according to socioeconomic group. Despite these issues causing inequality in access to such treatments, the evidence was not strong enough, and the potential resource impact too high, to make this available to people with mild to moderate acne.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1, 1.5.2 and 1.5.5 to 1.5.14 (excluding 1.5.6 which is underpinned by evidence report L, 1.5.10 and bullet points 2 and 3 of recommendation 1.5.12 which are underpinned by evidence report F1) and 3 research recommendations on the effectiveness of chemical peels, the effectiveness of physical modalities and the effectiveness of hormone-modifying agents. Other evidence supporting these recommendations as well as the committee's discussion of the can be found in the evidence reviews on mild to moderate acne pairwise analysis (evidence report E2).

References

Abels 2011b

Abels, C., Kaszuba, A., Michalak, I., Werdier, D., Knie, U., Kaszuba, A. A 10% glycolic acid containing oil-in-water emulsion improves mild acne: a randomized double-blind placebo-controlled trial. Journal of Cosmetic Dermatology, 2011, 10(3):202-9

Akarsu 2012

Akarsu, S., Emel, F., Yücel, F., Gül, E., Günes, A. T. Efficacy of the addition of salicylic acid to clindamycin and benzoyl peroxide combination for acne vulgaris. Journal of Dermatology 2012, 39(5):433-8

Alba 2017

Alba, M. N., Gerenutti, M., Yoshida, V. M., Grotto, D. Clinical comparison of salicylic acid peel and LED-Laser phototherapy for the treatment of Acne vulgaris in teenagers. Journal of Cosmetic and Laser Therapy, 2017, 19(1):49-53

Alirezai 2005

Alirezai, M., Gerlach, B., Horvath, A., Forsea, D. Briantais, P., Guyomar, M. 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. European Journal of Dermatology, 2005, 15(4):274-8

Alora Palli 2013

Alora Palli, M. B., Reyes-Habito, C. M., Lima, X. T., Kimball, A. B. A single-center, randomized double-blind, parallel-group study to examine the safety and efficacy of 3mg drospirenone/0.02mg ethinyl estradiol compared with placebo in the treatment of moderate truncal acne vulgaris. Journal of Drugs in Dermatology, 2013, 12(6):633-7

Babaeinejad 2013

Babaeinejad, S. H., Fouladi, R. F. The efficacy, safety, and tolerability of adapalene versus benzoyl peroxide in the treatment of mild acne vulgaris: a randomized trial. Journal of Drugs in Dermatology, 2013, 12(7):790-4

Babayeva 2011

Babayeva, L. Akarsu, S., Fetil, E., Gunes, A. T. Comparison of tretinoin 0.05% cream and 3% alcohol-based salicylic acid preparation in the treatment of acne vulgaris. Journal of the European Academy of Dermatology and Venereology, 2011, 25(3):328-3

Barbareschi 1991

Barbareschi, M., Hendricks., I., Angius, A., Cattaneo, M., Monti, M. The anticomedonic activity of azelaic acid investigated by means of scanning electron microscopy on horny layer biopsy. Journal of Dermatological Treatment, 1991, 2(2): 55-57

Barolet 2010

Barolet, D., Boucher, A. Radiant near infrared light emitting diode exposure as skin preparation to enhance photodynamic therapy inflammatory type acne treatment outcome. Lasers in Surgery and Medicine, 2010, 42(2):171-8

Becker 1981

Becker, L. E., Bergstresser, P. R., Whiting, D. A., Clendenning, W. E., Dobson, R. L., Jordan, W. P., Abell, E., LeZotte, L. A., Pochi, P. E., Shupack, J. L., et al., Topical clindamycin therapy for acne vulgaris. A cooperative clinical study. Archives of Dermatology, 1981, 117(8):482-5

Bernhardt 2016

Bernhardt, M. J., Mynti, M. F. Topical treatment with an agent disruptive to P. acnes biofilm provides positive therapeutic response: Results of a randomized clinical trial. Journal of Drugs in Dermatology, 2016, 15(6):677-83

Bleeker 1983

Bleeker, J. Tolerance and efficacy of erythromycin stearate tablets versus enteric-coated erythromycin base capsules in the treatment of patients with acne vulgaris. Journal of International Medical Research, 1983, 11(1):38-41

Boutli 2003

Boutli, F., Zioga, M., Koussidou, T., Ioannides, D., Mourellou, O. Comparison of chloroxylenol 0.5% plus salicylic acid 2% cream and benzoyl peroxide 5% gel in the treatment of acne vulgaris: a randomized double-blind study. Drugs Under Experimental and Clinical Research, 2003, 29(3):101-5

Callender 2012b

Callender, V. D., Young, C. M., Kindred, C., Taylor, S. C. Efficacy and safety of clindamycin phosphate 1.2% and tretinoin 0.025% gel for the treatment of acne and acne-induced post-inflammatory hyperpigmentation in patients with skin of color. Journal of Clinical and Aesthetic Dermatology, 2012, 5(7):25-32

Capizzi 2004

Capizzi, F., Landi, F., Milani, M., Amerio, P. Skin tolerability and efficacy of combination therapy with hydrogen peroxide stabilized cream and adapalene gel in comparison with benzoyl peroxide cream and adapalene gel in common acne. A randomized, investigator-masked, controlled trial. British Journal of Dermatology, 2004, 151(2):481-4

Carey 1996

Carey, W., Bakbo, J. C. A Canadian multicentre study to compare fusidic acid lotion and erythromycin solution in the treatment of acne vulgaris of the face. European Journal of Clinical Research, 1996, 8:171-81

Charakida 2007

Charakida, A., Charakida, M., Chu, A. C. Double-blind, randomized, placebo-controlled study of a lotion containing triethyl citrate and ethyl linoleate in the treatment of acne vulgaris. British Journal of Dermatology, 2007, 157(3):569-74

Cheema 2018

Cheema, A. N., Ameen, U., Javaid, R., Bokhari, M. A. Efficacy and safety of blue light versus 4% topical benzoyl peroxide in mild to moderate acne. Journal of Pakistan Association of Dermatologists, 2018, 28(1):79-84

Choi 2010

Choi, Y. S., Suh, H. S., Yoon, M. Y., Min, S. U., Lee, D. H., Suh, D. H. Intense pulsed light vs. pulsed-dye laser in the treatment of facial acne: A randomized split-face trial. Journal of the European Academy of Dermatology and Venereology, 2010, 24(7):773-80

Chottawornsak 2019

Chottawornsak, N., Chongpison, Y., Asawanonda, P., Kumtornrut, C. Topical 2% ketoconazole cream monotherapy significantly improves adult female acne: A double-blind, randomized placebo-controlled trial. Journal of Dermatology, 2019, 46(12): 1184-9

Cunliffe 2002b

Cunliffe, W. J., Holland, K. T., Bojar, R., Levy, S. F. A randomized, double-blind comparison of a clindamycin phosphate/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. Clinical Therapeutics, 2002, 24(7):1117-33

Cunliffe 2005

Cunliffe, W. J., Fernandez, C., Bojar, R., Kanis, R., West, F. An observer-blind, parallel-group, randomized, multicentre clinical and microbiological study of a topical clindamycin/zinc gel and a topical clindamycin lotion in patients with mild/moderate acne. Journal of Dermatological Treatment, 2005, 16(4):213-8.

Dayal 2017

Dayal, S., Amrani, A., Sahu, P., Jain, V. K. Jessner's solution vs. 30% salicylic acid peels: a comparative study of the efficacy and safety in mild-to-moderate acne vulgaris. Journal of Cosmetic Dermatology, 2017, 16(1):43-51

Darrah 1996

Darrah, A. J., Gray, P. L. Treatment of inflammatory acne with a 1450-nm smoothbeam diode laser: A split-face randomized single-blinded controlled trial. European Journal of Clinical Research, 1996, 8:97 – 107

Dayal 2020

Dayal, S., Kalra, K. D., Sahu, P. Comparative study of efficacy and safety of 45% mandelic acid versus 30% salicylic acid peels in mild-to-moderate acne vulgaris. Journal of Cosmetic Dermatology, 2020, 19(2):393-9

Draelos 2002

Draelos, Z. D., Tanghetti, E. A. Optimizing the use of tazarotene for the treatment of facial acne vulgaris through combination therapy. Cutis, 2002, 69(2 Suppl):20-9

Dubey 2016

Dubey, A., Amane, H. Comparison of efficacy and safety of adapalene and benzoyl peroxide-clindamycin combination in the topical treatment of acne vulgaris. International Journal of Basic and Clinical Pharmacology, 2016, 5(5):1727-32

Eichenfield 2013a

Eichenfield, L. F., Draelos, Z., Lucky, A. W., Hebert, A. A., Sugarman, J., Gold, L. S., Rudisill, D., Liu, H., Manna, V. Preadolescent moderate acne vulgaris: A randomized trial of the efficacy and safety of topical adapalene-benzoyl peroxides. Journal of Drugs in Dermatology, 2013, 12(6):611-8

Elgendy 2015

Elgendy A, Khalil K, Alshawadfy E, Wadea N, Alkady O. Blue light therapy versus low dose isotretinoin in mild to moderate acne. Global Dermatology, 2015, 2(3):131-4

Glass 1999

Glass, D., Boorman, G. C., Stables, G. I., Cunliffe, W. J., Goode, K. A placebo-controlled clinical trial to compare a gel containing a combination of isotretinoin (0.05%) and erythromycin (2%) with gels containing isotretinoin (0.05%) or erythromycin (2%) alone in the topical treatment of acne vulgaris. Dermatology, 1999, 199(3):242-7

Gollnick 2009

Gollnick, H. P. M., Draelos, Z., Glenn, M. J., Rosoph, L. A., Kaszuba, A., Cornelison, R., Gore, B., Liu, Y. Graeber, M. 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. British Journal of Dermatology, 2009, 161(5):1180-9

Guerra-Tapia 2012

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. Journal of Drugs in Dermatology, 2012, 11(6):714-22

Gupta 2003

Gupta, A. K., Lynde, C. W., Kunynetz, R. A., Amin, S., Choi, K., Goldstein, E. A randomized, double-blind, multicenter, parallel group study to compare relative efficacies of the topical gels 3% erythromycin/5% benzoyl peroxide and 0.025% tretinoin/erythromycin 4% in the treatment of moderate acne vulgaris of the face. Journal of Cutaneous Medicine & Surgery, 2003, 7(1):31-7

Hajheydari 2011

Hajheydari, Z., Mahmoudi, M., Vahidshahi, K., Nozari, A. Comparison of efficacy of Azithromycin vs. Clindamycin and erythromycin in the treatment of mild to moderate acne vulgaris. Pakistan Journal of Medical Sciences, 2011, 27(1):68-72

Hansted 1985

Hansted, B., Jorgensen, J., Reymann, F., Christiansen, J. Fucidin cream for topical treatment of acne vulgaris. Current Therapeutic Research, Clinical and Experimental, 1985, 37:249–53

Henderson 1995

Henderson, T. A., Olson, W. H., Leach, A. D. A single-blind, randomized comparison of erythromycin pledgets and clindamycin lotion in the treatment of mild to moderate facial acne vulgaris. Advances in Therapy, 1995, 12(3):172-7

Hughes 1992

Hughes, B. R., Norris, J. F., Cunliffe, W. J. A double-blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. Clinical and Experimental Dermatology, 1992, 17(3):165-8

Hunt 1992

Hunt, M. J., Barnetson, R. S. A comparative study of gluconolactone versus benzoyl peroxide in the treatment of acne. The Australasian Journal of Dermatology, 1992, 33(3):131-4

Ianosi 2013

Ianosi, S., Neagoe, D., Calbureanu, M., Ianosi, G. Investigator-blind, placebo-controlled, randomized comparative study on combined vacuum and intense pulsed light versus intense pulsed light devices in both comedonal and papulopustular acne. Journal of Cosmetic and Laser Therapy, 2013, 15(5):248-54

Iraji 2007

Iraji, F., Sadeghinia, A., Shahmoradi, Z., Siadat, A. H., Jooya, A. Efficacy of topical azelaic acid gel in the treatment of mild-moderate acne vulgaris. Indian Journal of Dermatology, Venereology and Leprology, 2007, 73(2):94-6

Jaisamrarn 2014

Jaisamrarn, U., Chaovisitsaree, S., Angsuwathana, S., Nerapusee, O. A comparison of multiphasic oral contraceptives containing norgestimate or desogestrel in acne treatment: A randomized trial. Contraception, 2014, 90(5):535-41.

Jung 2009

Jung, J. Y., Choi, Y. S., Yoon, M. Y., Min, S. U., Suh, D. H. Comparison of a pulsed dye laser and a combined 585/1,064-nm laser in the treatment of acne vulgaris. Dermatologic Surgery, 2009, 35(8): 1181-7

Katsambas 1989

Katsambas, A., Graupe, K., Stratigos, J. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. Acta Dermato-Venereologica, Supplementum, 1989, 143:35-9

Kaur 2015

Kaur, J., Sehgal, V. K., Gupta, A. K., Singh, S. P. A comparative study to evaluate the efficacy and safety of combination topical preparations in acne vulgaris. International Journal of Applied & Basic Medical Research, 2015, 5(2): 106–110

Korkut 2005

Korkut, C., Piskin, S. Benzoyl peroxide, adapalene, and their combination in the treatment of acne vulgaris. 2005. Journal of Dermatology, 2005, 32(3): 169-73

Kwon 2019

Kwon, H. H., Choi, S. C., Jung, J. Y., Bae, Y., Park, G. H. A Novel Combined Light-Based Treatment of Acne Vulgaris with 1,450-nm Diode Laser and 450-nm Blue Light. Dermatologic Surgery, 2019, 45(9):1147-54

Langner 2007

Langner, A., Sheehan-Dare, R., Layton, A. A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide (Duac) and erythromycin + zinc acetate (Zineryt) in the treatment of mild to moderate facial acne vulgaris. Journal of the European Academy of Dermatology & Venereology, 2007, 21(3):311-9

Langner 2008

Langner, A., Chu, A., Goulden, V., Ambroziak, M. A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide and adapalene in the treatment of mild to moderate facial acne vulgaris. British Journal of Dermatology, 2008, 158(1):122-9

Leheta 2009

Leheta, T. M. Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities. Journal of Cosmetic and Laser Therapy, 2009, 11(2):118-24

Leyden 1987

Leyden, J. J., Shalita, A. R., Saatjian, G. D., Sefton, J. Erythromycin 2% gel in comparison with clindamycin phosphate 1% solution in acne vulgaris. Journal of the American Academy of Dermatology, 1987, 16(4):822-7

Leyden 2001

Leyden, J., Grove, G. L. Randomized facial tolerability studies comparing gel formulations of retinoids used to treat acne vulgaris. Cutis, 2001, 67(6 Suppl):17-27

Leyden 2002

Leyden, J. J., Tanghetti, E. A., Miller, B., Ung, M., Berson, D., Lee, J. Once-daily tazarotene 0.1 % gel versus once-daily tretinoin 0.1 % microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. Cutis, 2002, 69(2 Suppl):12-9

Lucky 2001

Lucky, A., Jorizzo, J. L., Rodriguez, D., Jones, T. M., Stewart, D. M., Tschen, E. H., Kanof, N. B., Miller, B. H., Wilson, D. C., Loven, K. H. Efficacy and tolerance of adapalene cream 0.1% compared with its cream vehicle for the treatment of acne vulgaris. Cutis, 2001, 68(4 Suppl):34-40

Maleszka 2011

Maleszka, R., Turek-Urasinska, K., Oremus, M., Vukovic, J., Barsic, B. Pulsed azithromycin treatment is as effective and safe as 2-week longer daily doxycycline treatment of acne vulgaris: a randomized, double-blind, noninferiority study. Skinmed, 2011, 9(2):86-94.

Marazzi 2002a

Marazzi, P., Boorman, G.C., Donald, A.E., Davies, H.D. Clinical evaluation of Double Strength Isotrexin versus Benzamycin in the topical treatment of mild to moderate acne vulgaris. Journal of Dermatological Treatment, 2002, 13(3):111-7

Milani 2003

Milani, M., Bigardi, A., Zavattarelli, M. Efficacy and safety of stabilised hydrogen peroxide cream (Crystacide) in mild-to-moderate acne vulgaris: A randomised, controlled trial versus benzoyl peroxide gel. Current Medical Research and Opinion, 2003, 19(2):135-8

Mills 1986

Mills Jr, O. H., Kligman, A. M., Pochi, P., Comite, H. Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. International Journal of Dermatology, 1986, 25(10): 664-7

Mills 1992

Mills, O. H., Berger, R. S., Kligman, A. M., McElroy, J. A., Di Matteo, J. A comparative study of Erycette vs Cleocin-T. Advances in Therapy, 1992, 9(1):14-20

Mohammadi 2019

Mohammadi, S., Pardakhty, A., Khalili, M., Fathi, R., Rezaeizadeh, M., Farajzadeh, S., Mohebbi, A., Aflatoonian, M. Niosomal benzoyl peroxide and clindamycin lotion versus niosomal clindamycin lotion in treatment of acne vulgaris: a randomized clinical trial. Advanced Pharmaceutical Bulletin, 2019, 9(4): 578–83

Mokhtari 2017

Mokhtari, F., Gholami, M., Siadat, A. H., Jafari-Koshki, T., Faghihi, G., Nilforoushzadeh, M. A., Hosseini, S. M., Abtahi-Naeini, B. Efficacy of intense-pulsed light therapy with topical benzoyl peroxide 5% versus benzoyl peroxide 5% alone in mild-to-moderate acne vulgaris: A randomized controlled trial. Journal of Research in Pharmacy Practice, 2017, 6(4): 199–205

Na 2007

Na, J. I., Suh, D. H. Red light phototherapy alone is effective for acne vulgaris: Randomized, single-blinded clinical trial. Dermatologic Surgery, 2007, 33(10): 1228-33

Nestor 2016

Nestor, M. S., Swenson, N., Macri, A., Manway, M., Paparone, P. Efficacy and tolerability of a combined 445nm and 630nm over-the-counter light therapy mask with and without topical salicylic acid versus topical benzoyl peroxide for the treatment of mild-to-moderate acne vulgaris. Journal of Clinical and Aesthetic Dermatology, 2016, 9(3):25-35

Ozolins 2004

Ozolins, M., Eady, E. A., Avery, A. J., Cunliffe, W. J., Wan Po, A. L., O'Neill, C., Simpson, N. B., Walters, C. E., Carnegie, E., Lewis, J. B., Dada, J., Haynes, M., Williams, K., Williams, H. C. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet, 2004, 364(9452):2188-95

Palombo-Kinne 2009

Palombo-Kinne, E., Schellschmidt, I., Schumacher, U., Graser, T. Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. Contraception, 2009, 79(4):282-9

Papageorgiou 2000a

Papageorgiou, P., Katsambas, A., Chu, A. Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris. British Journal of Dermatology, 2000, 142(5):973-8

Papageorgiou 2000b

Papageorgiou, P. P., Chu, A.C. Chloroxylenol and zinc oxide containing cream (Nels cream) vs. 5% benzoyl peroxide cream in the treatment of acne vulgaris. A double-blind, randomized, controlled trial. Clinical and Experimental Dermatology, 2000, 25(1):16-20

Pazoki-Toroudi 2010

Pazoki-Toroudi, H., Nassiri-Kashani, M., Tabatabaie, H., Ajami, M., Habibey, R., Shizarpour, M., Babakoohi, S., Rahshenas, M., Firooz, A. Combination of azelaic acid 5% and erythromycin 2% in the treatment of acne vulgaris. Journal of Dermatological Treatment, 2010, 21(3):212-6

Pazoki-Toroudi 2011

Pazoki-Toroudi, H., Nilforoushzadeh, M. A., Ajami, M., Jaffary, F., Aboutaleb, N., Nassiri-Kashani, M., Firooz, A. Combination of azelaic acid 5% and clindamycin 2% for the treatment of acne vulgaris. Cutaneous and Ocular Toxicology, 2011, 30(4):286-91

Phillippo 2019

Phillippo, D.M., Dias, S., Welton, N.J., Caldwell, D.M., Taske, N., Ades, A.E. Threshold Analysis as an Alternative to GRADE for Assessing Confidence in Guideline Recommendations Based on Network Meta-analyses. Annals of Internal Medicine, 2019, 170(8):538-46.

Poli 2005

Poli, F., Ribet, V., Lauze, C., Adhoute, H., Morinet, P. Efficacy and safety of 0.1% retinaldehyde/ 6% glycolic acid (diacneal) for mild to moderate acne vulgaris. A multicentre, double-blind, randomized, vehicle-controlled trial. Dermatology (Basel, Switzerland), 2005, 210 Suppl 1:14-21

Rademaker 2014

Rademaker, M., Wishart, J. M., Birchall, N. M. Isotretinoin 5 mg daily for low-grade adult acne vulgaris - A placebo-controlled, randomized double-blind study. Journal of the European Academy of Dermatology and Venereology, 2014, 28(6):747-54

Ragab 2014

Ragab, M., Hussein, T., Salem, M. Photodynamic therapy using 5-aminolevulinic acid and intense pulsed light against intense pulsed light alone in the treatment of acne vulgaris. Journal of the Egyptian Women's Dermatologic Society, 2014, 11(3):173–180

Rao 2009

Rao, G. R. R., Ghosh, S., Dhurat, R., Sharma, A., Dongre, P., Baliga, V. P. Efficacy, safety, and tolerability of microsphere adapalene vs. conventional adapalene for acne vulgaris. International Journal of Dermatology, 2009, 48(12): 1360-5

Redmond 1997

Redmond, G. P., Olson, W. H., Lippman, J. S., Kafrissen, M. E., Jones, T. M., Jorizzo, J. L. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: A randomized, placebo-controlled trial. Obstetrics and Gynecology, 1997, 89(4):615-22

Rizer 2001

Rizer, R. L., Sklar, J. L., Whiting, D., Bucko, A., Shavin, J., Jarratt, M. Clindamycin phosphate 1% gel in acne vulgaris. Advances in Therapy, 2001, 18:244–52

Rosen 2003

Rosen, M. P., Breitkopf, D. M., Nagamani, M. A randomized controlled trial of second- versus third-generation oral contraceptives in the treatment of acne vulgaris. American Journal of Obstetrics and Gynecology, 2003, 188(5):1158-60

Sadick 2010b

Sadick, N. S., Laver, Z., Laver, L. Treatment of mild to moderate acne vulgaris using a combined light and heat energy device: home-use clinical study. Lasers in Surgery and Medicine, 2010, 12(6):276-83

Sagi 2000

Sagi, E., Vardy, D., Shemer, A., Laver, Z., Amichi, B., Shiri, J., Zuckerman, F., Oren, I., Friedman, R., David, M. Topical treatment of acne vulgaris with a combination of erythromycin 2% plus bifonazole 1% once daily compared to erythromycin 2% alone twice daily: A randomized, double-blind, controlled, clinical study. Journal of Dermatological Treatment, 2000, 11(4):247-51

Schaller 2016

Schaller, M., Sebastian, M., Rees, C., Seidel, D., Hennig, M. 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. Journal of the European Academy of Dermatology and Venereology,2016, 30(6):966-73

Seaton 2003

Seaton, E. D., Charakida, A., Mouser, P. E., Grace, I., Clement, R. M., Chu, A. C. Pulsed-dye laser treatment for inflammatory acne vulgaris: randomised controlled trial. Lancet, 2003, 362(9393):1347-52

Shalita 1984

Shalita, A. R., Smith, E.B., Bauer E. Topical Erythromycin v Clindamycin Therapy for Acne. A Multicenter, Double-blind Comparison. Archives of Dermatology, 1984, 120(3):351-5

Shalita 1999

Shalita, A. R., Chalker, D. K., Griffith, R. F., Herbert, A. A., Hickman, J. G., Maloney, J. M., Miller, B. H., Tschen, E. H., Chandraratna, R. A., Gibson, J. R. et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. Cutis, 1999, 63(6):349-54

Shalita 2005

Shalita, A., Miller, B., Menter, A., Abramovits, W., Loven, K., Kakita, L. Tazarotene cream versus adapalene cream in the treatment of facial acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. Journal of Drugs in Dermatology, 2005, 4(2):153-8

Shwetha 2014

Shwetha, H., Geetha, A., Revathi, T. N. A comparative study of efficacy and safety of combination of topical 1% clindamycin and 0.1% adapalene with 1% clindamycin and 2.5% benzoyl peroxide in mild to moderate acne at a tertiary care hospital. Journal of Chemical and Pharmaceutical Research, 2014, 6(2):736-41

Smith 1980b

Smith, E. B., Padilla, R. S., McCabe, J. M., Becker, L. E. Benzoyl peroxide lotion (20 percent) in acne. Cutis, 1980, 25(1):90-2

Smith 2006

Smith, S. R., Kemper, S. A study of 5.5% benzoyl peroxide microsphere cream versus 6% benzoyl peroxide gel in the treatment of acne vulgaris. Cosmetic Dermatology, 2006, 19(8):537-42

Sommer 1997

Sommer, S., Bojar, R., Cunliffe, W. J., Holland, D., Holland, K. T., Naags, H. Investigation of the mechanism of action of 2% fusidic acid lotion in the treatment of acne vulgaris. Clinical and Experimental Dermatology, 1997, 22(5): 211-15

Stinco 2007

Stinco, G., Bragadin, G., Trotter, D., Pillon, B., Patrone, P. Relationship between sebostatic activity, tolerability and efficacy of three topical drugs to treat mild to moderate acne. Journal of the European Academy of Dermatology and Venereology, 2007, 21(3):320-5

Stoughton 1987

Stoughton, R. B., Leyden, J. J. Efficacy of 4 percent chlorhexidine gluconate skin cleanser in the treatment of acne vulgaris. Cutis, 1987, 39(6):551-3

Strauss 1984b

Strauss, J. S., Stranieri, A. M. Acne treatment with topical erythromycin and zinc: effect of Propionibacterium acnes and free fatty acid composition. Journal of the American Academy of Dermatology, 1984, 11(1):86-89

Swinyer 1988

Swinyer, L. J., Baker, M. D., Swinyer, T. A., Mills, O. H., Jr. A comparative study of benzoyl peroxide and clindamycin phosphate for treating acne vulgaris. British Journal of Dermatology, 1988, 119(5): 615-22

Tan 2018

Tan, J., Bissonnette, R., Gratton, D., Kerrouche, N., Canosa, J. M. The safety and efficacy of four different fixed combination regimens of adapalene 0.1%/benzoyl peroxide 2.5% gel for the treatment of acne vulgaris: results from a randomised controlled study. European Journal of Dermatology, 2018, 28(4):502-8.

Thiboutot 2001a

Thiboutot, D., Gold, M. H., Jarratt, M. T., Kang, S., Kaplan, D. L., Millikan, L., Wolfe, J., Loesche, C., Baker, M. Randomized controlled trial of the tolerability, safety, and efficacy of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. Cutis, 2001, 68(4 Suppl):10-9

Thiboutot 2006

Thiboutot, D., Pariser, D. M., Egan, N., Flores, J., Herndon J. H. Jr, Kanof, N. B., Kempers, S. E., Maddin, S., Poulin, Y. P., Wilson, D. C., Hwa, J., Liu, Y., Graeber, M. Adapalene Study Group. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. Journal of the American Academy of Dermatolology, 2006, 54(2):242-50

Thiboutot 2007

Thiboutot, D. M., Weiss, J., Bucko, A., Eichenfield, L., Jones, T., Clark, S., Liu, Y., Graeber, M., Kang, S. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: Results of a multicenter, randomized double-blind, controlled study. Journal of the American Academy of Dermatology, 2007, 57(5):791-9

Thiboutot 2009

Thiboutot, D., Eichenfield, L., Shalita, A., Del Rosso, J. Q., Swinyer, L., Tanghetti, E., Tschen, E., Parr, L. A 3-step acne system containing solubilized benzoyl peroxide versus clindamycin-benzoyl peroxide. Cutis, 2009, 84(1):48-55

Thielitz 2015

Thielitz, A., Lux, A., Wiede, A., Kropf, S., Papakonstantinou, E., Gollnick, H. 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. Journal of the European Academy of Dermatology and Venereology, 2015, 29(4):789-96

Thorneycroft 2004

Thorneycroft, I. H., Gollnick, H., Schellschmidt, I. Superiority of a combined contraceptive containing drospirenone to a triphasic preparation containing norgestimate in acne treatment. Cutis, 2004, 74(2):123-30

Tirado-Sanchez 2009

Tirado-Sanchez, A., Ponce-Olivera, R. M. Efficacy and tolerance of superoxidized solution in the treatment of mild to moderate inflammatory acne. A double-blinded, placebo- controlled, parallel-group, randomized, clinical trial. Journal of Dermatological Treatment, 2009, 20(5): 289-292

Tirado-Sanchez 2013

Tirado-Sanchez, A., Espindola, Y. S., Ponce-Olivera, R. M., Bonifaz, A. 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). Journal of Cosmetic Dermatology, 2013, 12(2):103-7

Tong 1994

Tong, D., Peters., W., Barnetson, R. S. C. Evaluation of 0.75% metronidazole gel in acne - A double-blind study. Clinical and Experimental Dermatology, 1994, 19(3): 221-3

Van Vloten 2002

Van Vloten, W. A., Van Haselen, C. W., Van Zuuren, E. J., Gerlinger, C., Heithecker, R. The effect of 2 combined oral Contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. Cutis, 2002, 69(4 Suppl):2-15

Wiegell 2006b

Wiegell, S. R., Wulf, H. C. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: A blinded, randomized, controlled trial. British Journal of Dermatology, 2006, 154(5): 969-76

Wolf 2003

Wolf, J. E., Jr., Kaplan, D., Kraus, S. J., Loven, K. H., Rist, T., Swinyer, L. J., Baker, M. D., Liu, Y. S., Czernielewski, J. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. Journal of the American Academy of Dermatology, 2003, 49(3):211-17

Xu 2016

Xu, J. H., Lu, Q. J., Huang, J. H., Hao, F., Sun, Q. N., Fang, H., Gu, J., Dong, X. Q., Zheng, J., Luo, D., 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. Journal of the European Aacademy of Dermatology and Venereology, 2016, 30(7):1176-8

Yentzer 2010

Yentzer, B. A., Ade, R. A., Fountain, J. M., Clark, A. R., Taylor, S. L., Fleischer, A. B., Feldman, S. R. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: a randomized controlled trial. Cutis, 2010, 86(2):103-8

Zayed 2019

Zayed, A. A., Sobhi, R. M., El Aguizy, R. M. S., Sabry, D., Mahmoud, S. B. Sequential peeling as a monotherapy for treatment of milder forms of acne vulgaris. Journal of Cosmetic Dermatology, 2019, 19(6): 1381-7

Zheng 2019

Zheng, Y., Yin, S., Xia, Y., Chen, J., Ye, C., Zeng, Q., Lai, W. Efficacy and safety of 2% supramolecular salicylic acid compared with 5% benzoyl peroxide/0.1% adapalene in the acne treatment: a randomized, split-face, open-label, single-center study. Cutaneous and Ocular Toxicology, 2019, 38(1):48-54

Appendices

Appendix A – Review protocol

Review protocol for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

A single review protocol and literature search was used to identify randomised trials of treatments for acne. Outcomes were prioritised for either pairwise or network meta-analysis (NMA) and the evidence was divided according to the severity of acne into mild to moderate and moderate to severe categories. The evidence was then summarised in four separate reviews covering the treatment of:

- mild to moderate acne (NMA)
- mild to moderate acne (pairwise meta-analysis)
- moderate to severe acne (NMA)
- moderate to severe acne (pairwise meta-analysis)

Table 6: Review protocol

Field	Content
PROSPERO registration number	CRD42020154100
Review title	Comparative effectiveness, acceptability and tolerability of topical or oral pharmacological and physical interventions in the treatment of acne vulgaris: a systematic review using network and pairwise meta-analysis
Review question	2.1 What is the effectiveness of topical treatments individually or in combination in the treatment of acne vulgaris? 3.1 What is the effectiveness of oral antibiotic treatments in the treatment of acne vulgaris? 4.1 What is the effectiveness of combining an oral antibiotic with a topical agent compared to an oral antibiotic alone in the treatment of acne vulgaris? 5.1 What is the optimal duration of antibiotic treatments (topical and systemic) for acne vulgaris? 6.1 What is the effectiveness of oral hormonal contraceptives in the treatment of acne vulgaris? 6.2 What is the effectiveness of non- hormonal contraceptive anti-androgens (including spironolactone) in the treatment of acne vulgaris? 6.3 What is the effectiveness of metformin in the treatment of acne vulgaris?

Field	Content
	8.1 What is the effectiveness of oral isotretinoin in the treatment of acne vulgaris? 9.1 What is the effectiveness of physical treatments for acne vulgaris?
Objective	The objective of this review is to establish which topical or oral pharmacological and physical interventions are effective, acceptable and tolerable in the treatment of acne vulgaris.
Searches	• The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date: No restriction • Language of publication: English language only • Publication status: Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias. Unpublished data will also be excluded. • Standard exclusions filter (animal studies/low level publication types) will be applied • For each search, the principal database search strategy is quality assured by a second information specialist using an adaption of the PRESS 2015 Guideline Evidence-Based Checklist Other search methods will involve scanning the reference lists of all eligible systematic reviews for published studies meeting inclusion criteria.
Condition or domain being studied	Acne vulgaris
Population	Inclusion: People with acne vulgaris, of all ages and levels of symptom severity. Studies need to provide data specific to people with mild to moderate acne, and/or people with moderate to severe acne. See under 'Analysis of sub-groups' for the approach followed in order to categorise population in the studies into mild to moderate acne or moderate to severe acne. All settings (community, primary, secondary, and tertiary health care) will be considered. Exclusions: • Neonatal acne • People with post-inflammatory dyspigmentation • Trials recruiting specifically people with acne vulgaris and polycystic ovary syndrome (PCOS) • Trials of maintenance treatment ('relapse prevention' trials), which recruit people currently in remission or people who have responded to treatment or who have had successful treatment or who are reported to have received primary or 'acute' treatment immediately prior to randomisation to maintenance treatment.

Field	Content
	• Trials that have specifically recruited people who have not responded to previous treatment (refractory or resistant acne) for the same episode of acne; however, trials of people with recurrent or persistent acne, who are treated for a new episode of acne, will be included • Trials that include all ranges of severity • Trials with indirect population: Where studies with a mixed population (i.e. include people with acne vulgaris and another condition, e.g. hirsutism) are identified, those with <66% of the relevant population will be excluded, unless subgroup analysis for acne vulgaris is reported.
Intervention	Interventions will be categorised into the following classes, and, if relevant, subclasses (the list is non-exhaustive): ➢ **TOPICAL TREATMENTS** **Abrasive/cleaning agents** • Aluminium oxide [own class] **Anthelmintics** • Cysticide (praziquantel) [own class] • Class of avermectins: ivermectin **Antibacterials** • Class of triclocarban and triclozan **Antibiotics** • Class of sulphones (dapsone) • Fusidic acid (sodium fusidate) [own class] • Class of lincosamides (for example clindamycin) • Class of macrolides (for example clarithromycin, erythromycin with zinc acetate dihydrate) • Class of nitroimidazoles (metronidazole) • Class of carboxylic acids (mupirocin) • Class of penicillins ○ Sub-class of natural (for example almecillin) ○ Sub-class of aminopenicillins (for example ampicillin) ○ Sub-class of β-lactamase-resistant (for example methicillin) ○ Sub-class of carboxypenicillins (for example ticarcillin) ○ Sub-class of ureidopenicillins (for example azlocillin) ○ Sub-class of other penicillins (mecillinam, pivmecillinam hydrochloride) • Class of pleuromutilins (for example retapamulin)

Field	Content
	Antiseptics • Benzoyl peroxide (trade: Acnecide, Brevoxyl, Panoxyl) [own class] • Chlorhexidine gluconate (trade: Acnemed, Cepton) or digluconate [own class] **Dicarboxylic acids** • Azelaic acid [own class] **Vitamin B3** • Nicotinamide (niacinamide) [own class] **Retinoids or retinoid-like agents** • Class of retinoids or retinoid-like agents (adapalene, isotretinoin, retinol, tazarotene, tretinoin) **Combined interventions** • Benzoyl peroxide & potassium hydroxyguinoline sulfate [own class] • Class of benzoyl peroxide & retinoid (benzoyl peroxide + adapalene) • Class of benzoyl peroxide & lincosamide (benzoyl peroxide + clindamycin) • Class of lincosamides & retinoid (clindamycin + tretinoin) • Class of macrolides & retinoid (erythomycin + retinoid) [topical] • Germolene (phenol 1.2% + chlorhexidine diculconate [own class] ➢ **ORAL ANTIBIOTICS** • Class of carbapenems (for example imipenem, meropenem) • Class of carbapenems with cilastatin (imipenem with cilastatin) • Class of carbapenems with b lactamase inhibitor (meropenem with vaborbactam) • Class of cephamycins/cephalosporins ○ Sub-class of 1st-generation (for example cefadroxil) ○ Sub-class of 2nd-generation (for example cefaclore) ○ Sub-class of 3rd-generation (for example cefdinir) ○ Sub-class of 4th-generation (for example cefozopran) ○ Sub-class of 5th-generation (for example ceftolozane) • Class of cephamycins/cephalosporins with β-lactamase inhibitor (for example ceftraroline or ceftazidime with avibactam, cefoperazone with sulbactam, ceftolozane with tazobactam) • Class of sulphones (dapsone) • Fusidic acid (sodium fusidate) [own class] • Class of lincosamides (for example clindamycin) • Class of macrolides (for example clarithromycin, erythromycin)

Field	Content

	• Class of monobactams (aztreonam)
	• Class of monobactams with β-lactamase inhibitor (aztreonam with avibactam)
	• Class of penicillins
	  ○ Sub-class of natural (for example almecillin)
	  ○ Sub-class of aminopenicillins (for example ampicillin)
	  ○ Sub-class of β-lactamase-resistant (for example methicillin)
	  ○ Sub-class of carboxypenicillins (for example ticarcillin)
	  ○ Sub-class of ureidopenicillins (for example azlocillin)
	  ○ Sub-class of other penicillins (mecillinam, pivmecillinam hydrochloride)
	• Class of penicillin with β-lactamase inhibitor (for example co-amoxiclav [amoxicillin with clavulanic acid], piperacillin with tazobactam, ticaricillin with clavulanic acid, sultamicillin [ampicillin with sulbactam])
	• Class of penicillin with flucloxacilin (co-fluampicil [ampicillin + flucloxacilin])
	• Class of pleuromutilins (for example retapamulin)
	• Class of quinolones
	  ○ Sub-class of 1st-generation (for example rosoxacin)
	  ○ Sub-class of 2nd-generation (for example ofloxacin)
	  ○ Sub-class of 3rd-generation (for example temafloxacin)
	  ○ Sub-class of 4th-generation (for example sitafloxacin)
	• Class of tetracyclines (for example doxycycline, oxytetracycline)
	• Trimethoprim [own class]
	• Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMX) [own class]
	
	➢ **TOPICAL TREATMENTS COMBINED WITH ORAL ANTIBIOTICS**
	
	➢ **ORAL HORMONAL CONTRACEPTIVES AND HORMONE-MODIFYING AGENTS**
	• Co-cyprindiol (ethinylestradiol + cyproterone acetate) [own class of combined oral contraceptive]
	• Class of combined oral contraceptives
	  ○ Sub-class of 2nd generation (oestrogen, for example ethinylestradiol or estradiol or mestranol combined with levonorgestrel or norethisterone)
	  ○ Sub-class of 3rd generation (oestrogen, for example ethinylestradiol combined with desogestrel or gestodene or norgestimate)
	  ○ Sub-class of 4th generation (oestrogen, for example ethinylestradiol or estradiol combined with dienogest or drospirenone or nomegestrol acetate)
	
	Monophasic and phasic combined oral contraceptives containing the same hormones will be analysed as separate interventions within their sub-class.
	
	• Class of progestogen-only oral contraceptives
	  ○ Sub-class of 1st generation (for example medroxyprogesterone acetate)
	  ○ Sub-class of 2nd generation (for example levonorgestrel, norethisterone/ norethindrone)

Field	Content
	○ Sub-class of 3rd generation (for example desogestrel, norgestimate, gestodene) ○ Sub-class of 4th generation (for example dienogest, drospirenone, nomegestrol acetate) • Class of selective aldosterone receptor antagonists (for example spironolactone alone or combined with furosemide or hydroflumethiazide [co-flumactone], eplerenone, canrenone) • Class of 5α-reductase inhibitors (dutasteride, finasteride, tamsulosin with dutasteride) • Class of other non-steroidal anti-androgens (for example abiraterone acetate, apalutamide, bicalutamide, cyproterone acetate, clormadinone acetate, enzalutamide, flutamide) • Metformin [own class] ➢ **ORAL ISOTRETINOIN** • Class of oral retinoid and total cumulative dose ≥ 120mg/kg (single course) ○ Sub-class of daily dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ○ Sub-class of alternate day dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ○ Sub-class of less frequent or other dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) • Class of oral retinoid and total cumulative dose < 120mg/kg (single course) ○ Sub-class of daily dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ○ Sub-class of alternate day dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ○ Sub-class of less frequent or other dosing (dose ≥0.5mg/kg/day or <0.5mg/kg/day) ➢ **PHYSICAL TREATMENTS** • Class of chemical peels ○ Sub-class of superficial peels ○ Sub-class of moderate peels ○ Sub-class of deep peels for example amino fruit acid, glycolic acid, Jessner's peel, lactic acid, salicylic acid, trichloroacetic acid [TCA]; these will be categorised into different sub-classes as reported in the included studies, according to the concentration of their active ingredient and treatment duration. • Comedone extraction [own class] • Class of photothermal therapy (for example fractional erbium glass laser) • Class of photochemical therapy (for example blue or red light and their combination) • Class of photochemical and photothermal therapy (for example potassium titanyul phosphate laser, Intense Pulsed Light [IPL], Pulsed Dye Laser) • Class of photodynamic therapy (for example 5-aminolevuliniv acid [ALA], liposomal methylene blue gel, methylaminolevulinate [MAL]) • Smoothbeam™ laser [own class] • Photopneumatic therapy (for example intense pulsed light + vacuum)

Field	Content
	• Radiofrequency (for example fractional microneedling, bipolar) Combined interventions within and across classes will be considered. Only drug classes available in the UK will be considered. To estimate class effects, we will consider any intervention belonging to a class, irrespective of its availability in the UK. However, we will only report individual drug effects for interventions that are currently (or soon expected to be) available in the UK. These may include pharmacological interventions that are (or soon expected to be) licensed in the UK for the treatment of acne or another condition. If existing evidence is not adequate to allow estimation of individual drug effects within each class, we will exclude drugs that are not available in the UK. We will include pharmacological interventions listed above, alone or in combinations, administered in fixed or flexible doses within the therapeutic range recommended by the British National Formulary (BNF), or, if not available in the UK, recommended by the US Food and Drug Administration (FDA). The only exception will be oral isotretinoin, for which we will allow lower doses to be considered, as there is indication that these are efficacious while the rate of isotretinoin-related side effects is lower. Trial arms evaluating a class or sub-class of pharmacological interventions that is of interest, as determined above (for example a mixture of oral macrolides, a mixture of COC), rather than an individual drug, will be included as separate nodes within the class. However, trial arms evaluating broad types of interventions that are wider than classes as defined above (for example oral antibiotics) will be excluded from consideration. We will consider substantially different durations of treatment within the same class/drug as different interventions, that is as different network nodes, as duration of treatment may impact on its effects. We will consider the following durations of treatment: 0 to <6 weeks; ≥6 to <12 weeks, ≥12 to <24 weeks, ≥24 weeks. We will not consider in the NMA interventions that do not meet inclusion criteria, unless they act as the sole connectors of the interventions of interest in the network. In this case, interventions not meeting inclusion criteria will be included in the NMA but will not form part of the decision problem. A network diagram for all outcomes of interest will be constructed to explore whether all interventions are connected to the network. If more than one networks are formed, then separate NMAs will be conducted for each network, as long as the network contains at least 3 interventions that are part of the decision problem. If pairs of interventions are not connected to a network, they will be analysed in pairwise meta-analysis. We assume that any individual that meets all inclusion criteria is, in principle, equally likely to be randomized to any of the interventions in the synthesis comparator set.
Comparator	• No treatment • Waiting list • Pill placebo • Other active intervention

Field	Content
	• Sham physical treatment
Types of study to be included	Included study designs: • Systematic reviews/meta-analyses of randomised controlled trials (RCTs) • RCTs (individual or cluster); this includes RCTs of topical or physical treatments that randomise different parts of body (for example left-right side of face/body) in each participant Excluded study designs: • Quasi-randomised or non-randomised controlled trials • Case-control studies • Cohort studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Non-comparative studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	• Trials with <50% completion data (drop-out of ≥ 50%)
Context	Recommendations will apply to those receiving care in any healthcare setting (for example community, primary care, secondary care, tertiary care). For antibiotics, the committee will consider the evidence in conjunction with considerations regarding antimicrobial resistance patterns (for example ESPAUR report), the safety of the specific antibiotic as determined by any relevant MHRA Drug Safety Update (https://www.gov.uk/drug-safety-update) and Summary of Product characteristics (https://www.medicines.org.uk/emc), and the principle that the use of antibiotics should be limited or optimised where possible. Only the short-term safety of interventions in the treatment of acne vulgaris will be covered. For the long-term safety of interventions, see BNF and MHRA. Relevant legislation and national policy will also inform the guideline [see 'Developing NICE guidelines: the manual' (p. 102)].

Primary outcomes (critical outcomes)	**Critical outcomes**
	Efficacy
	• Clinician-rated improvement at treatment endpoint
	  ○ % change in acne lesion count
	  ○ change or final score on a validated acne severity scale
	We will prioritise for extraction and analysis the mean of the % change in acne lesion count, where reported together with a standard error (or a standard error can be derived). If this is not reported, mean change in lesion counts from baseline will be

Field	Content
	prioritised, as long as it is reported with a standard error and also mean and standard error of counts at baseline. If this is not reported, the mean counts and standard error at baseline and treatment endpoint will be prioritised, accounting for correlations between baseline and final counts, exploring such correlations from studies reporting change, baseline and final scores. In studies where such data on lesion counts are not reported, we will extract data on validated acne severity scale scores, if the latter are available. We will prioritise mean % change in scale if it is reported with a standard error, followed by mean change from baseline if it is reported with a standard error, and baseline mean score and standard error are available. If neither of these are reported we will extract mean scores at baseline and treatment endpoint, accounting for correlations between baseline and final scores using a correlation based on studies that report all of change, baseline and final scores. These two types of data will be synthesised, where appropriate (as explained below), to jointly estimate treatment effects on the two outcomes, to estimate a single clinician-rated measure of outcome, expressing mean % of improvement of acne symptoms. <u>Regarding mean % change in acne lesion count:</u> If summaries for total lesion count are reported, these will be extracted and used in the analysis. In studies that do not report total lesion count, but do report count of different types of lesions, we will estimate the change in total lesion count from reported data, where this is possible. If this is not possible, we will extract the change in lesion count for the following types of lesions in this hierarchy, as a proxy for total lesion count: • All inflammatory lesions (pustules, papules, nodules, cysts) • Sum of any of the types of inflammatory lesions, according to data availability • Pustules • Papules • Nodules • Cysts • Non-inflammatory lesions (comedones) <u>Regarding data on validated acne severity scale scores:</u> We will compare the relative effects on mean % change in acne scale scores and mean % change in acne lesion score in studies that report both. This will be achieved by visual inspection of a scatter plot of relative effect on the scale vs count, by scale, and also by weighted linear regression. Only scales with a sufficiently good visual fit and model fit in the regression will be included. For scales where these relative effects are found to be sufficiently linearly related, we will include the respective extracted scale score data in the NMA from studies reporting only this type of outcome, using a bivariate NMA model. For scales where relative effects measured using the two types of outcomes are not sufficiently linearly related, the extracted data will not be considered in the NMA and studies reporting only symptom scale scores on those scales (and not acne lesion count) will be excluded from the analysis.

Field	Content

	Only one acne symptom scale will be used per study. If a study reports data on more than one scale, we will prioritise data from scales according to the extent of the strength of the linear relationship between their relative effects and the relative effects obtained from change in acne lesion count.
	
	Correlations between counts of different types of acne lesions and between acne lesions and acne symptom scales will also be sought in published literature (for example Allen & Smith, 1982).
	
	• Participant-reported improvement at treatment endpoint
	  ○ Change in acne severity or symptoms (e.g. assessed using global acne score)
	
	• Prevention of scarring at any follow-up
	  ○ Final / change in number of scars from baseline
	  ○ Incidence of scarring
	
	Reference:
	Allen BS, Smith JG Jr. Various parameters for grading acne vulgaris. Archives of Dermatology 1982; 118(1): 23-5.

Secondary outcomes (important outcomes)	**Important outcomes** ***Acceptability*** • Treatment discontinuation for any reason (numbers of trial participants “leaving the study early”, “leaving the study before treatment completion” or “loss to follow-up”) by treatment endpoint ***Tolerability*** • Treatment discontinuation due to side effects by treatment endpoint ***Relapse*** • Relapse after treatment at follow-up ***Side effects*** The following specific short-term side effects will be assessed for comparisons of treatments within the same class or those that involve an inactive arm (e.g. placebo, no or sham treatment): - Topical treatments, oral antibiotics or combination treatments: skin irritation (e.g. burning or tingling, dryness/irritation, swelling) - Topical retinoids: sensitivity to light - Oral antibiotics: gastrointestinal side effects; thrush candidiasis

Field	Content
	- Hormonal contraceptives and hormone-modifying agents: breast tenderness; neurological side effects (headache/migraine, mood disturbance, nausea); sexual dysfunction - Hormonal contraceptives: breakthrough bleeding; mood disturbance - Hormone-modifying agents: hepatobiliary side effects. For aldosterone receptor antagonists: renal side effects - Metformin: gastrointestinal side effects - Oral isotretinoin: change in mucosal and/or cutaneous condition (e.g. new chelitis); change in participant's mood (as assessed by score on validated scale); diagnosis of any psychiatric disorder (e.g. depressive disorder); suicidality - Physical treatments: persistent skin redness of 'treated' area; changes in pigmentation (e.g. hypopigmentation) - Chemical peels: heart, kidney or liver damage; infection of 'treated' area - Comedone extraction: infection of 'treated' area; pain of 'treated' area - Energy-based devices: skin irritation
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. As the review question was selected as high priority for health economic analysis, it will be subject to dual weeding and study selection; any discrepancies above 10% of the dual weeded resources will be resolved through discussion between the first and second reviewers or by reference to a third person. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). All data extraction will quality assured by a senior reviewer. Draft excluded studies and evidence tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair. An intention-to-treat (ITT) approach will be taken and where possible ITT data will be extracted; if both ITT and completer data are reported, the former will be preferred; completer data will be used only if ITT data are not reported**.**
Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the relevant version of the Cochrane RoB tool, v2. checklist (i.e. for parallel group or individually-randomised cross-over trials), as described in Developing NICE guidelines: the manual.
Strategy for data synthesis	**Method of analysis** <u>Network meta-analysis</u> Network meta-analysis (NMAs) will be used to synthesise clinician-rated improvement, prevention of scarring, acceptability and tolerability for all eligible interventions that are connected to one or more networks of at least 3 interventions. NMA will be conducted within a Bayesian framework using Markov Chain Monte Carlo simulation techniques implemented in WinBUGS 1.4.3 (Lunn 2000; Spiegelhalter 2003). Non-informative priors will be initially used, but if the data are sparse or there are convergence problems, then we will use evidence-based priors for the between studies standard deviation (Turner 2015, Rhodes 2015). To test whether prior estimates have an impact on the results, two chains with different initial values will be run simultaneously for each analysis. Convergence will be assessed by visually inspecting the mixing of the two chains in the history plots and the Brooks Gelman-Rubin diagram in WinBUGS (Brooks 1998).

Field	Content
	For the synthesis of dichotomous outcomes (discontinuation for any reason; discontinuation due to side effects) a binomial likelihood and logit link model will be used (Dias 2013a). The output of this analysis will be expressed as log-odds ratios (LORs) with 95% credible intervals (95% CrI) between all pairs of treatments assessed. For the synthesis of rate data (incidence of scarring) a Poisson likelihood and log link will be used. The output of this analysis will be expressed as log-rate ratios (LRRs) with 95% CrIs between all pairs of treatments assessed. For the synthesis of continuous data (mean of the % change in the total lesion count) a normal likelihood will be used with an identity link for the proportionate reduction in counts at treatment endpoint relative to baseline. The output of this analysis will be expressed, for each treatment relative to the reference treatment, as the difference in the mean percentage reduction in total lesions between baseline and treatment endpoint. If some studies do not report data on total lesion counts, a bivariate NMA model will be fitted which relates the treatment effects on a clinician-related acne symptom scale to treatment effects on the mean proportionate reduction from baseline. We will also evaluate the ranking of each treatment and 95% CrI in each analysis, where a rank of 1 indicates best treatment. The goodness of fit of each model will be tested by comparing the posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, with the number of data points in the model (Dempster 1997). Smaller values of the residual deviance are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the analysis (each study arm contributes one data point) (Spiegelhalter 2002). Models will also be compared using the deviance information criterion (DIC), a measure of model fit that is equal to the sum of the posterior mean deviance and the effective number of parameters, thus penalising model fit for model complexity; lower values are preferred and typically differences of at least 3 points are considered meaningful (Dias 2013a; Spiegelhalter 2002). The posterior median between-study standard deviation, which measures the heterogeneity of treatment effects estimated by trials within contrasts, will also be used to compare models. Inconsistency between direct and indirect evidence will be explored by comparing the fit of a model assuming consistency with a model which allowed for inconsistency (also known as an unrelated mean effects model (Dias 2013b). Deviance plots, in which the posterior mean deviance of the individual data points in the inconsistency model are plotted against their posterior mean deviance in the consistency model, will be inspected in order to identify studies which may have contributed to loops of evidence where inconsistency may be present. If these analyses identify potential inconsistency, further checks will be conducted using a node-split approach implemented in R using the gemtc package in R. This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared (Dias 2013b; van Valkenhoef & Kuiper, 2016). If we find evidence of inconsistency, studies contributing to loops of evidence where there may be inconsistency will be checked for data accuracy and assessment of study inclusion will be revisited against inclusion/exclusion criteria. Baseline characteristics will be checked to identify any differences in effect modifiers across studies in loops identified as potentially inconsistent. Analyses will be repeated if corrections in the data extraction or study inclusion are made. If an important effect modifier is identified, then this may be explored in subgroup analyses if sufficient evidence is available. However, if evidence of inconsistency is still present following data corrections, revisiting inclusion criteria, exploring effect modification, no further studies will be excluded from the analysis, as their results cannot be considered as less valid than those of other studies solely

Field	Content
	because of the inconsistency findings. The presence of inconsistency in the NMA will be highlighted and results will be interpreted accordingly. Sensitivity analysis: If there is sufficient evidence, we will explore bias adjustment models, where evidence from studies at high or unclear risk of bias will be down-weighted (Dias 2010; Welton 2009). Appraisal of methodological quality of the NMA: To test the robustness of the treatment recommendations based on the NMA to potential biases or sampling variation in the included evidence, we will undertake threshold analyses (Phillippo 2019). These will be carried out at two levels: (i) at a study level, assessing the influence of individual study estimates on the conclusion of the analysis and (ii) at a contrast level, where the influence of the combined evidence on each treatment contrast is considered (Caldwell 2016; Phillippo 2018; Phillippo 2019) (see appendix N). <u>Pairwise meta-analysis</u> Pairwise meta-analysis will be used for all outcomes not included in NMA, i.e. participant-reported improvement, relapse and side effects. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/. **References** Brooks SP, Gelman A (1998) Alternative methods for monitoring convergence of iterative simulations. Journal of Computational and Graphical Statistics, 7, 434-455. Caldwell DM, Ades AE, Dias S, Watkins S, Li T, Taske N, Naidoo B, Welton NJ (2016) A threshold analysis assessed the credibility of conclusions from network meta-analysis. Journal of Clinical Epidemiology, 80, 68-76. Dempster A (1997) The direct use of likelihood for significance testing. Statistics and Computing, 7, 247-252.

Field	Content
	Dias S, Welton NJ, Marinho VCC, Salanti G, Higgins JPT, Ades AE (2010) Estimation and adjustment of bias in randomised evidence by using Mixed Treatment Comparison Meta-analysis. Journal of the Royal Statistical Society (A), 173(3), 613-629. Dias S, Sutton AJ, Ades AE, Welton NJ (2013a) Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical Decision Making, 33, 607-617. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE (2013b) Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Medical Decision Making, 33, 641-656. Lunn DJ, Thomas A, Best N, Spiegelhalter D (2000) WinBUGS-A Bayesian modelling framework: Concepts, structure, and extensibility. Statistics and Computing, 10, 325-337. Phillippo DM, Dias S, Ades AE, Didelez V, Welton NJ (2018) Sensitivity of treatment recommendations to bias in network meta-analysis. Journal of the Royal Statistical Society: Series A, 181, 843-867. Phillippo DM, Dias S, Welton NJ, Caldwell DM, Taske N, Ades AE (2019) Threshold Analysis as an Alternative to GRADE for Assessing Confidence in Guideline Recommendations Based on Network Meta-analyses. Annals of Internal Medicine, 170, 538-546. Rhodes KM, Turner RM, Higgins JPT (2015) Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. Journal of Clinical Epidemiology, 68, 52-60. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A (2002) Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B, 64, 583-616. Spiegelhalter D, Thomas A, Best N, Lunn DJ (2003) WinBUGS user manual: version 1.4. Cambridge: MRC Biostatistics Unit. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT (2015) Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in Medicine, 34, 984-998. van Valkenhoef G, Kuiper J (2016) gemtc: Network Meta-Analysis Using Bayesian Methods. R package version 0.8-2. Available from: https://cran.r-project.org/web/packages/gemtc/index.html Welton NJ, Ades AE, Carlin, JB, Altman DG, Sterne JAC (2009) Models for potentially biased evidence in meta-analysis using empirically based priors. Journal of the Royal Statistical Society (A), 172(1), 119-136.

Field	Content

Analysis of sub-groups	**Severity**
	For all outcomes, we will conduct separate analyses for people with
	• mild to moderate acne vulgaris
	• moderate to severe acne vulgaris.
	We will categorise studies according to level of severity as defined in each study. The committee will be consulted to classify a study to the appropriate network/analysis if acne severity of included participants is described as moderate or it is unclear (for example it includes participants on basis of lesion counts). The committee agreed the following criteria to categorise studies into one of two severity groups, when the study population is described as having moderate acne or if the level of severity is unclear:
	• If the number of nodules in every study participant is at least 3, the study population will be categorised as having moderate to severe acne.
	• If study participants have only non-inflammatory lesions (regardless of their number) and no inflammatory lesions, the study population will be categorised as having mild to moderate acne.
	• If all study participants have fewer than 35 inflammatory lesions each, the study population will be categorised as having mild to moderate acne.
	• If all study participants have ≥ 35 inflammatory lesions each, the study population will be categorised as having moderate to severe acne.
	• If the number of inflammatory lesions varies across the study participants, and the mean number of inflammatory lesions at baseline is
	  ○ ≤ 30, the study population will be categorised as having mild to moderate acne
	  ○ ≥40, the study population will be categorised as having moderate to severe acne
	  ○ above 30 but below 40, the study will be excluded as the population is not possible to assign to a mild to moderate or moderate to severe level.
	• If a study does not report the mean number of inflammatory lesions at baseline, it will be excluded.
	• If a study includes all ranges of severity, from mild to severe, without providing sub-group analyses by level of acne severity, it will be excluded.
	Sex
	Separate NMAs will be run for decisions regarding the male and female populations, in accordance with data reported in the included studies, where only appropriate interventions for each sex are included in the network (for example, excluding hormonal contraceptives for males). We assume there is no interaction between sex and treatment effects for interventions that are suitable for both sexes.
	Age
	If possible, a random effects meta-regression according to age will be conducted for NMA of efficacy (% change in acne lesion count), to specify outcomes for people ≤25 years of age and those >25 years of age.

Field	Content		
	In order to include studies that do not report results by age-group, we will need to estimate proportion of participants below/above 25 years of age in studies of mixed population that don't report results by age. If this is not reported, proportions in age group can be approximated if the study reports age ranges, mean age and standard deviation, median age and quartile range, etc. This requires an assumption as to the distribution of age in the study population, which can be based on inspection of the reported summaries (normal if evidence of symmetry or log-normal if skewed). We will perform this analysis by age only if at least 90% of the studies meeting inclusion criteria provide sufficient information that would allow us to estimate the proportion of participants >25 and ≤25 years of age. If we are able to follow this approach, we will exclude the remaining studies that do not provide this information. If <90% of studies meeting inclusion criteria provide relevant information on age, then we will include all studies, irrespective of the age of their population, in the NMA of efficacy (% change in acne lesion count), but will not perform meta-regression.		
Type and method of review	☒	Intervention	
	☐	Diagnostic	
	☐	Prognostic	
	☐	Qualitative	
	☐	Epidemiologic	
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	20 October 2019		
Anticipated completion date	13 January 2021		
Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
	Preliminary searches		
	Piloting of the study selection process		

Field	Content		
	Formal screening of search results against eligibility criteria		
	Data extraction		
	Risk of bias (quality) assessment		
	Data analysis		
Named contact	**5a. Named contact** National Guideline Alliance **5b. Named contact e-mail** AcneManagement@nice.org.uk **5e. Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: http://www.nice.org.uk/guidance/NG198/history NICE Guidelines Technical Support Unit: Professor Nicky J Welton, NICE Guidelines Technical Support Unit, Department of Population Health Sciences, Bristol Medical School Miss Caitlin Daly, NICE Guidelines Technical Support Unit, Department of Population Health Sciences, Bristol Medical School		

Field	Content	
Other registration details	Not applicable	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=154100	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. • Peer-reviewed publications	
Keywords	Acne; acne severity; chemical peels; energy-based devices; hormone therapy; isotretinoin; laser therapy; light therapy; management; network meta-analysis; oral antibiotics; physical; systematic review; topical antibiotics; topical retinoids; treatment.	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information		
Details of final publication	www.nice.org.uk	

1 *CrI: credibility interval; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; RCT: randomised controlled trial*

Appendix B – Literature search strategies

Literature search strategies for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Clinical search

Topical interventions (including topical retinoids)

Date of initial search: 07/08/2019

Additional terms added and searched: 10/09/2019

Last searched: 07/05/2020

Database(s): Embase Classic+Embase 1947 to 2020 May 06, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 06, 2020

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	exp topical antiinfective agent/ use emczd
6	exp Anti-Infective Agents, Local/ use ppez
7	5 or 6
8	exp antibiotic agent/ use emczd
9	exp Anti-Bacterial Agents/ use ppez
10	exp anthelmintic agent/ use emczd
11	exp Anthelmintics/ use ppez
12	(antibiotic* or anti biotic* or anti bacteri* or antibacteri* or bacteriocid*).tw.
13	(anthelminti* or antihelmint?i* or anti-helmint?i* or antiparasit* or anti-parasit* or vermifug*).tw.
14	adapalene/
15	aluminum oxide/ use emczd
16	amoxicillin/
17	ampicillin/
18	avermectin/ use emczd
19	azelaic acid/
20	benzoyl peroxide plus clindamycin/ use emczd
21	benzoyl peroxide/
22	(Benzoyl Peroxide/ and Clindamycin/) use ppez
23	cefaclor/
24	cefadroxil/
25	cefalexin/ use emczd
26	Cephalexin/ use ppez
27	cefixime/
28	cefotaxime/
29	cefradine/ use emczd
30	Cephradine/ use ppez
31	ceftaroline/ use emczd
32	ceftazidime/
33	ceftriaxone/
34	cefuroxime/
35	chlorhexidine gluconate/
36	clarithromycin/
37	clindamycin/
38	dapsone/
39	doxycycline/
40	erythromycin/
41	erythromycin plus isotretinoin/ use emczd
42	flucloxacillin/ use emczd
43	Floxacillin/ use ppez

#	Searches
44	fusidic acid/
45	isotretinoin/
46	isotretinoin/ and clindamycin/
47	ivermectin/
48	lymecycline/
49	metronidazole/
50	minocycline/
51	nadifloxacin/
52	nicotinamide/ use emczd
53	Niacinamide/ use ppez
54	nitroimidazole/ use emczd
55	ozenoxacin/
56	oxytetracycline/
57	penicillin G/
58	penicillin V/
59	(phenol/ and chlorhexidine digluconate/) use emczd
60	(phenol/ and chlorhexidine/) use ppez
61	piperacillin/
62	(pleuromutilin/ or pleuromutilin antibiotic agent/) use emczd
63	praziquantel/
64	pseudomonic acid/ use emczd
65	Mupirocin/ use ppez
66	retapamulin/ use emczd
67	retinol/ use emczd
68	Vitamin A/ use ppez
69	tetracycline/
70	ticarcillin/
71	retinoic acid/ use emczd
72	tazarotene/ use emczd
73	temocillin/ use emczd
74	tretinoin/ use ppez
75	triclocarban/ use emczd
76	triclosan/
77	trimethoprim/
78	zinc acetate/
79	(adapalene or aluminum oxide or ampicillin or amoxicillin or avermectin or az?laic acid or benzylpenicillin or benzyl penicillin or benzoyl peroxide or cefaclor or cefadroxil or cefalexin or cephalexin or cefixime or cefotaxime or cefradine or ceftaroline or ceftazidime or ceftriaxone or cefuroxime or cephalexin or cephalosporin* or cephamycin* or cephradine or chlorhexidine digluconate or chlorhexidine gluconate or clarithromycin or clindamycin or dapsone or diaminodiphenyl sulfone or doxycyclin* or erythromycin or floxacillin or flucloxacillin or fucidin or fusidic acid or fusidate sodium or sodium fusidate or germolene or isotretinoi* or ivermectin or lincosamide* or lymecycline or macrolide* or metronidazole or minocycline or nadifloxacin or niacinamide or nicotinamide or nitroimidazole or ozenoxacin or oxytetracyline or penicillin* or phenol or phenoxymethylpenicillin or piperacillin or pleuromutilin or praziquantel or cysticide or pseudomonic acid or mupirocin or quinoderm or quinolon* or retapamulin or retinoi* or retinol or tazarotene or temocillin or tetracyclin* or ticarcillin or tretinoin or triclocarban or triclosan or triclozan or trimethoprim or vitamin a or vitamin b3 or zinc acetate).tw.
80	or/7-79
81	(topical or topically or cream? or emulsi* or gel? or foam? or ointment* or solution? or lotion? or pad?).tw.
82	(ointment/ or exp gel/) use emczd
83	(Ointments/ or exp Gels/) use ppez
84	skin cream/
85	(cutaneous drug administration/ or topical drug administration/) use emczd
86	(Administration, Topical/ or Administration, Cutaneous/) use ppez
87	topical drug administration.fs.
88	(cutaneous or dermal or skin or transcutaneous or transdermal or percutaneous).tw.
89	or/81-88
90	4 and 80 and 89
91	limit 90 to english language
92	Letter/ use ppez
93	letter.pt. or letter/ use emczd
94	note.pt.
95	editorial.pt.
96	Editorial/ use ppez
97	News/ use ppez
98	exp Historical Article/ use ppez
99	Anecdotes as Topic/ use ppez
100	Comment/ use ppez
101	Case Report/ use ppez
102	case report/ or case study/ use emczd

#	Searches
103	(letter or comment*).ti.
104	or/92-103
105	randomized controlled trial/ use ppez
106	randomized controlled trial/ use emczd
107	random*.ti,ab.
108	or/105-107
109	104 not 108
110	animals/ not humans/ use ppez
111	animal/ not human/ use emczd
112	nonhuman/ use emczd
113	exp Animals, Laboratory/ use ppez
114	exp Animal Experimentation/ use ppez
115	exp Animal Experiment/ use emczd
116	exp Experimental Animal/ use emczd
117	exp Models, Animal/ use ppez
118	animal model/ use emczd
119	exp Rodentia/ use ppez
120	exp Rodent/ use emczd
121	(rat or rats or mouse or mice).ti.
122	or/109-121
123	91 not 122
124	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
125	124 use ppez
126	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
127	126 use ppez
128	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
129	128 use emczd
130	125 or 127
131	129 or 130
132	Meta-Analysis/
133	exp Meta-Analysis as Topic/
134	systematic review/
135	meta-analysis/
136	(meta analy* or metanaly* or metaanaly*).ti,ab.
137	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
138	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
139	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
140	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
141	(search* adj4 literature).ab.
142	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
143	cochrane.jw.
144	((pool* or combined) adj2 (data or trials or studies or results)).ab.
145	(or/132-134,136,138-143) use ppez
146	(or/134-137,139-144) use emczd
147	or/145-146
148	network meta-analysis/
149	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
150	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
151	or/148-150
152	131 or 147 or 151
153	123 and 152

1 Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 5 of
2 12, May 2020; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020

#	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne:ti,ab
#3	#1 or #2
#4	(topical or topically or cream or creams or emulsi* gel or gels or foam or foams or ointment* or solution or solutions or lotion or lotions or pad or pads):ti,ab
#5	MeSH descriptor: [Ointments] this term only
#6	MeSH descriptor: [Gels] explode all trees
#7	MeSH descriptor: [Skin Cream] this term only

#	Searches
#8	MeSH descriptor: [Administration, Topical] this term only
#9	MeSH descriptor: [Administration, Cutaneous] this term only
#10	(cutaneous or dermal or skin or transcutaneous or transdermal or percutaneous):ti,ab
#11	{or #4-#10}
#12	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#13	MeSH descriptor: [Anthelmintics] explode all trees
#14	(antibiotic* or "anti biotic*" or "anti bacteri*" or antibacteri* or bacteriocid*):ti,ab
#15	(anthelminti* or antihelminthi* or antithelminti* or anti-helminthi* or anti-helminti* or antiparasit* or anti-parasit* or vermifug*):ti,ab
#16	MeSH descriptor: [Adapalene] this term only
#17	MeSH descriptor: [Aluminum Oxide] this term only
#18	MeSH descriptor: [Amoxicillin] this term only
#19	MeSH descriptor: [Ampicillin] this term only
#20	MeSH descriptor: [Benzoyl Peroxide] this term only
#21	MeSH descriptor: [Cefaclor] this term only
#22	MeSH descriptor: [Cefadroxil] this term only
#23	MeSH descriptor: [Cephalexin] this term only
#24	MeSH descriptor: [Cefixime] this term only
#25	MeSH descriptor: [Cefotaxime] this term only
#26	MeSH descriptor: [Cephradine] this term only
#27	MeSH descriptor: [Ceftazidime] this term only
#28	MeSH descriptor: [Ceftriaxone] this term only
#29	MeSH descriptor: [Cefuroxime] this term only
#30	MeSH descriptor: [Clarithromycin] this term only
#31	MeSH descriptor: [Clindamycin] this term only
#32	MeSH descriptor: [Dapsone] this term only
#33	MeSH descriptor: [Doxycycline] this term only
#34	MeSH descriptor: [Erythromycin] this term only
#35	MeSH descriptor: [Floxacillin] this term only
#36	MeSH descriptor: [Fusidic Acid] this term only
#37	MeSH descriptor: [Isotretinoin] this term only
#38	MeSH descriptor: [Ivermectin] this term only
#39	MeSH descriptor: [Lymecycline] this term only
#40	MeSH descriptor: [Minocycline] this term only
#41	MeSH descriptor: [Mupirocin] this term only
#42	MeSH descriptor: [Niacinamide] this term only
#43	MeSH descriptor: [Oxytetracycline] this term only
#44	MeSH descriptor: [Penicillin G] this term only
#45	MeSH descriptor: [Penicillin V] this term only
#46	MeSH descriptor: [Phenol] this term only
#47	MeSH descriptor: [Piperacillin] this term only
#48	MeSH descriptor: [Praziquantel] this term only
#49	MeSH descriptor: [Vitamin A] this term only
#50	MeSH descriptor: [Tetracycline] this term only
#51	MeSH descriptor: [Ticarcillin] this term only
#52	MeSH descriptor: [Tretinoin] this term only
#53	MeSH descriptor: [Trimethoprim] this term only
#54	MeSH descriptor: [Zinc Acetate] this term only
#55	(adapalene or aluminum oxide or ampicillin or amoxicillin or avermectin or azaelaic acid or azelaic acid or benzylpenicillin or benzyl penicillin or benzoyl peroxide or cefaclor or cefadroxil or cefalexin or cephalexin or cephalosporin* or cephamycin* or cefixime or cefotaxime or cefradine or ceftaroline or ceftazidime or ceftriaxone or cefuroxime or cephalexin or cephradine or chlorhexidine digluconate or chlorhexidine gluconate or clarithromycin or clindamycin or dapsone or diaminodiphenyl sulfone or doxycyclin* or erythromycin or floxacillin or flucloxacillin or fucidin or fusidic acid or fusidate sodium or sodium fusidate or germolene or isotretinoi* or ivermectin or lincosamide* or lymecycline or macrolide* or minocycline or mupirocin or pseudomonic acid or nadifloxacin or niacinamide or nicotinamide or nitroimidazole or ozenoxacin or oxytetracyline or penicillin* or phenol or phenoxymethylpenicillin or piperacillin or pleuromutilin or praziquantel or cysticide or quinoderm or quinolone* or retapamulin or retino* or retinol or temocillin or tetracyclin* or ticarcillin or tretinoin or trimethoprim or vitamin a or zinc acetate):ti,ab
#56	{or #12-#55}
#57	#3 and #11 and #56

1 **Oral antibiotics and oral isotretinoin**

2 Database(s): Embase Classic+Embase 1947 to 2020 May 06, Ovid MEDLINE(R) and Epub
3 Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 06, 2020

1 Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of
2 Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	exp antibiotic agent/ use emczd
6	exp Anti-Bacterial Agents/ use ppez
7	(antibiotic* or anti biotic* or anti bacteri* or antibacteri* or bacteriocid*).tw.
8	exp carbapenem derivative/ use emczd
9	exp Carbapenems/ use ppez
10	exp cephalosporin derivative/ use emczd
11	exp Cephalosporins/ use ppez
12	exp cephamycin derivative/ use emczd
13	exp Cephamycins/ use ppez
14	dapsone/
15	exp lincosamide/ use emczd
16	exp Lincosamide/ use ppez
17	exp macrolide/ use emczd
18	exp Macrolides/ use ppez
19	exp monobactam derivative/ use emczd
20	exp Monobactams/ use ppez
21	exp penicillin derivative/ use emczd
22	exp Penicillins/ use ppez
23	exp quinoline derived antiinfective agent/ use emczd
24	exp Quinolones/ use ppez
25	exp retinoid/ use emczd
26	exp Retinoids/ use ppez
27	exp tetracycline derivative/ use emczd
28	exp Tetracyclines/ use ppez
29	trimethoprim/
30	(carbapenem* or biapenem or doripenem or ertapenem or imipenem or meropenem or panipenem or betamipron or tebipenem).tw.
31	(cephamycin* or cephalosporin* or carbacephem or loracarbef or cefacetrile or cefaclor or cefadroxil or cefalexin or cefaloglycin or cefalonium or cefaloridine or cefalotin or cefamandole or cefapirin or cefatrizine or cefazaflur or cefazedone or cefazolin or cefbuperazone or cefcapene or cefdaloxime or cefdinir or cefditoren or cefepime or cefetamet or cefixime or cefmenoxime or cefmetazole or cefminox or cefodizime or cefonicid or cefoperazone or cefoperazone or ceforanide or cefotaxime or cefotetan or cefotiam or cefozopran or cefpiramide or cefpirome or cefpodoxime or cefprozil or cefquinome or cefradine or cefroxadine or cefsulodin or ceftaroline fosamile or ceftazidime or ceftazidime or cefteram or ceftezole or ceftibiprole or ceftibuten or ceftiolene or ceftolozane or ceftolozane or ceftraroline or ceftriaxone or cefuroxime or cefuzonam or cephamycin or depfimizole or flomoxef or latamoxef or oxacephem).tw.
32	dapsone.tw.
33	(isotretinoi* or iso tretinoin or isoretinoin or isotren or isotrex* or accutane or roaccutan* or roaccuttan* or roacuttan* or roacutan* or retinoic acid).tw.
34	(lincosamide* or clindamycin or lincomycine or linkomycine).tw.
35	(macrolide* or azithromycin or carbomycin a or clarithromycin or erythromycin or fidaxomicin or josamycin or kitasamycin or midecamycin or oleandomycin or roxithromycin or solithromycin or spiramycin or telithromycin or troleandomycin).tw.
36	(monobactam* or mono- bactam* or aztreonam).tw.
37	(penicillin* or almecillin or amoxicillin or ampicillin or azlocillin or bacampicillin or benzathine benzylpenicillin or benzylpenicillin sodium or carbenicillin or carindacillin or cloxacillin or co-amoxiclav or co-fluampicil or co-trimoxazole or dicloxacillin or epicillin or flucloxacillin or hetacillin or mecillinam or metampicillin or methicillin or mezlocillin or nafcillin or oxacillin or phenoxymethylpenicillin or piperacillin or pivampicillin or pivmecillinam hydrochloride or procaine benzylpenicillin or sultamicillin or talampicillin or temocillin or ticarcillin).tw.
38	(quinolone* or balofloxacin or besifloxacin or ciprofloxacine or clinafloxacin or delafloxacin or enoxacin or fleroxacin or gatifloxacin or gemifloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or nadifloxacin or norfloxacin or ofloxacin or oxolinic acid or ozenoxacin or pazufloxacin or pefloxacin or prulifloxacin or rosoxacin or rufloxacin or sitafloxacin or sparfloxacin or temafloxacin or tosufloxacin).tw.
39	(tetracylcline* or chlortetracycline or demeclocycline or doxycycline or eravacycline or lymecycline or methacycline or minocycline or omadacycline or oxytetracycline or rolitetracycline or sarecycline or tetracycline or tigecycline).tw.
40	trimethoprim.tw.
41	or/5-40
42	oral drug administration/ use emczd
43	Administration, Oral/ use ppez
44	oral drug administration.fs.
45	(oral* or per os).tw.
46	or/42-45
47	4 and 41 and 46
48	Letter/ use ppez

#	Searches
49	letter.pt. or letter/ use emczd
50	note.pt.
51	editorial.pt.
52	Editorial/ use ppez
53	News/ use ppez
54	exp Historical Article/ use ppez
55	Anecdotes as Topic/ use ppez
56	Comment/ use ppez
57	Case Report/ use ppez
58	case report/ or case study/ use emczd
59	(letter or comment*).ti.
60	or/48-59
61	randomized controlled trial/ use ppez
62	randomized controlled trial/ use emczd
63	random*.ti,ab.
64	or/61-63
65	60 not 64
66	animals/ not humans/ use ppez
67	animal/ not human/ use emczd
68	nonhuman/ use emczd
69	exp Animals, Laboratory/ use ppez
70	exp Animal Experimentation/ use ppez
71	exp Animal Experiment/ use emczd
72	exp Experimental Animal/ use emczd
73	exp Models, Animal/ use ppez
74	animal model/ use emczd
75	exp Rodentia/ use ppez
76	exp Rodent/ use emczd
77	(rat or rats or mouse or mice).ti.
78	or/65-77
79	47 not 78
80	limit 79 to english language
81	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
82	81 use ppez
83	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
84	83 use ppez
85	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
86	85 use emczd
87	82 or 84
88	86 or 87
89	Meta-Analysis/
90	exp Meta-Analysis as Topic/
91	systematic review/
92	meta-analysis/
93	(meta analy* or metanaly* or metaanaly*).ti,ab.
94	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
95	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
96	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
97	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
98	(search* adj4 literature).ab.
99	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
100	cochrane.jw.
101	((pool* or combined) adj2 (data or trials or studies or results)).ab.
102	(or/89-91,93,95-100) use ppez
103	(or/91-94,96-101) use emczd
104	or/102-103
105	network meta-analysis/
106	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
107	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
108	or/105-107
109	88 or 104 or 108
110	80 and 109

1 Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 5 of
2 12, May 2020; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020

#	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne:ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#5	(antibiotic* or "anti biotic*" or "anti bacteri*" or antibacteri* or bacteriocid*):ti,ab
#6	MeSH descriptor: [Amoxicillin] this term only
#7	MeSH descriptor: [Ampicillin] this term only
#8	MeSH descriptor: [Azithromycin] this term only
#9	MeSH descriptor: [Azlocillin] this term only
#10	MeSH descriptor: [Penicillin G] this term only
#11	MeSH descriptor: [Carbenicillin] this term only
#12	MeSH descriptor: [Cefaclor] this term only
#13	MeSH descriptor: [Cefadroxil] this term only
#14	MeSH descriptor: [Cephalexin] this term only
#15	MeSH descriptor: [Cefixime] this term only
#16	MeSH descriptor: [Cefotaxime] this term only
#17	MeSH descriptor: [Cephradine] this term only
#18	MeSH descriptor: [Ceftazidime] this term only
#19	MeSH descriptor: [Ceftriaxone] this term only
#20	MeSH descriptor: [Chlortetracycline] this term only
#21	MeSH descriptor: [Clarithromycin] this term only
#22	MeSH descriptor: [Clindamycin] this term only
#23	MeSH descriptor: [Cloxacillin] this term only
#24	MeSH descriptor: [Amoxicillin-Potassium Clavulanate Combination] this term only
#25	MeSH descriptor: [Trimethoprim, Sulfamethoxazole Drug Combination] this term only
#26	(amoxicillin or ampicillin or azithromycin or azlocillin or bacampicillin or benzylpenicillin sodium or "penicillin g" or biapenem or carbenicillin or carbomycin or cefaclor or cefadroxil or cefalexin or cephalexin or cefixime or cefotaxime or cephotaxim* or cefradine or cephradine or ceftaroline or ceftazidime or ceftriaxone or cefuroxime or chlortetracyline or clarithromycin or clindamycin or cloxacillin or co amoxiclav or coamoxiclav or co fluampcil or cofluampcil or co trimoxazole or cotrimoxazole):ti,ab
#27	MeSH descriptor: [Demeclocycline] this term only
#28	MeSH descriptor: [Dicloxacillin] this term only
#29	MeSH descriptor: [Doripenem] this term only
#30	MeSH descriptor: [Doxycycline] this term only
#31	MeSH descriptor: [Ertapenem] this term only
#32	MeSH descriptor: [Erythromycin] this term only
#33	MeSH descriptor: [Fidaxomicin] this term only
#34	MeSH descriptor: [Floxacillin] this term only
#35	(demeclocycline or dicloxacillin or doripenem or doxycycline or epicillin or eravacycline or ertapenem or erythromycin or fidaxomicin or floxacillin or flucloxacillin):ti,ab
#36	MeSH descriptor: [Imipenem] this term only
#37	MeSH descriptor: [Cilastatin, Imipenem Drug Combination] this term only
#38	MeSH descriptor: [Josamycin] this term only
#39	MeSH descriptor: [Kitasamycin] this term only
#40	MeSH descriptor: [Lymecycline] this term only
#41	MeSH descriptor: [Meropenem] this term only
#42	MeSH descriptor: [Methacycline] this term only
#43	MeSH descriptor: [Methicillin] this term only
#44	MeSH descriptor: [Mezlocillin] this term only
#45	MeSH descriptor: [Miocamycin] this term only
#46	MeSH descriptor: [Nafcillin] this term only
#47	(hetacillin or imipenem or isotretinoi* or josamycin* or kitasamycin or leucomycin or lymecycline or meropenem or metampicillin or methampicillin or metacycline or methacycline or methicillin or mezlocillin or midecamycin or minocycline or miocamycin* or miokamycin* or nafcillin):ti,ab
#48	MeSH descriptor: [Oleandomycin] this term only
#49	MeSH descriptor: [Oxacillin] this term only
#50	MeSH descriptor: [Oxytetracycline] this term only
#51	MeSH descriptor: [Penicillin V] this term only
#52	MeSH descriptor: [Piperacillin] this term only
#53	MeSH descriptor: [Piperacillin, Tazobactam Drug Combination] this term only
#54	MeSH descriptor: [Amdinocillin Pivoxil] this term only
#55	MeSH descriptor: [Rolitetracycline] this term only
#56	MeSH descriptor: [Roxithromycin] this term only
#57	MeSH descriptor: [Spiramycin] this term only
#58	MeSH descriptor: [Talampicillin] this term only
#59	MeSH descriptor: [Tetracycline] this term only
#60	MeSH descriptor: [Ticarcillin] this term only

#	Searches
#61	MeSH descriptor: [Tigecycline] this term only
#62	MeSH descriptor: [Trimethoprim] this term only
#63	MeSH descriptor: [Troleandomycin] this term only
#64	(oleandomycin or omadacycline or "PTK-0796" or oxacillin* or oxytetracycline or panipenem or betamipron or carbenin or phenoxymethylpenicillin or "penicillin v" or piperacillin or pivmeillinam or amdinocillin pivoxil or retinoi* or rolitetracycline or roxithromycin or sarecycline or solithromycin or spiramycin or talampicillin or tebipenem or telithromycin or temocillin or tetracylin* or ticarcillin or timentin or tigecycline or trimethoprim or troleandomycin):ti,ab
#65	{or #4-#64}
#66	#3 and #65
#67	MeSH descriptor: [Administration, Oral] explode all trees
#68	(oral or per os):ti,ab
#69	#67 or #68
#70	#66 and #69

1 **Hormonal interventions**

2 Database(s): Embase Classic+Embase 1947 to 2020 May 06, Ovid MEDLINE(R) and Epub
3 Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 06, 2020

4 Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of
5 Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	exp aldosterone antagonist/ use emczd
6	exp Mineralocorticoid Receptor Antagonists/ use ppez
7	spironolactone/
8	hydroflumethiazide plus spironolactone/ use emczd
9	canrenone/
10	eplerenone/
11	furosemide plus spironolactone/ use emczd
12	(aldactone or spironolactone or canrenone or co-flumactone or coflumactone or eplerenon* or furosemide).tw.
13	or/5-12
14	exp alpha adrenergic receptor blocking agent/ use emczd
15	exp Adrenergic alpha-Antagonists/ use ppez
16	alfuzosin/ use emczd
17	doxazosin/
18	indoramin/
19	prazosin/
20	tamsulosin/
21	dutasteride plus tamsulosin/ use emczd
22	solifenacin plus tamsulosin/ use emczd
23	terazosin/ use emczd
24	(alfuzosin or doxazosin or uroprost or indoramin or prazosin or tamsulosin or terazosin).tw.
25	or/14-24
26	exp steroid 5alpha reductase inhibitor/ use emczd
27	exp 5-alpha Reductase Inhibitors/ use ppez
28	dutasteride/
29	finasteride/
30	(5a reductase inhibitor* or 5-alpha reductase inhibitor* or dutastaride or finasteride).tw.
31	or/26-30
32	exp antiandrogen/ use emczd
33	exp Androgen Antagonists/ use ppez
34	metformin/
35	abiraterone acetate/
36	apalutamide/ use emczd
37	bicalutamide/ use emczd
38	cyproterone acetate plus ethinylestradiol/ use emczd
39	cyproterone acetate/
40	enzalutamide/ use emczd
41	flutamide/
42	(antiandrogen* or anti-androgen* or androgen antagonist* or abiraterone acetate or apalutamide or bicalutamide or cocyprindiol or co-cyprindiol or cyproterone acetate or enzalutamide or flutamide or metformin).tw.
43	or/32-42
44	exp oral contraceptive agent/ use emczd

#	Searches
45	exp Contraceptives, Oral, Combined/ use ppez
46	exp gestagen/ use emczd
47	exp Progestins/ use ppez
48	(chlormadinone acetate plus ethinylestradiol/ or desogestrel plus ethinylestradiol/ or dienogest plus ethinylestradiol/ or drospirenone plus ethinylestradiol/ or dydrogesterone plus estradiol/ or estradiol plus levonorgestrel/ or estradiol plus nomegestrol acetate/ or estradiol plus norethisterone acetate/ or ethinylestradiol plus etonogestrel/ or ethinylestradiol plus gestodene/ or ethinylestradiol plus levonorgestrel/ or ethinylestradiol plus norelgestromin/ or ethinylestradiol plus norethisterone/ or ethinylestradiol plus norgestimate/) use emczd
49	Ethinyl Estradiol-Norgestrel Combination/ use ppez
50	(Ethinyl Estradiol/ use ppez and (Chlormadinone Acetate/ or Desogestrel/ or Levonorgestrel/ or Norethindrone/ or Norgestrel/)) use ppez
51	(Mestranol/ and (Norethindrone/ or Norethynodrel/)) use ppez
52	(Estradiol/ and (Dydrogesterone/ or Levonorgestrel/ or Medroxyprogesterone Acetate/ or Norethindrone/)) use ppez
53	((oral* adj contracept*) or progest?gen* or gestagen* or progestin*).tw.
54	((ethinyl?estradiol or ethinyl estradiol or ethinyl oestradiol) adj3 (chlormadinone acetate or desogestrel or dienogest or drospirenone or etonogestrel or gestodene or levonorgestrel or nomogestrol or norelgestromin* or norethindrone or norethisterone or norgestimate or norgestrel)).tw.
55	(mestranol adj3 (norethindrone or norethisterone or noretynodrel or norethynodrel)).tw.
56	((estradiol or oestradiol) adj3 (dienogest or dydrogesterone or levonorgestrel or medroxyprogesterone acetate or nomegestrol or norethindrone or norethisterone)).tw.
57	or/44-56
58	or/13,25,31,43,57
59	4 and 58
60	limit 59 to english language
61	Letter/ use ppez
62	letter.pt. or letter/ use emczd
63	note.pt.
64	editorial.pt.
65	Editorial/ use ppez
66	News/ use ppez
67	exp Historical Article/ use ppez
68	Anecdotes as Topic/ use ppez
69	Comment/ use ppez
70	Case Report/ use ppez
71	case report/ or case study/ use emczd
72	(letter or comment*).ti.
73	or/61-72
74	randomized controlled trial/ use ppez
75	randomized controlled trial/ use emczd
76	random*.ti,ab.
77	or/74-76
78	73 not 77
79	animals/ not humans/ use ppez
80	animal/ not human/ use emczd
81	nonhuman/ use emczd
82	exp Animals, Laboratory/ use ppez
83	exp Animal Experimentation/ use ppez
84	exp Animal Experiment/ use emczd
85	exp Experimental Animal/ use emczd
86	exp Models, Animal/ use ppez
87	animal model/ use emczd
88	exp Rodentia/ use ppez
89	exp Rodent/ use emczd
90	(rat or rats or mouse or mice).ti.
91	or/78-90
92	60 not 91
93	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
94	93 use ppez
95	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
96	95 use ppez
97	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
98	97 use emczd
99	94 or 96
100	98 or 99
101	Meta-Analysis/

#	Searches
102	exp Meta-Analysis as Topic/
103	systematic review/
104	meta-analysis/
105	(meta analy* or metanaly* or metaanaly*).ti,ab.
106	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
107	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
108	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
109	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
110	(search* adj4 literature).ab.
111	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
112	cochrane.jw.
113	((pool* or combined) adj2 (data or trials or studies or results)).ab.
114	(or/101-103,105,107-112) use ppez
115	(or/103-106,108-113) use emczd
116	or/114-115
117	network meta-analysis/
118	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
119	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
120	or/117-119
121	100 or 116 or 120
122	92 and 121

Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 5 of 12, May 2020; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020

#	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne*:ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
#5	MeSH descriptor: [Spironolactone] this term only
#6	MeSH descriptor: [Eplerenone] this term only
#7	(aldactone or spironolactone or co-flumactone or coflumactone or eplerenon* or furosemide):ti,ab
#8	{or #4-#7}
#9	MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees
#10	MeSH descriptor: [Doxazosin] this term only
#11	MeSH descriptor: [Indoramin] this term only
#12	MeSH descriptor: [Prazosin] this term only
#13	MeSH descriptor: [Tamsulosin] this term only
#14	(alfuzosin or doxazosin or uroprost or indoramin or prazosin or tamsulosin or terazosin):ti,ab
#15	{or #9-#14}
#16	MeSH descriptor: [5-alpha Reductase Inhibitors] explode all trees
#17	MeSH descriptor: [Dutasteride] this term only
#18	MeSH descriptor: [Finasteride] this term only
#19	("5a reductase inhibitor*" or "5-alpha reductase inhibitor*" or dutastaride or finasteride):ti,ab
#20	{or #16-#19}
#21	MeSH descriptor: [Androgen Antagonists] explode all trees
#22	MeSH descriptor: [Metformin] this term only
#23	MeSH descriptor: [Abiraterone Acetate] this term only
#24	MeSH descriptor: [Cyproterone Acetate] this term only
#25	MeSH descriptor: [Flutamide] this term only
#26	(antiandrogen* or "anti androgen*" or "androgen antagonist*" or "abiraterone acetate" or apalutamide or bicalutamide or cocyprindiol or "co cyprindiol" or "cyproterone acetate" or enzalutamide or flutamide or metformin):ti,ab
#27	{or #21-#26}
#28	MeSH descriptor: [Contraceptives, Oral, Combined] explode all trees
#29	MeSH descriptor: [Progestins] explode all trees
#30	MeSH descriptor: [Ethinyl Estradiol-Norgestrel Combination] this term only
#31	MeSH descriptor: [Ethinyl Estradiol] this term only
#32	MeSH descriptor: [Estradiol] this term only
#33	MeSH descriptor: [Mestranol] this term only
#34	((oral* next contracept*) or progestogen* or progestagen* or gestagen* or progestin*):ti,ab
#35	((ethinylestradiol or ethinyloestradiol or ethinyl estradiol or ethinyl oestradiol) near/3 (chlormadinone acetate or desogestrel or dienogest or drospirenone or etonogestrel or gestodene or levonorgestrel or nomogestrol or norelgestromin* or norethindrone or norethisterone or norgestimate or norgestrel)):ti,ab
#36	((estradiol or oestradiol) near/3 (dienogest or dydrogesterone or levonorgestrel or medroxyprogesterone acetate or nomegestrol or norethindrone or norethisterone)):ti,ab
#37	(mestranol near/3 (norethindrone or norethisterone or noretynodrel or norethynodrel)):ti,ab

#	Searches
#38	{or #28-#37}
#39	#8 or #15 or #20 or #27 or #38
#40	#3 and #39

Physical interventions

Database(s): Embase Classic+Embase 1947 to 2019 August 12, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 06, 2020

Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	chemexfoliation/
6	(amino acid/ or 2 hydroxyacid/) use emczd
7	(Amino Acids/ or Hydroxy Acids/) use ppez
8	glycolic acid/ use emczd
9	Glycolates/ use ppez
10	lactic acid/
11	mandelic acid/ use emczd
12	Mandelic Acids/ use ppez
13	pyruvic acid/
14	salicylic acid/
15	trichloroacetic acid/
16	(chemical adj1 (exfoliat* or peel* or resurfac*)).tw.
17	(chemoexfoliat* or chemexfoliat* or chemo exfoliat*).tw.
18	((amino or glycol* or lactic or mandelic or pyruvic or salicylic or trichloroa?cetic or salicylic-mandelic or alpha hydroxy or "amino fruit") adj acid*).tw.
19	(hydroxyacid* or hydroxy acid*).tw.
20	((Jessner* or phenol or pheno or Baker-Gordon) adj (peel* or solution*)).tw.
21	or/5-20
22	comedo/th use emczd
23	((blackhead* or comedo* or whitehead*) adj (extract* or remov*)).tw.
24	triamcinolone acetonide/
25	(adrenal cortex hormone* or triamcinolone acetonide).tw.
26	or/22-25
27	exp laser/
28	exp phototherapy/
29	exp photodynamic therapy/
30	exp photochemotherapy/
31	exp photolysis/
32	exp sunlight/
33	exp photosensitizing agent/
34	radiofrequency/ or radiofrequency ablation/
35	aminolevulinic acid/
36	methylene blue/
37	aminolevulinic acid methyl ester/
38	(or/27-37) use emczd
39	exp Lasers/
40	exp Phototherapy/
41	exp Laser Therapy/
42	exp Photochemotherapy/
43	exp Photolysis/
44	exp Sunlight/
45	exp Ultraviolet Therapy/
46	exp Photosensitizing Agents/
47	exp Radiofrequency Therapy/
48	Aminolevulinic Acid/
49	Methylene Blue/
50	(or/39-49) use ppez

#	Searches
51	(laser* or light therap* or light treatment* or aminolevulinic acid or blue light* or red light* or intense pulsed light* or IPL or methyl aminolevulinate or methylene blue gel or microneedl* or micro needl* or photochemical therap* or photochemical treatment* or photo chemical therap* or photo chemical treatment* or photochemotherap* or photodynamic therap* photodynamic treatment* or photo dynamic therap* or photo dynamic treatment* or photolysis or photopneumatic therap* or photopneumatic treatment* or photo pneumatic therap* or photo pneumatic treatment* or photosensiti?ing agent* or photo-sensiti?ing agent* or phototherap* or photo-therap* or photothermal therap* or photothermal treatment* or photo-thermal therap* or photo-thermal treatment* or radiofrequenc* or radio frequenc* or smoothbeam or sunlight or ultraviolet).tw.
52	or/21,26,38,50-51
53	4 and 52
54	Letter/ use ppez
55	letter.pt. or letter/ use emczd
56	note.pt.
57	editorial.pt.
58	Editorial/ use ppez
59	News/ use ppez
60	exp Historical Article/ use ppez
61	Anecdotes as Topic/ use ppez
62	Comment/ use ppez
63	Case Report/ use ppez
64	case report/ or case study/ use emczd
65	(letter or comment*).ti.
66	or/54-65
67	randomized controlled trial/ use ppez
68	randomized controlled trial/ use emczd
69	random*.ti,ab.
70	or/67-69
71	66 not 70
72	animals/ not humans/ use ppez
73	animal/ not human/ use emczd
74	nonhuman/ use emczd
75	exp Animals, Laboratory/ use ppez
76	exp Animal Experimentation/ use ppez
77	exp Animal Experiment/ use emczd
78	exp Experimental Animal/ use emczd
79	exp Models, Animal/ use ppez
80	animal model/ use emczd
81	exp Rodentia/ use ppez
82	exp Rodent/ use emczd
83	(rat or rats or mouse or mice).ti.
84	or/71-83
85	53 not 84
86	limit 85 to english language
87	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
88	87 use ppez
89	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
90	89 use ppez
91	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
92	91 use emczd
93	88 or 90
94	92 or 93
95	Meta-Analysis/
96	exp Meta-Analysis as Topic/
97	systematic review/
98	meta-analysis/
99	(meta analy* or metanaly* or metaanaly*).ti,ab.
100	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
101	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
102	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
103	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
104	(search* adj4 literature).ab.
105	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
106	cochrane.jw.
107	((pool* or combined) adj2 (data or trials or studies or results)).ab.

#	Searches
108	(or/95-97,99,101-106) use ppez
109	(or/97-100,102-107) use emczd
110	or/108-109
111	network meta-analysis/
112	((network adj (MA or MAs)) or (NMA or NMAs)).tw.
113	((indirect or mixed or multiple or multi-treatment* or simultaneous) adj1 comparison*).tw.
114	or/111-113
115	94 or 110 or 114
116	86 and 115

Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 5 of 12, May 2020; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020

#	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne*:ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Chemexfoliation] this term only
#5	MeSH descriptor: [Amino Acids] this term only
#6	MeSH descriptor: [Hydroxy Acids] this term only
#7	MeSH descriptor: [Glycolates] this term only
#8	MeSH descriptor: [Lactic Acid] this term only
#9	MeSH descriptor: [Mandelic Acids] this term only
#10	MeSH descriptor: [Pyruvic Acid] this term only
#11	MeSH descriptor: [Salicylic Acid] this term only
#12	MeSH descriptor: [Trichloroacetic Acid] this term only
#13	(chemical near/1 (exfoliat* or peel* or resurfac*)):ti,ab
#14	(chemoexfoliat* or chemexfoliat* or chemo exfoliat*):ti,ab
#15	((amino or glycol* or lactic or mandelic or pyruvic or salicylic or trichloroaecetic or trichloroacetic or "salicylic mandelic" or "alpha hydrox" or "amino fruit") next acid*):ti,ab
#16	(hydroxyacid* or "hydroxy acid*").ti,ab
#17	((Jessner* or phenol or pheno or "Baker Gordon") next (peel* or solution*)).ti,ab
#18	{or #4-#17}
#19	((blackhead* or comedo* or whitehead*) near/2 (extract* or remov*)):ti,ab
#20	MeSH descriptor: [Triamcinolone Acetonide] this term only
#21	("adrenal cortex hormone*" or "triamcinolone acetonide").ti,ab
#22	{or #19-#21}
#23	MeSH descriptor: [Lasers] explode all trees
#24	MeSH descriptor: [Phototherapy] explode all trees
#25	MeSH descriptor: [Photochemotherapy] explode all trees
#26	MeSH descriptor: [Photochemotherapy] explode all trees
#27	MeSH descriptor: [Photolysis] explode all trees
#28	MeSH descriptor: [Sunlight] explode all trees
#29	MeSH descriptor: [Photosensitizing Agents] explode all trees
#30	MeSH descriptor: [Radiofrequency Therapy] explode all trees
#31	MeSH descriptor: [Aminolevulinic Acid] this term only
#32	MeSH descriptor: [Methylene Blue] this term only
#33	MeSH descriptor: [Ultraviolet Therapy] explode all trees
#34	(laser* or light therap* or light treatment* or aminolevulinic acid or blue light* or red light* or intense pulsed light* or IPL or methyl aminolevulinate or methylene blue gel or microneedl* or micro needl* or photochemical therap* or photochemical treatment* or photo chemical therap* or photo chemical treatment* or photochemotherap* or photodynamic therap* photodynamic treatment* or photo dynamic therap* or photo dynamic treatment* or photolysis or photopneumatic therap* or photopneumatic treatment* or photo pneumatic therap* or photo pneumatic treatment* or photosensitising agent* or photosensitizing agent* or photo-sensitising agent* or photo-sensitizing agent* or phototherap* or photo-therap* or photothermal therap* or photothermal treatment* or photo-thermal therap* or photo-thermal treatment* or radiofrequenc* or radio frequenc* or smoothbeam or sunlight or ultraviolet):ti,ab
#35	{or #23-#34}
#36	#18 or #22 or #35
#37	#3 and #18

Health Economics search

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

Database{s): Embase 1980 to 2020 May 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 05, 2020

Multifile database codes: emez = Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez
3	acne.tw.
4	or/1-3
5	Economics/
6	Value of life/
7	exp "Costs and Cost Analysis"/
8	exp Economics, Hospital/
9	exp Economics, Medical/
10	Economics, Nursing/
11	Economics, Pharmaceutical/
12	exp "Fees and Charges"/
13	exp Budgets/
14	(or/5-13) use ppez
15	health economics/
16	exp economic evaluation/
17	exp health care cost/
18	exp fee/
19	budget/
20	funding/
21	(or/15-20) use emez
22	budget*.ti,ab.
23	cost*.ti.
24	(economic* or pharmaco?economic*).ti.
25	(price* or pricing*).ti,ab.
26	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
27	(financ* or fee or fees).ti,ab.
28	(value adj2 (money or monetary)).ti,ab.
29	or/22-27
30	14 or 21 or 29
31	4 and 30
32	limit 31 to english language
33	limit 32 to yr="2004 -Current"
34	remove duplicates from 33

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

Databases(s): NIHR Centre for Reviews and Dissemination: Health Technology Assessment Database (HTA) and the NHS Economic Evaluation Database (NHS EED)

#	Searches
1	MeSH DESCRIPTOR Acne Vulgaris EXPLODE ALL TREES
2	(acne) IN NHSEED, HTA FROM 2004 TO 2018
3	#1 OR #2

Search for health utility values

Date of initial search: 29/01/2019

Date of updated search: 06/05/2020

Database{s): Embase 1980 to 2020 May 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 05, 2020

Multifile database codes: emez = Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez

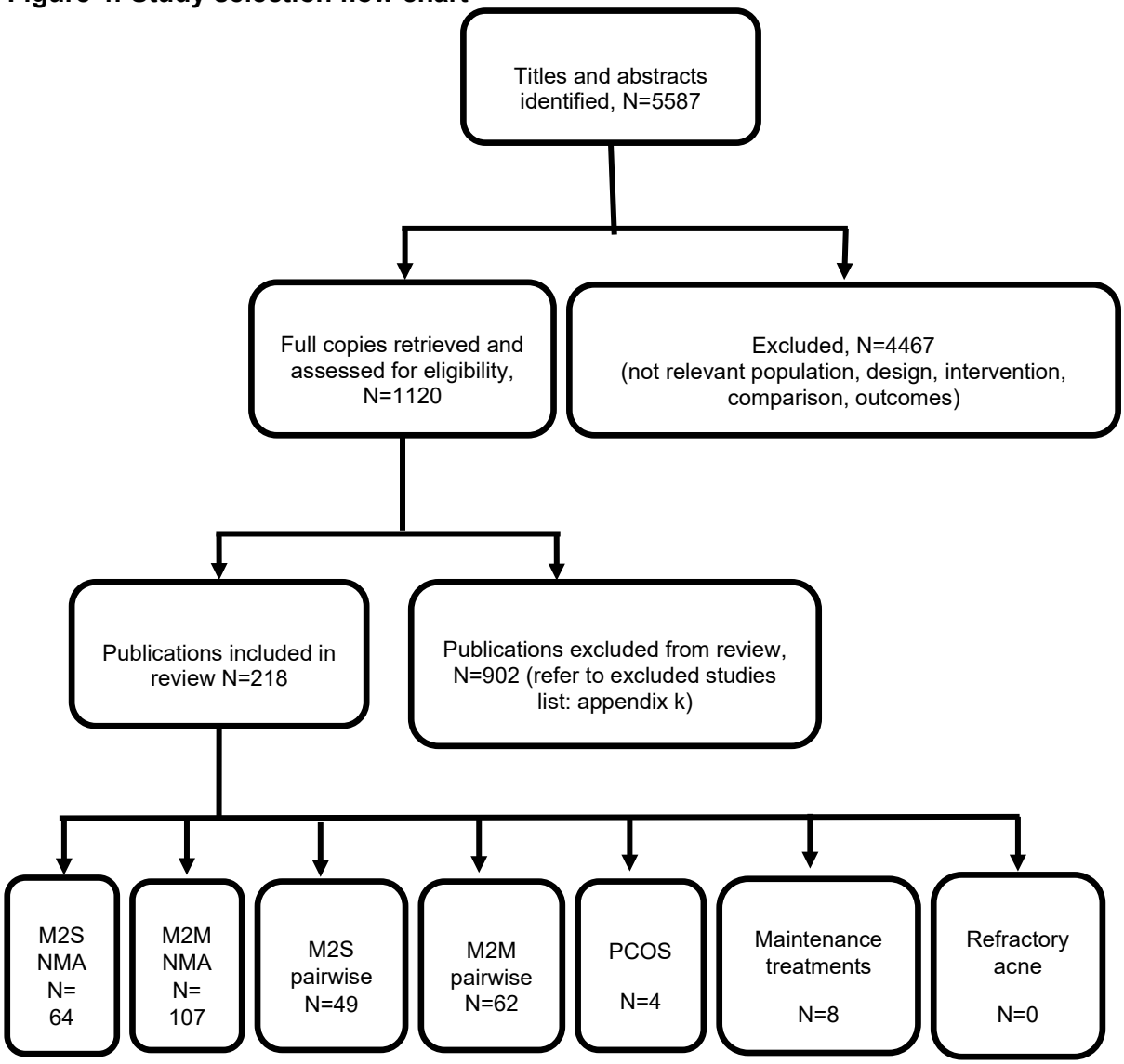
#	Searches
3	acne.tw.
4	or/1-3
5	Quality-Adjusted Life Years/ use ppez
6	Sickness Impact Profile/
7	quality adjusted life year/ use emez
8	"quality of life index"/ use emez
9	(quality adjusted or quality adjusted life year*).tw.
10	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
11	(illness state* or health state*).tw.
12	(hui or hui2 or hui3).tw.
13	(multiattibute* or multi attribute*).tw.
14	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
15	utilities.tw.
16	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
17	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
18	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
19	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
20	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
21	Quality of Life/ and ec.fs.
22	Quality of Life/ and (health adj3 status).tw.
23	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
24	(quality of life or qol).tw. and cost benefit analysis/ use emez
25	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
26	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
27	cost benefit analysis/ use emez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
28	*quality of life/ and (quality of life or qol).ti.
29	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
30	quality of life/ and health-related quality of life.tw.
31	Models, Economic/ use ppez
32	economic model/ use emez
33	or/5-32
34	4 and 33
35	limit 34 to english language
36	limit 35 to yr="2004 -Current"
37	remove duplicates from 36

1
2

Appendix C – Clinical evidence study selection

Study selection for: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Figure 4: Study selection flow chart



Appendix D – Clinical evidence tables

Evidence tables for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Table 7: Clinical evidence tables (for data extraction see supplement 4)

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Abels, C. K., A.,Michalak, I.,Werdier, D.,Knie, U.,Kaszuba, A.A 10% glycolic acid containing oil-in-water emulsion improves mild acne: a randomized double-blind placebo-controlled trial. 2011b. Journal of cosmetic dermatology **Trial ID** Abels 2011b **Country** Europe **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** na	N=120 **Characteristics** **Sex** mixed **age (mean±SD)** 21±5.8 **age (median)** 20 **age (min/max)** 12/53 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Aged 12 years or older with mild facial acne (Leeds score 0.25; 0.5; 0.75; 1.00) **Exclusion details** History of hypersensitivity against one of the ingredients of the study preparations; ‘‘Sandpaper-acne’’; Additional therapy of the facial skin alongside the study preparations; Use of systemic	**Interventions** **Treatment duration (weeks)** 13 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** GLY 10% lotion topical **Intervention: arm 2** PLC-topical **Coded intervention: arm 1** GLY topical **Coded intervention: arm 2** PLC-topical	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; Randomisation was computer assisted in blocks of 6 using the SAS operation PROC PLAN. Participants were numbered in ascending order. Verum and placebo were packed and labeled identically **2. Deviation from intervention** Low; double-blinded; all participants were included in the analysis except for cases with retrospective data documentation; ITT analysis was performed **3. Missing outcome data (efficacy)** Low; <5% loss to follow-up or withdrawals **4. Outcome measurement (efficacy)** Some concerns; efficacy assessed using the Leeds score; blinding not specified

Study details	Participants	Interventions	Outcomes and results	Comments
	steroids, anti-inflammatory agents, or antimycotic; Alcohol and / or drug abuse; Incapacity of duly participating in the study procedures; Participation in another study within the past 4 weeks and / or simultaneously to this study; Use of acne influencing contraceptives. **Number included** **Number randomised: arm 1** 59 **Number randomised: arm 2** 61 **Number completed: arm 1** 57 **Number completed: arm 2** 58			**5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Akarsu, S. F., E.,Yücel, F.,Gül, E.,Günes, A. T.Efficacy of the addition of salicylic acid to clindamycin and benzoyl peroxide combination for acne vulgaris. 2012. Journal of dermatology **Trial ID** Akarsu 2012 **Country** Turkey **Study type** RCT **Source of funding** Unstated	N=50 **Characteristics** **Sex** mixed **age (median)** 19 **age (min/max)** 18/29 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Mild to moderate AV, between the ages of 18 and 35 years, and with between 10–50 IL	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** SAL 3% + CLIND-topical 1% + BPO-topical 5% **Intervention: arm 2** CLIND-topical 1% + BPO-topical 5%	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; not clear if participants and personnel were blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Low; less than 5% loss to follow-up or withdrawals **4. Outcome measurement (efficacy)** Low; investigator-blinded;

Study details	Participants	Interventions	Outcomes and results	Comments
Analysis method **Intention to treat or completers analysis** completers	and 10–100 NIL above the mandibular line at baseline. **Exclusion details** Cystic or nodular acne lesions, those who had used topical anti-acne preparations within the prior 2 weeks, used systemic antibiotics for acne within the prior 1 month, used systemic retinoids within the prior 6 months, or received a facial cosmetic procedure within the prior 6 months. Also pregnant or lactating women, who had known allergy or hypersensitivity to any of the study medication ingredients, or a history of regional enteritis, ulcerative colitis or antibacterial-associated colitis. **Number included** **Number randomised: arm 1** 25 **Number randomised: arm 2** 25 **Number completed: arm 1** 24 **Number completed: arm 2** 25	**Coded intervention: arm 1** SAL topical + CLIND-topical + BPO-topical **Coded intervention: arm 2** CLIND-topical + BPO-topical		outcomes - lesion counting, adverse effects, biophysical measurements, quality of life **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Alba, M. N. G., M.,Yoshida, V. M.,Grotto, D.Clinical comparison of salicylic acid peel and LED-Laser phototherapy for the treatment of Acne vulgaris in teenagers.	N=22 **Characteristics** **Sex** mixed **age (mean±SD)** 15.6±1.3	**Interventions** **Treatment duration (weeks)** 10 **Treatment duration category** 6 to <12 weeks **Treatment intensity** 10 sessions	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants were randomly allocated, but no other methods reported **2. Deviation from intervention**

Study details	Participants	Interventions	Outcomes and results	Comments
2017. Journal of cosmetic and laser therapy **Trial ID** Alba 2017 **Country** Brazil **Study type** RCT **Source of funding** Not industry funded	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Sinclair 2005 **Inclusion details** Adolescents aged between 12 and 18 years old, with grades I and II comedonal and papulopustular acne, and who sought help at the clinic in the trial period. **Exclusion details** Pregnancy, breastfeeding, hypersensitivity to light, use of contraception or tetracycline base antibiotic, use of derivatives of vitamin A (retinoic acid, retinol A, tretinoin, isotretinoin, etc.), and grades III and IV acne. **Number included** **Number randomised: arm 1** 11 **Number randomised: arm 2** 11 **Number completed: arm 1** 11 **Number completed: arm 2** 11	**Number of arms** 2 **Split face design** No **Intervention: arm 1** SAL 10% **Intervention: arm 2** BLUE + RED LIGHT (Spectra G3 machine, Tonederm) **Coded intervention: arm 1** SAL peel **Coded intervention: arm 2** BR-LED		Some concerns; single-blinded (examiners analysing the photographs of lesions); not reported if ITT analysis was performed **3. Missing outcome data (efficacy)** Low; it appears that all participants completed the study **4. Outcome measurement (efficacy)** Low; investigator-blinded; outcomes - lesion counting, adverse effects, biophysical measurements, quality of life **5. Selective reporting** Some concerns; a protocol was approved and registered by the University of Sorocaba Research Ethics Committee, but no further details provided **6. Overall bias** Some concerns
Study details **Reference** Alirezai, M. G., B.,Horvath, A.,Forsea, D.,Briantais, P.,Guyomar, M.Results of a randomised, multicentre study	N=592 **Characteristics** **Sex** mixed **age (mean±SD)** 20.5±5.10	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants were randomised in a 4:4:1 ratio, but methods not reported for allocation concealment

Study details	Participants	Interventions	Outcomes and results	Comments
comparing a new water-based gel of clindamycin 1% versus clindamycin 1% topical solution in the treatment of acne vulgaris. 2005. European Journal of Dermatology **Trial ID** Alirezai 2005 **Country** Europe **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	**age (min/max)** 12/35 **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** At least age 12, acne vulgaris on face (severity grade of 2 to 5 on the Leeds revised scale), and 15-50 inflammatory facial lesions. **Exclusion details** Acne conglobata, acne fulminans, chloracne, drug enduced acne, pregnant or nursing or planning for a baby, and men with beards that may interfere with assessment. **Number included** **Number randomised: arm 1** 265 **Number randomised: arm 2** 261 **Number randomised: arm 3** 66 **Number completed: arm 1** 233 **Number completed: arm 2** 240 **Number completed: arm 3** 57	**Number of arms** 3 **Split face design** No **Intervention: arm 1** CLIND-topical 1% gel **Intervention: arm 2** CLIND-topical 1% topical solution **Intervention: arm 3** Vehicle gel **Coded intervention: arm 1** CLIND-topical **Coded intervention: arm 2** CLIND-topical **Coded intervention: arm 3** Vehicle	**Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**2. Deviation from intervention** Some concerns; participants aware of treatment regimen and product packaging and asked not to inform the Investigator in order to maintain blinding; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; more than 5% loss to follow-up or withdrawals (10.5%) - similar between arms **4. Outcome measurement (efficacy)** Low; investigator-blinded; outcomes - lesion counting, Global Assessment of Improvement, adverse effects **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Alora Palli, M. R.-H., C. M.,Lima, X. T.,Kimball, A. B.A single-center, randomized double-blind, parallel-group study to examine the safety and efficacy of 3mg drospirenone/0.02mg ethinyl estradiol compared with placebo in the treatment of moderate truncal acne vulgaris. 2013. Journal of drugs in dermatology **Trial ID** Alora Palli 2013 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** completers	N=30 **Characteristics** **Sex** female **age (mean±SD)** 24±4.5 **age (min/max)** 19/40 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Female, age 18 to 45 years, who achieved spontaneous menarche, desired contraception and had a diagnosis of truncal acne of 10 to 50 inflammatory lesions on the back and chest combined with not more than 5 nodules **Exclusion details** Smokers, medical conditions that increased their risk of developing adverse events from study medication, participants who had used topical acne medications (tretinoin, benzoyl peroxide, or topical antibiotics) within 2 weeks, systemic antibiotics or oral steroids within 4 weeks, oral contraceptive within 12 weeks, isotretinoin in the past six months, and phototherapy	**Interventions** **Treatment duration (weeks)** 24 **Treatment duration category** 24+ weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** EE-oral 0.02 mg + DROS-oral 3mg od **Intervention: arm 2** PLC-oral **Coded intervention: arm 1** EE-oral + DROS-oral **Coded intervention: arm 2** PLC-oral	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomly assigned in 1:1 ratio by Research Randomiser; methods not reported for allocation concealment **2. Deviation from intervention** Low; double-blinded (participants and study staff not aware of treatment assignment); ITT analysis appears to have been performed **3. Missing outcome data (efficacy)** High; 40% loss to follow-up or withdrawals - more in the active arm; last observation carried forward **4. Outcome measurement (efficacy)** Low; assessor was blinded; outcomes - lesion counting, Investigator and Subject Global Assessment, quality of life, adverse effects **5. Selective reporting** Low; registered with ClinicalTrials.gov **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	devices (ClearLight, Zenozapper, tanning booths or lamps) within 1 week. **Number included** **Number randomised: arm 1** 16 **Number randomised: arm 2** 14 **Number completed: arm 1** 11 **Number completed: arm 2** 10			
Study details **Reference** Babaeinejad, S. H. F., R. F.The efficacy, safety, and tolerability of adapalene versus benzoyl peroxide in the treatment of mild acne vulgaris; a randomized trial. 2013. Journal of Drugs in Dermatology **Trial ID** Babaeinejad 2013 **Country** Iran, Islamic Republic of **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** completers	N=60 **Characteristics** **Sex** mixed **age (mean±SD)** 21.1±3.64 **age (min/max)** 18/31 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Evaluator's Global Severity Scale (EGSS) **Inclusion details** Mild acne vulgaris (Evaluator Global Severity Score, EGSS, of 2) **Exclusion details** Severe acne or other dermatologic conditions requiring	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** BPO 2.5% gel **Intervention: arm 2** ADAP 0.1% gel **Coded intervention: arm 1** BPO-topical **Coded intervention: arm 2** ADAP-topical	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation conducted using standard computer randomisation software; medications were in identical tubes and coding not disclosed until after data were analysed **2. Deviation from intervention** Some concerns; double blind; not reported if ITT analysis performed **3. Missing outcome data (efficacy)** Low; all participants completed the study **4. Outcome measurement (efficacy)** Low; outcomes - lesion count, adverse effects, overall satisfaction **5. Selective reporting** Some concerns; not reported

Study details	Participants	Interventions	Outcomes and results	Comments
	systemic therapy, nursing/pregnant women, and those who were planning for pregnancy. No use within the past 2 weeks of topical antibiotics and corticosteroid, 1 month of oral antibiotics and corticosteroid, and 6 months of oral retinoid agent. **Number included** **Number randomised: arm 1** 30 **Number randomised: arm 2** 30 **Number completed: arm 1** 30 **Number completed: arm 2** 30			whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Babayeva, L. A., S.,Fetil, E.,Gunes, A. T.Comparison of tretinoin 0.05% cream and 3% alcohol-based salicylic acid preparation in the treatment of acne vulgaris. 2011. Journal of the European Academy of Dermatology and Venereology **Trial ID** Babayeva 2011 **Country** Turkey **Study type** RCT	N=46 **Characteristics** **Sex** mixed **age (mean±SD)** 20.78±2.69 **age (min/max)** 18/31 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** 18 and 35 years of age, with 10–50 inflammatory lesions and 10–100 non-Inflammatory	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** SAL 3% + CLIND-topical 1% **Intervention: arm 2** TRET-topical 0.05% + CLIND-topical 1% **Coded intervention: arm 1** SAL topical + CLIND-topical	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using 1:1 ratio (no other information provided); unclear whether allocation sequence concealed **2. Deviation from intervention** Some concerns; single-blinded but not clear who was blinded; not reported if ITT analysis was performed **3. Missing outcome data (efficacy)** Low; all participants completed the study

Study details	Participants	Interventions	Outcomes and results	Comments
Source of funding Not industry funded **Analysis method** **Intention to treat or completers analysis** completers	lesions above the mandibular line at baseline **Exclusion details** Pregnant or lactating women, participants who had known sensitivity to any of the study medication ingredients, those who used topical anti-acne preparations, medicated shampoos or cleansers within 2 weeks; systemic antibiotic treatments for acne within 1 month; or systemic retinoid treatments within 6 months, prior to start of the study. **Number included** **Number randomised: arm 1** 23 **Number randomised: arm 2** 23 **Number completed: arm 1** 23 **Number completed: arm 2** 23	**Coded intervention: arm 2** TRET-topical + CLIND-topical		**4. Outcome measurement (efficacy)** High; "Evaluations were performed by an investigator aware of the treatment allocation" **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol, but all outcomes mentioned appear to have findings reported **6. Overall bias** High
Study details **Reference** Barbareschi, M. H., I.,Angius, A.,Cattaneo, M.,Monti, M.The anticomedonic activity of azelaic acid investigated by means of scanning electron microscopy on horny layer biopsy. 1991. Journal of Dermatological Treatment **Trial ID** Barbareschi 1991	N=30 **Characteristics** **Sex** mixed **age (min/max)** 15/28 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None	**Interventions** **Treatment duration (weeks)** 17 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** AZE-topical 20% twice daily	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomly allocated to 3 groups, but no other methods reported **2. Deviation from intervention** High; Open study; not reported if ITT analysis performed

Study details	Participants	Interventions	Outcomes and results	Comments
Country Italy **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** completers	**Inclusion details** Comedonic acne. **Exclusion details** - **Number included** **Number randomised: arm 1** 10 **Number randomised: arm 2** 10 **Number randomised: arm 3** 10 **Number completed: arm 1** 10 **Number completed: arm 2** 10 **Number completed: arm 3** 10	**Intervention: arm 2** TRET-topical 0.05% **Intervention: arm 3** PLC-topical **Coded intervention: arm 1** AZE-topical **Coded intervention: arm 2** TRET-topical **Coded intervention: arm 3** PLC-topical		**3. Missing outcome data (efficacy)** Low; appears that all participants completed the study ("clinical assessment in all participants at the beginning of the study and after 4 months of treatment") **4. Outcome measurement (efficacy)** High; Open study **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol, but all outcomes mentioned appear to have findings reported **6. Overall bias** High
Study details **Reference** Barolet, D. B., A.Radiant near infrared light emitting diode exposure as skin preparation to enhance photodynamic therapy inflammatory type acne treatment outcome. 2010. Lasers in Surgery and Medicine **Trial ID** Barolet 2010 **Country** Canada **Study type** RCT	N=20 **Characteristics** **Sex** mixed **age (mean±SD)** 26.2 **age (min/max)** 13/54 **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Comprehensive Acne Severity Scale (CAAS) **Inclusion details** Mild to moderate acne based on the Combined Acne	**Interventions** **Treatment intensity** 1 treament session **Number of arms** 2 **Split face design** Yes **Intervention: arm 1** IRL and then 5ALA-RED-PDT **Intervention: arm 2** 5ALA-RED-PDT **Coded intervention: arm 1** 5ALA-RED-PDT + IRL **Coded intervention: arm 2** 5ALA-RED-PDT	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; coin flip procedure used for randomising participant treatment sides; methods not reported for allocation concealment **2. Deviation from intervention** High; not reported if participants were blinded; no ITT analysis was done (per protocol completion rate) **3. Missing outcome data (efficacy)**

Study details	Participants	Interventions	Outcomes and results	Comments
Source of funding Industry funded **Analysis method** **Intention to treat or completers analysis** completers	Severity Classification with a lesion count of at least 10 and skin type I to III according to the Fitzpatrick Classification System **Exclusion details** Currently taking cortisone (Prednisone), anticoagulant therapy, or any drug known to increase photosensitivity. No use of isotretinoin (Accutane), or applied topical steroids on the site to be treated in the past 12 months. Also, no oral antibiotics use, laser or topical antiacne medication at the to-be-treated site in the past 8 weeks. **Number included** **Number randomised: arm 1** 10 **Number randomised: arm 2** 10 **Number completed: arm 1** 9 **Number completed: arm 2** 9			High; more than 5% loss to follow-up (10% loss) **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol, but all outcomes mentioned appear to have findings reported **6. Overall bias** High
Study details **Reference** Becker, L. E. B., P. R.,Whiting, D. A.,Clendenning, W. E.,Dobson, R. L.,Jordan, W. P.,Abell, E.,LeZotte, L. A.,Pochi, P. E.,Shupack, J. L.,et al.,Topical clindamycin therapy for acne vulgaris. A	N=238 **Characteristics** **Sex** mixed **age (min/max)** 12/30 **age (other information)** mean age in clind-phosphate 21.7, and vehicle 21.4 years	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; 3 interventions were of identical appearance, but no other methods reported **2. Deviation from intervention** Some concerns; double-

Study details	Participants	Interventions	Outcomes and results	Comments
cooperative clinical study. 1981. Archives of dermatology **Trial ID** Becker 1981 **Country** United States **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** completers	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Age 12 to 30 with a minimum of 12 and a maximum of 70 inflammatory papules on the face. **Exclusion details** No other topical treatments, oral or topical antibiotics or eorticosteroids within 30 days of the beginning of the study. Participants with histories of gastrointestinal tract disease. **Number included** **Number randomised: arm 1** 124 **Number randomised: arm 2** 114 **Number completed: arm 1** 123 **Number completed: arm 2** 113	**Intervention: arm 1** CLIND-topical 1% (clindamycin phosphate) **Intervention: arm 2** Vehicle **Coded intervention: arm 1** CLIND-topical **Coded intervention: arm 2** Vehicle		blinded but not clear who was blinded; not reported if ITT analysis was not done **3. Missing outcome data (efficacy)** High; more than 5% loss to follow-up or withdrawals; not reported how many in each group (the 55 participants not included did not comply with study requirements) **4. Outcome measurement (efficacy)** Some concerns; not clear who was blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol, but all outcomes mentioned appear to have findings reported **6. Overall bias** High
Study details **Reference** Bernhardt, M. J. M., M. F.Topical treatment with an agent disruptive to P. acnes biofilm provides positive therapeutic response: Results of a randomized clinical trial. 2016. Journal of Drugs in Dermatology	N=68 **Characteristics** **Sex** mixed **age (mean±SD)** 19 **age (min/max)** 12/36	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; Participants randomised using 1:1 ratio, a randomised allocation table was used; methods not reported for allocation concealment **2. Deviation from intervention**

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Bernhardt 2016 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** completers	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Older than 12 years old with more than 1- inflammatory lesions **Exclusion details** No more than 2 modular cysts/nodules, allergy/reaction to topicals, malignancy, facial hair, significant medical problems **Number included** **Number randomised: arm 1** 35 **Number randomised: arm 2** 33 **Number completed: arm 1** 33 **Number completed: arm 2** 31	**Intervention: arm 1** Topical salicylic acid in "Next Science Acne" gel **Intervention: arm 2** Vehicle **Coded intervention: arm 1** SAL topical **Coded intervention: arm 2** Vehicle topical		Some concerns; double-blinded (investigators and participants blinded, but blinding removed after statistical analysis complete), vehicle and intervention gel composition the same to prevent identification and both identically labelled; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; 5.88% discontinued - balanced between arms (discontinuations because of failure to return for appointments, not resulting from treatment complications or adverse events) **4. Outcome measurement (efficacy)** Low; investigator was blinded **5. Selective reporting** Low; registered with ClinicalTrials.gov **6. Overall bias** Some concerns
Study details **Reference** Bleeker, J.Tolerance and efficacy of erythromycin stearate tablets versus enteric-coated erythromycin base capsules in the treatment of patients with acne vulgaris.	N=40 **Characteristics** **Sex** mixed **age (other information)** Mean age 20.6 in erythromycin	**Interventions** **Treatment duration (weeks)** 2 **Treatment duration category** 0 to <6 weeks **Number of arms** 2	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; not reported if

Study details	Participants	Interventions	Outcomes and results	Comments
1983. Journal of International Medical Research **Trial ID** Bleeker 1983 **Country** Sweden **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** completers	stearate group, 19.7 in the other **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Mild to moderate papulopustular acne **Exclusion details** Acne conglobata, comedonal ace, hypersensitivity to erythromycin, antibiotic treatment in the past month **Number included** **Number randomised: arm 1** 20 **Number randomised: arm 2** 20 **Number completed: arm 1** 18 **Number completed: arm 2** 16	**Split face design** No **Intervention: arm 1** Erythromycin stearate capsules 500mg b.d. **Intervention: arm 2** Erythromycin base capsules 500mg b.d. **Coded intervention: arm 1** ERYTH-oral **Coded intervention: arm 2** ERYTH-oral	**due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	participants were blinded; no ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 5% discontinued due to side effects (20% enteric-coated erythromycin base capsules vs 10% erythromycin stearate tablets) **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Boutli, F. Z., M.,Koussidou, T.,Ioannides, D.,Mourellou, O.Comparison of chloroxylenol 0.5% plus salicylic acid 2% cream and benzoyl peroxide 5% gel in the treatment of acne vulgaris: a randomized double-blind study. 2003. Drugs under experimental and clinical research	N=37 **Characteristics** **Sex** mixed **age (min/max)** 13/25 **age (other information)** mean age 21.4 in BP group & 20.8 in other group (SDs not reported)	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomised trial, but methods not reported **2. Deviation from intervention** Some concerns; double-blinded but not clear who was blinded; No ITT analysis was done **3. Missing outcome data (efficacy)**

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Boutli 2003 **Country** Greece **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** completers	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Pillsbury **Inclusion details** Age 13-25, moderate acne (grade 11, Pilsbury and Kligman), 20-50 comedones and 20-40 papulopustules **Exclusion details** Pregnant or nursing women, other systemic diseases, nodulocystic acne, taking oral contraceptives, taking systemic antibiotics, or any topical treatment for other reasons during the study **Number included** **Number randomised: arm 1** 19 **Number randomised: arm 2** 18 **Number completed: arm 1** 18 **Number completed: arm 2** 16	**Intervention: arm 1** Topical benzoil peroxide 5% gel **Intervention: arm 2** Topical Nisal cream (chloroxylenol 0.5% + salicylic acid 2%) **Coded intervention: arm 1** BPO-topical **Coded intervention: arm 2** NISAL topical		High; more than 5% discontinued or lost to follow-up (8.1%); 5.3% in group 1 and 11.1% in group 2 **4. Outcome measurement (efficacy)** Some concerns; blinding not reported **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Callender, V. D. Y., C. M.,Kindred, C.,Taylor, S. C.Efficacy and safety of clindamycin phosphate 1.2% and tretinoin 0.025% gel for the treatment of acne and acne-induced post-	N=33 **Characteristics** **Sex** mixed **age (mean±SD)** 28.3 **age (min/max)** 13/51	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; no methods reported **2. Deviation from intervention** Some concerns; double-blinded but not clear who was

Study details	Participants	Interventions	Outcomes and results	Comments
inflammatory hyperpigmentation in patients with skin of color. 2012b. Journal of Clinical and Aesthetic Dermatology **Trial ID** Callender 2012b **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** completers	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** 12 years of age or older with skin types IV to VI and exhibited mild-to-moderate facial acne and mild-to-moderate PIH **Exclusion details** Seborrheic dermatitis, PIH of solely dermal origin, acne vulgaris known to be resistant to oral antibiotics or had a history of Crohn's disease, regional enteritis, or ulcerative or antibiotic-related colitis. People taking erythromycin, neuromuscular blocking agents, hormone replacement or oral/transdermal contraceptive therapy, hydroquinone or other depigmenting medication within 14 days of the study, tetracycline or any other photosensitizing medication within 30 days of the study, isotretinoin, chemical peels, microdermabrasion or laser treatment within six months of the study. People with a known allergy or sensitivity to the study medication or its components. Women who	**Split face design** No **Intervention: arm 1** Topical clindamycin 1.2% + topical tretinoin 0.025% **Intervention: arm 2** Vehicle **Coded intervention: arm 1** CLIND-topical + TRET-topical **Coded intervention: arm 2** Vehicle	**Clinician rated improvement in acne** See supplement 4	blinded; no ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 5% discontinued (11.8% in clindamycin/tretinoin gel group and 6.25% in the placebo group); reasons for not completing the trial included loss to follow-up and withdrawal of consent **4. Outcome measurement (efficacy)** Some concerns; not clear if blinded **5. Selective reporting** Some concerns; protocol approved by a local institutional review board, but no further details provided **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	were pregnant or breastfeeding. **Number included** **Number randomised: arm 1** 17 **Number randomised: arm 2** 16 **Number completed: arm 1** 15 **Number completed: arm 2** 15			
Study details **Reference** Capizzi, F. L., F.,Milani, M.,Amerio, P.Skin tolerability and efficacy of combination therapy with hydrogen peroxide stabilized cream and adapalene gel in comparison with benzoyl peroxide cream and adapalene gel in common acne. A randomized, investigator-masked, controlled trial. 2004. British Journal of Dermatology **Trial ID** Capizzi 2004 **Country** Italy **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or**	N=52 **Characteristics** **Sex** mixed **age (mean±SD)** 25±6 **age (min/max)** 15/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Lehmann **Inclusion details** Aged 15– 35 years with mild to moderate AV defined as: at least 10 and <50 inflammatory lesions (IL), at least 10 and <100 noninflammatory lesions (NL) and no more than two nodulocystic lesions **Exclusion details** Acne conglobata, severe acne,	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Adapalene topical gel 0.1% + HPS-topical cream 1% **Intervention: arm 2** Adapalene topical gel 0.1% + BPO-topical cream 4% **Coded intervention: arm 1** ADAP-topical + HPS-topical **Coded intervention: arm 2** ADAP-topical + BPO-topical	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using a computer-generated randomisation list with a block of 6 in a 1:1 ratio; methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; not reported if participants were blinded; efficacy and tolerability assessed using ITT analysis **3. Missing outcome data (efficacy)** Low; all participants completed the trial **4. Outcome measurement (efficacy)** Low; investigator blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis ITT **Method of ITT imputation** na	or otherwise requiring more than topical treatment **Number included** **Number randomised: arm 1** 26 **Number randomised: arm 2** 26 **Number completed: arm 1** 26 **Number completed: arm 2** 26			**6. Overall bias** Some concerns
Study details **Reference** Carey, W. B., J. C.A Canadian multicentre study to compare fusidic acid lotion and erythromycin solution in the treatment of acne vulgaris of the face. 1996. European journal of clinical research **Trial ID** Carey 1996 **Country** Canada **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** na	N=499 **Characteristics** **Sex** mixed **age (mean±SD)** 18.2±3.5 **age (min/max)** 11/25 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Under 25 years, 15 - 75 inflammed lesions on the face **Exclusion details** Any established or suspected dermatalogical disease or who had used topical treatments within the past week. Women of childbearing age not considered to be using adequate contraception.	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Topical fusidic acid 2% **Intervention: arm 2** Topical erythromycin 2% **Coded intervention: arm 1** FCA-topical **Coded intervention: arm 2** ERYTH-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; computer-generated randomisation schedule used; methods not reported for allocation concealment **2. Deviation from intervention** High; open-labeled; ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 15% loss to follow-up or withdrawals (21.7% receiving fusidic acid lotion and 15.6% receiving erythromycin) **4. Outcome measurement (efficacy)** Low; evaluator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol

Study details	Participants	Interventions	Outcomes and results	Comments
	Received ultraviolet radiation treatment within the past 4 weeks, systemic anti-infectives or corticosteroids o and hormones (except contraception) within the previous 4 weeks, or acne treament with retinoid within the past 12 months. **Number included** **Number randomised: arm 1** 249 **Number randomised: arm 2** 250 **Number completed: arm 1** 195 **Number completed: arm 2** 211			**6. Overall bias** High
Study details **Reference** Charakida, A. C., M.,Chu, A. C.Double-blind, randomized, placebo-controlled study of a lotion containing triethyl citrate and ethyl linoleate in the treatment of acne vulgaris. 2007. British Journal of Dermatology **Trial ID** Charakida 2007 **Country** United Kingdom **Study type** RCT **Source of funding** Not industry funded	N=40 **Characteristics** **Sex** mixed **age (other information)** median (IQR) age: 24 (20-30.75) in active group, 27.5 (18.25 - 33) in vehicle group **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** People aged between 16 and 45 years with mild to moderate facial inflammatory acne defined as the presence of at	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ACNICARE (triethyl citrate + ethyl linoleate) topical b.d. **Intervention: arm 2** Vehicle topical b.d. **Coded intervention: arm 1** ACNICARE	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using computer-generated sequence; no other methods reported **2. Deviation from intervention** Low; double-blinded (2 lotions provided in identical bottles to ensure anonymity for both investigator and participants); ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 15% withdrew (15% intervention; 20% vehicle); participants withdrew

Study details	Participants	Interventions	Outcomes and results	Comments
Analysis method **Intention to treat or completers analysis** ITT **Method of ITT imputation** na	least 10 acne papules or pustules between the brow and jaw line and an acne severity score of between 2 and 7 on the Leeds revised acne grading system. **Exclusion details** Severe acne, rosacea, pregnancy, breastfeeding, known allergy to constituents of the lotions, use of medication for acne or use of antibiotics for other medical conditions **Number included** **Number randomised: arm 1** 20 **Number randomised: arm 2** 20 **Number completed: arm 1** 17 **Number completed: arm 2** 16	**Coded intervention: arm 2** Vehicle		from vehicle because of dissatisfaction with clinical response **4. Outcome measurement (efficacy)** Low; investigator-blinded; outcomes measured at 4, 8 and 12 weeks but only results at 4 and 12 weeks appear to have been reported. However, study endpoints appear to be change from baseline to after 12 weeks **5. Selective reporting** Some concerns; study protocol mention, but not clear whether this was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Cheema, A. N. A., U.,Javaid, R.,Bokhari, M. A.Efficacy and safety of blue light versus 4% topical benzoyl peroxide in mild to moderate acne. 2018. Journal of Pakistan Association of Dermatologists **Trial ID** Cheema 2018 **Country** Pakistan	N=140 **Characteristics** **Sex** mixed **age (mean±SD)** 23.02±6.33 **age (min/max)** 14/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None	**Interventions** **Treatment duration (weeks)** 6 **Treatment duration category** 6 to <12 weeks **Treatment intensity** 12 sessions twice a week for 6 weeks **Split face design** No **Intervention: arm 1** blue light (Soret Blue Light) 407-420nm high intensity light	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomly divided into 2 groups using random number table; no other methods reported **2. Deviation from intervention** Some concerns; blinding not reported; not reported if ITT was done **3. Missing outcome data (efficacy)**

Study details	Participants	Interventions	Outcomes and results	Comments
Study type RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** completers	**Inclusion details** Mild to moderate acne **Exclusion details** Systemic diseases, pregnant and lactating mothers, people with photosensitivity, herpes simplex virus infection on the treatment area, laser resurfacing, chemical peel or dermabrasion within the last 8 weeks and history of previous allergy to benzoyl peroxide or blue light were excluded **Number included** **Number randomised: arm 1** 70 **Number randomised: arm 2** 70 **Number completed: arm 1** 62 **Number completed: arm 2** 62	**Intervention: arm 2** BPO 4% topical cream o.d. **Coded intervention: arm 1** BLU-PT **Coded intervention: arm 2** BPO-topical		Some concerns; more than 10% withdrew because of poor compliance or minor side effects of topical benzoyl peroxide (n=8 participants in each treatment group; 11.4%) **4. Outcome measurement (efficacy)** Some concerns; participant's disease severity was assessed by a third observer unaware of the intervention, but no other details provided **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Choi, Y. S. S., H. S.,Yoon, M. Y.,Min, S. U.,Lee, D. H.,Suh, D. H.Intense pulsed light vs. pulsed-dye laser in the treatment of facial acne: A randomized split-face trial. 2010. Journal of the European Academy of Dermatology and Venereology **Trial ID** Choi 2010	N=40 **Characteristics** **Sex** mixed **age (mean±SD)** 26 **age (min/max)** 20/37 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Treatment intensity** 4 sessions - 2 weeks apart. Outcomes reported 4 weeks after final session **Number of arms** 2 **Split face design** Yes	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; a randomised code was used to determine which side of the face received with treatment (split face trial); methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; not reported if participants were blinded; not reported if ITT analysis was done

Study details	Participants	Interventions	Outcomes and results	Comments
Country Korea, Republic of **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** completers	**Inclusion details** Age >15 years, general good health, the ability to comply with the study protocol and an acne severity grade of 2–4, as defined by Cunliffe's grading system **Exclusion details** A history of keloid, a photosensitive disorder, or oral retinoid use within 6 months of study commencement, microdermabrasion on the face within 3 months of study commencement, the use of oral / topical antibiotics, topical retinoid or alpha-hydroxyl acid within 1 month of study commencement, or dermabrasion or laser resurfacing of facial skin. No medicine or procedures that might affect the course of acne were allowed during the 14-week study period **Number included** **Number randomised: arm 1** 20 **Number randomised: arm 2** 20 **Number completed: arm 1** 17 **Number completed: arm 2** 17	**Intervention: arm 1** INTENSE PULSED LIGHT [IPL] Ellipse Flex System **Intervention: arm 2** PULSED DYE LASER 585-nm (Cynergy; system) **Coded intervention: arm 1** IPL **Coded intervention: arm 2** PDL		**3. Missing outcome data (efficacy)** Some concerns; 15% discontinued - schedule conflict for 2 participants and pregnancy for 1 participant **4. Outcome measurement (efficacy)** Low; reported as "single-blinded" **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Chottawornsak, N., Chongpison, Y., Asawanonda, P., Kumtornrut, C.Topical 2% ketoconazole cream monotherapy significantly improves adult female acne: A double-blind, randomized placebo-controlled trial. 2019. Journal of Dermatology **Trial ID** Chottawornsak 2019 **Country** Thailand **Study type** RCT **Source of funding** Ratchadapisek Sompoch Endowment Fund (2017), Chulalongkorn University (grant no. RA61/023) and the Dermatological Society of Thailand. **Analysis method** **Intention to treat or completers analysis** Completers	N=41 **Characteristics** **Sex** female **age (mean±SD)** 34.6±6.3 **age (min/max)** 25/49 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Global Acne Severity Scale (GEA Scale) **Inclusion details** Participants were women aged above 25 years.Mild acne with an AFA score of 2 on the face based on the Global Acne Severity Scale **Exclusion details** 2-week use of topical and/or 4-week use of systemic acne medication prior to the study.Other special types of acne or conditions presenting with acne/acneiform eruptions (e.g. SAPHO syndrome).Irregular menstrual cycles or clinically suspected polycystic ovarian syndrome.Other facial rashes preventing the accurate assessment.Known or suspected allergy to the	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Topical 2% ketoconazole cream **Intervention: arm 2** Placebo **Coded intervention: arm 1** KETO-topical **Coded intervention: arm 2** PLC-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported for allocation **2. Deviation from intervention** Some concerns; double-blinded; not clear if an ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; 9.5% discontinued in placebo arm; no reasons given **4. Outcome measurement (efficacy)** Low; double-blinded **5. Selective reporting** Low **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	ingredients.Pregnancy or lactation **Number included** **Number randomised: arm 1** 20 **Number randomised: arm 2** 21 **Number completed: arm 1** 20 **Number completed: arm 2** 19			
Study details **Reference** Cunliffe, W. J. H., K. T.,Bojar, R.,Levy, S. F.A randomized, double-blind comparison of a clindamycin phosphate/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. 2002. Clinical Therapeutics **Trial ID** Cunliffe 2002b **Country** United Kingdom **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT	N=79 **Characteristics** **Sex** mixed **age (mean±SD)** 18.2±1.7 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Acne vulgaris, aged 13 to 30. Baseline or screening P acnes counts on facial skin (cheek or forehead) had to be at least 104 colony-forming units (CFUs) per square centimeter, of which no more than 104 CFU/cm 2 could be erythromycin or clindamycin resistant. Eligible people also had to have 15 to 100 inflammatory lesions, 15 to 100 comedones, and <2	**Interventions** **Treatment duration (weeks)** 16 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** topical clindamycin 1% / BPO 5% gel b.d. **Intervention: arm 2** topical clindamycin 1% **Coded intervention: arm 1** BPO-topical + CLIND-topical **Coded intervention: arm 2** CLIND-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants ranked in descending order in accordance with their total lesion counts at baseline and assigned to treatments alternatively; treatment assignments performed by statistician not involved in the data collection, management or analysis and medication dispensed by a pharmacist not an evaluator **2. Deviation from intervention** Low; double-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 5% withdrawals (15% combination gel; 7.7% clindamycin monotherapy) resulting from loss to follow-up

Study details	Participants	Interventions	Outcomes and results	Comments
Method of ITT imputation LOCF	nodules/cysts on the face. Sexually active females were required to use contraception for 28 days before the start and for the duration of the study. **Exclusion details** Excluded if they had used oral antibiotics, topical antibiotics, or systemic hormones, including tablets containing cyproterone acetate 2 mg plus ethinylestradiol 35 pg, within 12 weeks before the start of the study. They were not to have used topical steroids on the face for 2 weeks, topical retinoids for 4 weeks, or oral retinoids for 6 months before entry. People with beards and sideburns, or with systemic or dermatologic diseases that may have affected their acne conditions or treatment assessments, and people whose activities involved prolonged exposure to sunlight were excluded from the study. Pregnant or breast-feeding women and people with known sensitivity to any ingredients in the study medications also were excluded.			**4. Outcome measurement (efficacy)** Low; evaluator blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number included **Number randomised: arm 1** 40 **Number randomised: arm 2** 39 **Number completed: arm 1** 30 **Number completed: arm 2** 32			
Study details **Reference** Cunliffe, W. J. F., C.,Bojar, R.,Kanis, R.,West, F.An observer-blind, parallel-group, randomized, multicentre clinical and microbiological study of a topical clindamycin/zinc gel and a topical clindamycin lotion in patients with mild/moderate acne. 2005. Journal of Dermatological Treatment **Trial ID** Cunliffe 2005 **Country** Europe **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=246 **Characteristics** **Sex** mixed **age (min/max)** 12/40 **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Age between 12 and 40 years with mild to moderate acne graded between 2 and 7 with at least 15 inflammatory and 10 non-inflammatory lesions, but fewer than 75 lesions of either type **Exclusion details** Hypersensitive to active ingredients or excipients; had used topical or systemic antibiotics within 4 weeks of the start of treatment; had used systemic or topical retinoids within 6 months or 4	**Interventions** **Treatment duration (weeks)** 16 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** topical clindamycin 1% / zinc gel b.d. **Intervention: arm 2** topical clindamycin 1% / zinc gel q.d. **Intervention: arm 3** topical clindamycin 1% b.d. **Coded intervention: arm 1** CLIND-topical+ ZINC-topical **Coded intervention: arm 2** CLIND-topical+ ZINC-topical **Coded intervention: arm 3** CLIND-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; "The investigator and assessors of all clinical variables were blinded to treatment allocation to avoid bias". All randomised participants were included in PP analysis and participants with a baseline and at least 1 post-baseline assessment of efficacy were included in ITT analysis - 79/83, 77/80, 83/83; last observation carried forward used for ITT analyses **3. Missing outcome data (efficacy)** Some concerns; more than 5% withdrawals in PP analysis, reasons not reported (ITT 4.8% vs 3.75% vs 0% ; PP 12% vs 9% vs 7%

Study details	Participants	Interventions	Outcomes and results	Comments
	weeks, respectively, prior to the start of treatment; had used topical antimicrobials within 4 weeks prior to the start of treatment; had other facial dermatoses or medical conditions that may have interfered with study assessments; had significant nodulocystic acne; had more than three nodules at screening; had lack of adequate contraception; or were females who were pregnant or lactating. **Number included** **Number randomised: arm 1** 83 **Number randomised: arm 2** 80 **Number randomised: arm 3** 83 **Number completed: arm 1** 73 **Number completed: arm 2** 73 **Number completed: arm 3** 77			**4. Outcome measurement (efficacy)** Low; "The investigator and assessors of all clinical variables were blinded to treatment allocation to avoid bias." **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Darrah, A. J. G., P. L.Treatment of inflammatory acne with a 1450-nm smoothbeam diode laser: A split-face randomized single-blinded controlled trial. 1996.	N=188 **Characteristics** **Sex** mixed **age (mean±SD)** 18 **age (min/max)** 11/29	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; Methods not reported for allocation concealment **2. Deviation from intervention**

Study details	Participants	Interventions	Outcomes and results	Comments
European journal of clinical research **Trial ID** Darrah 1996 **Country** United Kingdom **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** ITT	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Aged 12 to 25 with diagnosis of mild-to-moderate acne vulgaris of the face, and history of acne for at least 3 months. Mild acne was defined as the presence of 5 to 20 papules and/or pustules, and moderate acne was defined as the presence of 21 to 50 papules and/or pustules on the right side of the face. **Exclusion details** Severe acne requiring significant treatment, presence of cysts or nodules, an established or suspected dermatalogical disease of the face, systemic antibiotics within 4 weeks prior to treatment, topical acne medications within 2 weeks, UV treatment within 4 weeks, retinoids or hormone preparations or corticosteroids, within the previous 52 weeks, pregnancy or breast-feeding, known hypersensitivity to fusidic acid or minocycline. Women of childbearing potential who were not considered to be using an	**Split face design** No **Intervention: arm 1** topical fusidic acid 2% lotion b.d. **Intervention: arm 2** oral minocycline 50mg b.d. **Coded intervention: arm 1** FCA-topical **Coded intervention: arm 2** MINO-oral	**due to side effects** See supplement 4	High; open study; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; more than 5% discontinued **4. Outcome measurement (efficacy)** High; open-study **5. Selective reporting** Some concerns; protocol approved by independent Local Research Ethics Committees (for each site) prior to commencement, but no further details provided **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	adequate method of conraception. **Number included** **Number randomised: arm 1** 95 **Number randomised: arm 2** 93 **Number completed: arm 1** 77 **Number completed: arm 2** 73			
Study details **Reference** Dayal, S. A., A.,Sahu, P.,Jain, V. K.Jessner's solution vs. 30% salicylic acid peels: a comparative study of the efficacy and safety in mild-to-moderate acne vulgaris. 2017. Journal of cosmetic dermatology **Trial ID** Dayal 2017 **Country** India **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** completers	N=40 **Characteristics** **Sex** mixed **age (mean±SD)** 17.3±2.0299999999999998 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Indian Grading Scale **Inclusion details** Mild-to-moderate (grade I and grade II) facial acne vulgaris, graded using a system taking into account the predominant lesions present: Grade 1 (mild): comedones, occasional papules. Grade 2 (moderate): papules, comedones, few pustules. Grade 3 (severe): predominant pustules, nodules, abscesses. Grade 4 (cystic): mainly cysts,	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Treatment intensity** 6 sessions (once every 2 weeks for 12 weeks) **Number of arms** 2 **Split face design** No **Intervention: arm 1** salicylic acid 30% **Intervention: arm 2** Jessner's peel **Coded intervention: arm 1** SAL peel **Coded intervention: arm 2** JES peel	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using computerised randomisation, no other methods reported **2. Deviation from intervention** Some concerns; not reported if participants or personnel were blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; not reported if/how many particiants discontinued **4. Outcome measurement (efficacy)** Low; evaluator blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol

Study details	Participants	Interventions	Outcomes and results	Comments
	abscesses, widespread scarring. **Exclusion details** People with severe acne vulgaris (people with abscesses and nodulo-cystic lesions), who were on any anti-acne therapy since last 4 weeks, pregnancy and lactation, history of hypersensitivity to formulations used, history of keloid formation, photosensitivity, active dermatoses such as facial warts or herpes simplex infection, and people with unrealistic expectations. **Number included** **Number randomised: arm 1** 20 **Number randomised: arm 2** 20 **Number completed: arm 1** 20 **Number completed: arm 2** 20			**6. Overall bias** Some concerns
Study details **Reference** Dayal, S., Kalra, K. D., Sahu, P.Comparative study of efficacy and safety of 45% mandelic acid versus 30% salicylic acid peels in mild-to-moderate acne vulgaris. 2020. Journal of Cosmetic DermatologyJ	N=50 **Characteristics** **Sex** mixed **age (mean±SD)** 19.5±2.2999999999999998 **Inclusion/exclusion criteria** **Used validated acne scale** no	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <26 weeks **Treatment intensity** Total 6 sessions **Number of arms** 2	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; insufficient information on methods **2. Deviation from intervention** Some concerns; not reported if participants were blinded **3. Missing outcome data (efficacy)**

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Dayal 2020 **Country** India **Study type** RCT **Source of funding** Not reported **Analysis method** **Intention to treat or completers analysis** Completers	**Acne scale** Vaishampayan scale **Inclusion details** Mild-to-moderate (grade I and grade II) facial acne vulgaris on the Vaishampayan grading system. **Exclusion details** People with infiltrates, abscesses, and nodulocystic lesions, taking any oral or topical treatment for acne for the past 4 weeks, pregnant and nursing women, history of hypersensitivity to study medication used,patients having keloidal tendency, history of photosensitivity, active or recurrent herpes simplex infection, facial warts or molluscum contagiosum, active dermatosis, and those having impractical expectations. **Number included** **Number randomised: arm 1** 25 **Number randomised: arm 2** 25 **Number completed: arm 1** 25 **Number completed: arm 2** 25	**Split face design** No **Intervention: arm 1** 30% salicylic acid peel **Intervention: arm 2** 45% mandelic acid peel **Coded intervention: arm 1** SAL peel **Coded intervention: arm 2** MAND peel		Low; it appears that all participants completed the study **4. Outcome measurement (efficacy)** Low; dermatologist was blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Draelos, Z. D. T., E. A. Optimizing the use of tazarotene for the treatment of facial acne vulgaris through combination therapy. 2002. Cutis; cutaneous medicine for the practitioner **Trial ID** Draelos 2002 **Country** United States **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** completers	N=440 **Characteristics** **Sex** mixed **age (mean±SD)** 21.2±9 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** At least 12 years of age, had mild-to-moderate facial acne vulgaris, and had not used any topical antiacne medication in the 14 days preceding study entry, any oral antiacne medication in the 28 days preceding study entry, or any investigational drug or device in the 30 days preceding study entry. **Exclusion details** Previous use of an oral retinoid; nodular or cystic lesions; spontaneously improving or rapidly deteriorating facial acne vulgaris; presence or history of other skin conditions that would interfere with the evaluation of the test medications; known sensitivity to any ingredient in the test medications; pregnancy,	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 5 **Split face design** No **Intervention: arm 1** topical tazarotene 0.1% o.d. **Intervention: arm 2** topical clindamycin b.d. **Intervention: arm 3** topical tazarotene 0.1% o.d. plus BPO 4% b.d. **Intervention: arm 4** topical tazarotene 0.1% o.d. plus topical erythromycin 3%/BPO 5% gel b.d. **Intervention: arm 5** topical tazarotene 0.1% o.d. plus topical clindamycin b.d. **Coded intervention: arm 1** TAZ-topical **Coded intervention: arm 2** CLIND-topical **Coded intervention: arm 3** TAZ-topical + BPO-topical **Coded intervention: arm 4** TAZ-topical + ERYTH-topical + BPO-topical **Coded intervention: arm 5** TAZ-topical + CLIND-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation using an electronic randomisation scheme; 2 sealed and coded kits for each treatment (n=5), sealed kit assigned to participants by study nurse and assigned in chronological order of study entry **2. Deviation from intervention** High; The nurse may be aware of the erythromycin/benzoyl peroxide treatment after randomisation; not clear if ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 5% discontinued - treatment 1: 7%; treatment 2: 15%; treatment 3: 5%; treatment 4: 13%; treatment 5: 11% (90% had data beyond the baseline visit - discontinuations because of adverse effects or lack of efficacy; 71% completed week 12 - reasons for discontinuation not provided) **4. Outcome measurement (efficacy)** Some concerns; investigator was masked **5. Selective reporting** Some concerns; not reported

Study details	Participants	Interventions	Outcomes and results	Comments
	nursing, or planning a pregnancy; not using a reliable contraceptive; or uncontrolled systemic disease. **Number included** **Number randomised: arm 1** 89 **Number randomised: arm 2** 85 **Number randomised: arm 3** 89 **Number randomised: arm 4** 90 **Number randomised: arm 5** 87 **Number completed: arm 1** 76 **Number completed: arm 2** 76 **Number completed: arm 3** 78 **Number completed: arm 4** 84 **Number completed: arm 5** 83			whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Dubey, A., Amane, H. Comparison of efficacy and safety of adapalene and benzoyl peroxide-clindamycin combination in the topical treatment of acne vulgaris. 2016. International journal of basic & clinical pharmacology	N=100 **Characteristics** **Sex** mixed **age (min/max)** 12/30 **age (other information)** Age (In years) = Number of patients (n = 93)	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <26 weeks **Number of arms** 2 **Split face design** No	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** High; open-label; not reported if ITT analysis was done **3. Missing outcome data (efficacy)**

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Dubey 2016 **Country** India **Study type** RCT **Source of funding** No funding sources **Analysis method** **Intention to treat or completers analysis** Completers	12-15 = 6 16-19 = 30 20-23 = 30 24-27 = 15 28-31 = 12 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Indian Grading Scale **Inclusion details** Male and non-pregnant participants aged between 12 and 30 years.Participants with mild to moderate acne vulgaris; based on simple acne grading scale (grade 1 to grade 4).Participants with only comedones as noninflammatory lesions, and papules and pustules as inflammatory lesions were included in the study (mild to moderate acne vulgaris-grades 1 and 2). **Exclusion details** Presence of severe inflammatory lesions of acne	**Intervention: arm 1** adapalene (0.1%) o.d. **Intervention: arm 2** benzoyl peroxide (2.5%) clindamycin (1%) combination o.d. **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** BPO-topical + CLIND-topical		High; more than 5% discontinued in both arms **4. Outcome measurement (efficacy)** High; open-label **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	like nodulo-cystic lesions (grades 3 and 4).Use of any other drug for the treatment of acne vulgaris within 1 month **Number included** **Number randomised: arm 1** 50 **Number randomised: arm 2** 50 **Number completed: arm 1** 47 **Number completed: arm 2** 46			
Study details **Reference** Eichenfield, L. F. D., Z.,Lucky, A. W.,Hebert, A. A.,Sugarman, J.,Gold, L. S.,Rudisill, D.,Liu, H.,Manna, V.Preadolescent moderate acne vulgaris: A randomized trial of the efficacy and safety of topical adapalene-benzoyl peroxides. 2013a. Journal of Drugs in Dermatology **Trial ID** Eichenfield 2013a **Country** north america **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or**	N=285 **Characteristics** **Sex** mixed **age group** =25 years **age (mean±SD)** 10.4±0.72 **age (min/max)** 9/11 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** 9 to 11 years of age, with a score of 3 (moderate) on the Investigator's Global Assessment (IGA) scale and 20-100 total lesions (non-	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** ADAP 0.1%/BPO 2.5% gel o.d. **Intervention: arm 2** Vehicle o.d. **Coded intervention: arm 1** ADAP-topical + BPO-topical **Coded intervention: arm 2** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** High; randomisation in a 1:1 ratio, but no other methods reported; "There was a higher total lesion count at baseline for vehicle than adapalene-BPO (56.4 vs 50.5, respectively, P=.015)" **2. Deviation from intervention** Low; double-blinded (blinding through using identical packaging and dispensed by a third party other than the investigator; only personnel directly responsible for labelling the study medictions had access to randomisation lists); ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 10%

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis ITT **Method of ITT imputation** LOCF	inflammatory and/or inflammatory) on the face, including the nose **Exclusion details** Acne nodules or cysts, severe acne requiring systemic treatment, or if they used hormonal contraceptives **Number included** **Number randomised: arm 1** 142 **Number randomised: arm 2** 143 **Number completed: arm 1** 134 **Number completed: arm 2** 126			discontiued in vehicle arm (adapalene-BPO 5.6% discontinued; vehicle 11.9% discontinued); discontinuations because of adverse events, participant requestion, loss to follow-up or other; last observation carried forward methods used **4. Outcome measurement (efficacy)** Low; appears investigators were blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Elgendy A, Khalil K, Alshawadfy E, Wadea N, Alkady O.Blue light therapy versus low dose isotretinoin in mild to moderate acne.. 2015. Glob Dermatol **Trial ID** Elgendy 2015 **Country** Egypt **Study type** RCT **Source of funding** Unstated	N=60 **Characteristics** **Sex** mixed **age (min/max)** 16/32 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Age at least 12 years, mild to moderate facial acne vulgaris which failed to respond to standard topical treatment	**Interventions** **Treatment duration (weeks)** 6 **Treatment duration category** 6 to <12 weeks **Treatment intensity** 12 sessions twice a week for 6 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Blue light: high intensity, enhanced, narrowband, blue, light source (cure light, Iclear XL)	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; no methods reported **2. Deviation from intervention** Some concerns; not clear if participants were blinded; not clear if ITT was done **3. Missing outcome data (efficacy)** Some concerns; 16.7% discontinued in the isotreinoin group and 10% in the blue light group for non-study-related reasons

Study details	Participants	Interventions	Outcomes and results	Comments
Analysis method **Intention to treat or completers analysis** Completers	**Exclusion details** Exclusion criteria for blue light therapy included the following: Known light sensitivity; history of phototoxicity and history of herpes simplex virus or cold sores on the treatment area. Severe facial acne vulgaris. Pregnant women or those who were planning to become pregnant during the course of treatment. **Number included** **Number randomised: arm 1** 30 **Number randomised: arm 2** 30 **Number completed: arm 1** 27 **Number completed: arm 2** 25	**Intervention: arm 2** isotretinoin 0.3 mg/kg/d in divided doses for six months **Coded intervention: arm 1** BLU-PT **Coded intervention: arm 2** ISO<120.Daily<0.5-oral		**4. Outcome measurement (efficacy)** Some concerns; not clear if blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Glass, D. B., G. C.,Stables, G. I.,Cunliffe, W. J.,Goode, K.A placebo-controlled clinical trial to compare a gel containing a combination of isotretinoin (0.05%) and erythromycin (2%) with gels containing isotretinoin (0.05%) or erythromycin (2%) alone in the topical treatment of acne vulgaris. 1999. Dermatology	N=160 **Characteristics** **Sex** mixed **age (mean±SD)** 18.55±2.41 **age (min/max)** 15/31 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 4 **Split face design** No **Intervention: arm 1** Topical ISO 0.05% + ERYTH 2% gel b.d.	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; allocation to treatment using a computer-generated randomisation schedule, no other methods reported **2. Deviation from intervention** Some concerns; double-blinded but it is not clear who was blinded; ITT was performed

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Glass 1999 **Country** United Kingdom **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** na	**Inclusion details** Between 15 and 100 inflammatory lesions and/or between 15 and 100 non-inflammatory lesions and no more than 3 nodules **Exclusion details** - **Number included** **Number randomised: arm 1** 40 **Number randomised: arm 2** 41 **Number randomised: arm 3** 40 **Number randomised: arm 4** 39 **Number completed: arm 1** 35 **Number completed: arm 2** 35 **Number completed: arm 3** 36 **Number completed: arm 4** 34	**Intervention: arm 2** Topical placebo gel **Intervention: arm 3** Topical ISO 0.05% gel b.d. **Intervention: arm 4** Topical ERYTH 2% gel b.d. **Coded intervention: arm 1** ISO-topical + ERYTH-topical **Coded intervention: arm 2** PLC-topical **Coded intervention: arm 3** ISO-topical **Coded intervention: arm 4** ERYTH-topical		**3. Missing outcome data (efficacy)** Some concerns; more than 10% discontinued in all arms, most because of personal reasons **4. Outcome measurement (efficacy)** Some concerns; not clear who was blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Gollnick, H. P. D., Z.,Glenn, M. J.,Rosoph, L. A.,Kaszuba, A.,Cornelison, R.,Gore, B.,Liu, Y.,Graeber, M.Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind,	N=1670 **Characteristics** **Sex** mixed **age (mean±SD)** 19 **age (min/max)** 12/55	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 4 **Split face design** No	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomised in a 1:1:1:1 ratio, but no other information provided on methods **2. Deviation from intervention** Low; double-blinded (blinding ensured through providing medication in identical

Study details	Participants	Interventions	Outcomes and results	Comments
controlled study in 1670 patients. 2009. British journal of dermatology **Trial ID** Gollnick 2009 **Country** North America/Europe **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** 12 years of age or older with acne vulgaris, having on the face 20–50 inflammatory lesions, 30–100 noninflammatory lesions and an Investigator's Global Assessment (IGA) score of 3, corresponding to moderate acne. **Exclusion details** No more than one active nodule at baseline. Severe acne requiring isotretinoin therapy or other dermatological conditions requiring interfering treatment. Women were excluded if they were pregnant, nursing or planning a pregnancy, as were men with facial hair that would interfere with the assessments. **Number included** **Number randomised: arm 1** 419 **Number randomised: arm 2** 418 **Number randomised: arm 3** 415	**Intervention: arm 1** Adapalene 0.1%–BPO 2.5% fixed combination topical gel o.d. **Intervention: arm 2** Adapalene 0.1% topical gel o.d. **Intervention: arm 3** BPO 2.5% topical gel o.d. **Intervention: arm 4** Vehicle topical o.d. **Coded intervention: arm 1** ADAP-topical + BPO-topical **Coded intervention: arm 2** ADAP-topical **Coded intervention: arm 3** BPO-topical **Coded intervention: arm 4** Vehicle	**Clinician rated improvement in acne** See supplement 4	packaging; a third party dispensed the treatment); ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; more than 10% discontinued in all arms (12.6%; 11.7%; 12.5%, 13.6%), reasons provided with most discontinuing through participant request or loss to follow-up; last observation carried forward used; sensitivity analysis conducted **4. Outcome measurement (efficacy)** Low; double-blinded (blinding ensured through providing medication in identical packaging; a third party dispensed the treatment) **5. Selective reporting** Low; registered with ClinicalTrials.gov **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 4 418 **Number completed: arm 1** 366 **Number completed: arm 2** 369 **Number completed: arm 3** 363 **Number completed: arm 4** 361			
Study details **Reference** 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. 2012. Journal of Drugs in Dermatology **Trial ID** Guerra-Tapia 2012 **Country** Spain **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=168 **Characteristics** **Sex** mixed **age (mean±SD)** 19.1 **age (min/max)** 12/39 **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Aged 12 to 39 years, with = 15 inflammatory lesions and/ or non-inflammatory lesions but = 3 nodulocystic lesions and an acne grade of = 2.0 and < 7.0 on the Leeds Revised Acne Grading System. **Exclusion details** The use of any significant concomitant medicinal product within the past month that may	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** topical BPO % + CLIND 1% o.d. **Intervention: arm 2** Adapalene 0.1% topical gel o.d. **Coded intervention: arm 1** BPO-topical + CLIND-topical **Coded intervention: arm 2** ADAP-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; participants randomised on a 1:1 ratio using a computer-generated table of random numbers; study treatments correlated with a participant number; participant numbers were allocated in strict ascending numerical order with no numbers omitted **2. Deviation from intervention** Some concerns; participants were not blinded because of treatment differences in appearance and size of tubes - participants were instructed to keep study treatment confidential; "unblinded pharmacists dispensed study products." ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; more than

Study details	Participants	Interventions	Outcomes and results	Comments
	have affected a patient's acne; a history of photosensitivity; severe systemic disease, including colitis; hypersensitivity to any of the investigational agents or their components; participation in an investigational drug study within 30 days of the baseline visit; pregnancy or breastfeeding; and sexually active patients who were not using medically safe contraception (oral or injectable contraceptives or implants, intrauterine devices, or correctly used barrier methods). Patients using contraceptives containing anti-androgens were excluded, as were those using oral or topical steroids or any type of oral treatment that may have interfered with acne. Patients who had used any form of topical treatment for acne (including natural or UV light) in the 2 weeks before enrollment were also excluded, and those using oral isotretinoin needed to have discontinued this agent 6 months before enrollment. **Number included** **Number randomised: arm 1** 83			30% discontinued in both arms, mainly because participants considered themselves cured or were lost to follow-up **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Low; registered with ClinicalTrials.gov **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 2 85 **Number completed: arm 1** 56 **Number completed: arm 2** 58			
Study details **Reference** Gupta, A. K. L., C. W.,Kunynetz, R. A.,Amin, S.,Choi, K.,Goldstein, E.A randomized, double-blind, multicenter, parallel group study to compare relative efficacies of the topical gels 3% erythromycin/5% benzoyl peroxide and 0.025% tretinoin/erythromycin 4% in the treatment of moderate acne vulgaris of the face. 2003. Journal of Cutaneous Medicine & Surgery **Trial ID** Gupta 2003 **Country** Canada **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** completers	N=112 **Characteristics** **Sex** mixed **age (mean±SD)** 19 **age (min/max)** 13/40 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** 13-40 years of age, with moderate acne vulgaris of the face. This was grade II-III with more than12 inflammatory lesions. **Exclusion details** Cystic or nodular acne, skin conditions that might interfere, makes with beards, females who were pregnant or lactating. Women who had stopped using oral contraceptive less than 3 months ago.	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Topical 3% Erythromycin/5% Benzoyl Peroxide b.d. **Intervention: arm 2** Topical 0.025% Tretinoin/Erythromycin 4% b.d. **Coded intervention: arm 1** BPO-topical + ERYTH-topical **Coded intervention: arm 2** ERYTH-topical + TRET-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; participants randomised centrally and investigators provided with treatments which were numbered sequentially; participants were assigned to treatment in this sequential order **2. Deviation from intervention** Some concerns; double-blinded (both evaluating physician and participant not informed on which treatment received); not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; 32% participants in etythromycin/benzoyl peroxide group discontinued and 23.7% in tretinoin/erythromycin group; mainly due to loss to follow-up **4. Outcome measurement (efficacy)** Low; evaluator-blinded **5. Selective reporting** Some concerns; not reported

Study details	Participants	Interventions	Outcomes and results	Comments
	Number included **Number randomised: arm 1** 53 **Number randomised: arm 2** 59 **Number completed: arm 1** 36 **Number completed: arm 2** 45			whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Hajheydari, Z. M., M.,Vahidshahi, K.,Nozari, A.Comparison of efficacy of Azithromycin vs. Clindamycin and erythromycin in the treatment of mild to moderate acne vulgaris. 2011. Pakistan Journal of Medical Sciences **Trial ID** Hajheydari 2011 **Country** Iran, Islamic Republic of **Study type** RCT **Source of funding** Not industry funded	N=96 **Characteristics** **Sex** mixed **age (mean±SD)** 19.53±3.45 **age (min/max)** 12/28 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Aged 12-28 years with mild to moderate acne vulgaris **Exclusion details** Patients using any kind of acne treatment in the previous month, using drugs, and females with polycystic ovarian syndrome were excluded. **Number included** **Number randomised: arm 1** 32	**Interventions** **Treatment duration (weeks)** 16 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** Topical azithromycin 2% b.d. **Intervention: arm 2** Topical erythromycin 2% b.d. **Intervention: arm 3** Topical clindamycin 2% b.d. **Coded intervention: arm 1** AZITH-topical **Coded intervention: arm 2** ERYTH-topical **Coded intervention: arm 3** CLIND-topical	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomised and divided into 3 groups , matched together based on Acne Severity Index; no other details reported **2. Deviation from intervention** Some concerns; double-blinded but it is not clear if participants were blinded (a pharmacist dispensed study treatment to maintain blinding); not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; not clear if all participants completed the study **4. Outcome measurement (efficacy)** Low; assessor were blinded **5. Selective reporting** Some concerns; not reported

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 2 32 **Number randomised: arm 3** 32 **Number completed: arm 1** na **Number completed: arm 2** na **Number completed: arm 3** na			whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Hansted, B. J., J.,Reymann, F.,Christiansen, J.Fucidin cream for topical treatment of acne vulgaris. 1985. Current Therapeutic Research - Clinical and Experimental **Trial ID** Hansted 1985 **Country** Denmark **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** completers	N=79 **Characteristics** **Sex** mixed **age (mean±SD)** 19 **age (min/max)** 14/30 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Mild to moderate acne vulgaris **Exclusion details** - **Number included** **Number randomised: arm 1** 40 **Number randomised: arm 2** 39 **Number completed: arm 1** 36	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Topical fucidin cream 2% **Intervention: arm 2** Topical placebo cream **Coded intervention: arm 1** FCA-topical **Coded intervention: arm 2** PLC-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; double-blinded but not clear who was blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; 10% participants receiving fusidin discontinued and 12.8% receiving placebo) , most due to not attending for control examinations, although 2 (5.1%) participants in the placebo group discontinued because of aggravation of their acne **4. Outcome measurement (efficacy)** Some concerns; not clear if blinded

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 2 34			**5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Henderson, T. A. O., W. H.,Leach, A. D.A single-blind, randomized comparison of erythromycin pledgets and clindamycin lotion in the treatment of mild to moderate facial acne vulgaris. 1995. Advances in Therapy **Trial ID** Henderson 1995 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** completers	N=120 **Characteristics** **Sex** mixed **age (mean±SD)** 21 **age (min/max)** 14/40 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** 10-50 inflammatory facial lesions and no more than 2 cysts. **Exclusion details** Treatment with isotretinoin or etretinate or any experimental drug or device within 30 days, or hypersensitivity to any components fo the study formulations. **Number included** **Number randomised: arm 1** 59 **Number randomised: arm 2** 61	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Clindamycin phosphate 1% topical solution o.d. **Intervention: arm 2** Erythromycin 2% topical pledgets o.d. **Coded intervention: arm 1** CLIND-topical **Coded intervention: arm 2** ERYTH-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using a pre-generated randomisation schedule; no other methods reported **2. Deviation from intervention** Some concerns; likely participants were aware of the intervention (single blind); ITT analysis was not done **3. Missing outcome data (efficacy)** High; more than 10% discontinued; drug-related adverse events that lead to discontinuation were reported in one arm only **4. Outcome measurement (efficacy)** Low; evaluator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 1 54 **Number completed: arm 2** 51			
Study details **Reference** Hughes, B. R. N., J. F.,Cunliffe, W. J.A double-blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. 1992. Clinical & Experimental Dermatology **Trial ID** Hughes 1992 **Country** United Kingdom **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** completers	N=77 **Characteristics** **Sex** mixed **age (mean±SD)** 18.7 **age (min/max)** 14/29 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** 15-100 inflamed and/or 15-100 non-inflamed lesions but no more than three nodulocystic lesions on the face **Exclusion details** Pregnant females and those using antiandrogen contraceptives were exclude **Number included** **Number randomised: arm 1** 25 **Number randomised: arm 2** 26 **Number randomised: arm 3** 26 **Number completed: arm 1** 24	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** Topical isotretinoin 0.05% b.d. **Intervention: arm 2** Topical BPO 5% b.d. **Intervention: arm 3** Vehicle b.d. **Coded intervention: arm 1** ISO-topical **Coded intervention: arm 2** BPO-topical **Coded intervention: arm 3** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; random allocation stratified for sex, age, duration and severity of acne; no other methods reported **2. Deviation from intervention** Some concerns; double-blinded but not clear who was blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; 8% participants receiving isotretinoin withdrew because of side effects; 3.8% in the placebo group because of lack of efficacy; 7.7% in the benzoyl peroxide group because of side effects or lack of efficacy **4. Outcome measurement (efficacy)** Some concerns; not clear who was blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 2 24 **Number completed: arm 3** 25			**6. Overall bias** High
Study details **Reference** Hunt, M. J. B., R. S.A comparative study of gluconolactone versus benzoyl peroxide in the treatment of acne. 1992. The Australasian journal of dermatology **Trial ID** Hunt 1992 **Country** Australia **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** completers	N=150 **Characteristics** **Sex** mixed **age (mean±SD)** 20.100000000000001 **age (min/max)** 13/36 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Mild to moderate acne, older than 12 years, free from intercurrent disease **Exclusion details** Not taking systemic antibiotics, corticosteroids, retinoids, anticonvulsants or androgens in the 30 days prior to starting the trial. No topical acne therapy was allowed in the two weeks before the trial. Female patients were not to have commenced or ceased the the oral contraceptive pill in the six months before the trial, and males were to be without beards and moustaches.	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** Topical gluconolactone lotion 14% **Intervention: arm 2** Topical BPO 5% lotion **Intervention: arm 3** Topical vehicle **Coded intervention: arm 1** GLUCON topical **Coded intervention: arm 2** BPO-topical **Coded intervention: arm 3** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported; a significant difference was seen in baseline assessment of skin scaling - greater in gluconolactone vs benzoyl peroxide group ($p<0.05$) **2. Deviation from intervention** Some concerns; double-blinded (both doctor and participants; treatments provided in identical numbered packages); no ITT analysis was done **3. Missing outcome data (efficacy)** High; 10% discontinued; not clear how many participants randomised to each arm and how many discontinued from each arm **4. Outcome measurement (efficacy)** Low; likely to be blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol

Study details	Participants	Interventions	Outcomes and results	Comments
	Number included **Number randomised: arm 1** 50 **Number randomised: arm 2** 50 **Number randomised: arm 3** 50 **Number completed: arm 1** 45 **Number completed: arm 2** 44 **Number completed: arm 3** 46			**6. Overall bias** High
Study details **Reference** Ianosi, S. N., D.,Calbureanu, M.,Ianosi, G.Investigator-blind, placebo-controlled, randomized comparative study on combined vacuum and intense pulsed light versus intense pulsed light devices in both comedonal and papulopustular acne. 2013. Journal of Cosmetic and Laser Therapy **Trial ID** Ianosi 2013 **Country** Romania **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or**	N=180 **Characteristics** **Sex** mixed **age (median)** 24.04 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Mild to moderate comedonal and inflammatory acne vulgaris, with one or more infl ammatory lesions, over 18 years with Fitzpatrick skin phototypes I – IV **Exclusion details** Open lesions, broken and extremely dry skin; Any active infections; History of skin	**Interventions** **Treatment duration (weeks)** 5 **Treatment duration category** 0 to <6 weeks **Treatment intensity** Total 5 sessions **Number of arms** 3 **Split face design** No **Intervention: arm 1** IPL+Vacuum **Intervention: arm 2** IPL **Intervention: arm 3** Sebium H 2 O Micellaire	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation using a computer-generated list of random numbers and patients allocated to treatment via phone to principal investigator by a computer specialist not involved in the study **2. Deviation from intervention** Some concerns; single-blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; between 27% and 40% discontinued; not sufficient information on reasons **4. Outcome measurement (efficacy)** Low; investigator-blinded

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis completers	cancer or precancerous lesions, herpes type I or II, lupus erythematous, porphyria, endocrine disorders; Patients who have used Accutane within the last 6 months or photosensitive medications; Patients who were recently tanned; Pregnant or nursing women **Number included** **Number randomised: arm 1** 60 **Number randomised: arm 2** 60 **Number randomised: arm 3** 60 **Number completed: arm 1** 44 **Number completed: arm 2** 43 **Number completed: arm 3** 36	Solution **Coded intervention: arm 1** IPL+VAC **Coded intervention: arm 2** IPL **Coded intervention: arm 3** PLC-topical		**5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Iraji, F. S., A.,Shahmoradi, Z.,Siadat, A. H.,Jooya, A.Efficacy of topical azelaic acid gel in the treatment of mild-moderate acne vulgaris. 2007. Indian Journal of Dermatology, Venereology and Leprology **Trial ID** Iraji 2007	**Characteristics** **Sex** mixed **age (min/max)** 15/35 **age (other information)** Mean age 18.33 for AZE 16.93 for vehicle **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** None	**Interventions** **Treatment duration (weeks)** 6.43 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** 20% azelaic acid gel b.d.	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; double-blinded (physicians and participants both blinded to treatment); not reported if ITT analysis was done **3. Missing outcome data (efficacy)**

Study details	Participants	Interventions	Outcomes and results	Comments
Country Iran, Islamic Republic of **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**Inclusion details** Age 15-35 years with mild to moderate acne **Exclusion details** A background of drug sensitivity, hepatic or kidney disease, malnutrition, pregnancy or lactation **Number included** **Number randomised: arm 1** na **Number randomised: arm 2** na **Number completed: arm 1** 30 **Number completed: arm 2** 30	**Intervention: arm 2** vehicle gel (contains carbapol 934 (1%), glycerin (5%) and triethanolamine (0.2-0.5%) b.d. **Coded intervention: arm 1** AZE-topical **Coded intervention: arm 2** Vehicle		Low; all participants completed the study **4. Outcome measurement (efficacy)** Low; double-blinded (physicians blinded) **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Jaisamrarn, U. C., S.,Angsuwathana, S.,Nerapusee, O.A comparison of multiphasic oral contraceptives containing norgestimate or desogestrel in acne treatment: A randomized trial. 2014. Contraception **Trial ID** Jaisamrarn 2014 **Country** Thailand **Study type** RCT **Source of funding** Not industry funded	N=201 **Characteristics** **Sex** female **age (mean±SD)** 30.2±6.15 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** None **Inclusion details** Healthy females aged between 18 and 45 years with mild to moderate acne vulgaris - defined as having no more than 5 comedones or papules and no pustule while moderate acne vulgaris was defined as	**Interventions** **Treatment duration (weeks)** 26 **Treatment duration category** 24+ weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** triphasic EE/NGM treatment at the dosage of 0.035/0.18, 0.035/0.215 and 0.035/0.25mg on days 1–7, 8–14 and 15–21, respectively, and took inactive	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomly assigned to treatment on a 1:1 ratio using pre-generated permuted block randomisation sheme; methods not reported for allocation concealment **2. Deviation from intervention** High; "lack of double-blind methodology was this study's important limitation because single-blinded (here, investigator-blinded) studies may be affected by bias"; per-protocol analysis was used for efficacy assessment (ITT

Study details	Participants	Interventions	Outcomes and results	Comments
Analysis method **Intention to treat or completers analysis** completers	6–15 comedones or papules and/or a maximum of three pustules. **Exclusion details** Subjects who were pregnant or breastfeeding; who had experienced hypersensitivity to EE, NGM, DSG or any of the study medication ingredients; the use of a concomitant medication that was likely to interfere with the safety of EE/NGM and or EE/DSG, the use of topical acne treatments, systemic antimicrobials or a systemic retinoid within 2 weeks, 1 month and 6 months prior to enrollment, respectively; having a contraindication to OCs **Number included** **Number randomised: arm 1** 100 **Number randomised: arm 2** 101 **Number completed: arm 1** 93 **Number completed: arm 2** 95	tablets for 7 days before starting the next treatment cycle **Intervention: arm 2** biphasic EE/DSG treatment at the dosage of 0.04/0.025 and 0.03/0.125mg on days 1–7 and 8–22 of each cycle, respectively, and discontinued treatment for 6 days before starting the next treatment cycle **Coded intervention: arm 1** EE-oral+NGM-oral **Coded intervention: arm 2** EE-oral+DSG-oral		analysis used for safety and tolerability) **3. Missing outcome data (efficacy)** High; more than 5% discontinued in both arms because of poor compliance, discomfort from adverse events and loss to follow-up with reason unknown **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Low; registered with ClinicalTrials.gov **6. Overall bias** High
Study details **Reference** Jung, J. Y. C., Y. S.,Yoon, M. Y.,Min, S. U.,Suh, D. H.Comparison of a pulsed dye laser and a combined 585/1,064-nm laser in the	N=36 **Characteristics** **Sex** mixed **age (mean±SD)** 26	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Treatment intensity** 3 treatment sessions @ 2	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; double-

Study details	Participants	Interventions	Outcomes and results	Comments
treatment of acne vulgaris. 2009. Dermatologic Surgery **Trial ID** Jung 2009 **Country** Korea, Republic of **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**age (min/max)** 20/31 **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Mild to moderate facial acne (acne severity grade of 2–5, as defined using the Cunliffe grading system), that hadn't improved for more than a year. **Exclusion details** Pregnancy and prior acne therapy, including isotretinoin therapy within 12 months, systemic antibiotic therapy (for any indication) within 1 month, and topical acne preparations or intralesional steroid injections within 2 weeks. **Number included** **Number randomised: arm 1** 18 **Number randomised: arm 2** 18 **Number completed: arm 1** 16 **Number completed: arm 2** 16	week intervals (at 0, 2 & 4 weeks) **Number of arms** 2 **Split face design** Yes **Intervention: arm 1** combined 585-nm PDL + 1,064-nm Nd:YAG lasers **Intervention: arm 2** 585-nm PDL laser **Coded intervention: arm 1** PDL+Nd:YAG **Coded intervention: arm 2** PDL		blinded but not clear if participants were blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; 11.11% discontinued due to personal reasons **4. Outcome measurement (efficacy)** Low; independent dermatologists **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Katsambas, A. G., K.,Stratigos, J.Clinical studies of 20% azelaic acid cream in the	N=92 **Characteristics** **Sex** mixed	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported

Study details	Participants	Interventions	Outcomes and results	Comments
treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. 1989. Acta Dermato-Venereologica, Supplement **Trial ID** Katsambas 1989;Trial 1 **Country** Greece **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	**age (median)** 19 **age (min/max)** 13/34 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Plewig & Kligman **Inclusion details** Papulo-pustular acne (degree II/III of Plewig-Kligmann) **Exclusion details** Multiple large nodules, cysts and draining sinuses **Number included** **Number randomised: arm 1** 43 **Number randomised: arm 2** 49 **Number completed: arm 1** 36 **Number completed: arm 2** 44	**Number of arms** 2 **Split face design** No **Intervention: arm 1** 20% azelaic acid cream **Intervention: arm 2** vehicle **Coded intervention: arm 1** AZE-topical **Coded intervention: arm 2** Vehicle	**Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**2. Deviation from intervention** Some concerns; double-blinding but not clear who was blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; 11.6% participants discontinued in the azlaic acid group and 6.1% in the vehicle group because of irritant effects or insufficient efficacy **4. Outcome measurement (efficacy)** Some concerns; not clear if blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Kaur, J. S., V. K.,Gupta, A. K.,Singh, S. P.A comparative study to evaluate the efficacy and safety of combination topical preparations in acne vulgaris. 2015. International Journal of Applied & Basic Medical Research	N=66 **Characteristics** **Sex** mixed **age (min/max)** 15/35 **Inclusion/exclusion criteria** **Used validated acne scale** no	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** High; open-labeled; ITT analysis was done **3. Missing outcome data (efficacy)** High; not reported how many

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Kaur 2015 **Country** India **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** na	**Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Age range of 15–35 years having =2 and =30 inflammatory and/or noninflammatory lesions with Investigator's Global Assessment score (IGA) 2 or 3. **Exclusion details** Regularly using any anti-acne medications in the last 30 days before study, having nodulocystic lesions, acne conglobata, acne fulminans, secondary acne (e.g., chloracne, drug-induced acne, or any other acne requiring systemic treatment). History of hypersensitivity to benzoyl peroxide or clindamycin or nadifloxacin or tretinoin and pregnant or lactating women. **Number included** **Number randomised: arm 1** 33 **Number randomised: arm 2** 33 **Number completed: arm 1** 30 **Number completed: arm 2** 30	**Intervention: arm 1** benzoyl peroxide 2.5% gel and clindamycin 1% gel **Intervention: arm 2** tretinoin 0.025% and clindamycin 1% gel **Coded intervention: arm 1** CLIND-topical + BPO-topical **Coded intervention: arm 2** TRET-topical+CLIND-topical		participants were randomised in each group (overall, 10% of participants did not attend follow-up) **4. Outcome measurement (efficacy)** High; open-labeled **5. Selective reporting** Some concerns; study protocol approved by institutional review board, but no further details provided **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Korkut, C. P., S.Benzoyl peroxide, adapalene, and their combination in the treatment of acne vulgaris. 2005. Journal of Dermatology **Trial ID** Korkut 2005 **Country** Turkey **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	N=105 **Characteristics** **Sex** Mixed **age (mean±SD)** 18.4 **age (min/max)** 12/32 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** None **Inclusion details** Diagnosis of acne vulgaris **Exclusion details** Patients who had been treated for acne with topical agents, systemic antibiotics, or isotretinoin within the preceding 15 days, one month, or six months, respectively, and those who had severe acne vulgaris according to the acne grading system of the American Academy of Dermatology. Pregnancy, usage of oral contraceptives or other drugs with possible effects on hormone levels, irregular menstruation, and hirsutismus. **Number included** **Number randomised: arm 1** 35	**Interventions** **Treatment duration (weeks)** 24 **Treatment duration category** 24+ weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** 0.1% adapalene gel, **Intervention: arm 2** 5% benzoyl peroxide lotion **Intervention: arm 3** combination of 0.1% adapalene gel +5% benzoyl peroxide **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** BPO-topical **Coded intervention: arm 3** ADAP-topical + BPO-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** High; open-labeled; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 5% dropouts in two arms and more than 17% in one arm; no reasons for each arm reported - just the overall information (non-compliance with treatment or follow-up or side effects) **4. Outcome measurement (efficacy)** High; open-labeled **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 2 35 **Number randomised: arm 3** 35 **Number completed: arm 1** 32 **Number completed: arm 2** 29 **Number completed: arm 3** 32			
Study details **Reference** Kwon, H. H. C., S. C.,Jung, J. Y.,Bae, Y.,Park, G. H.A Novel Combined Light-Based Treatment of Acne Vulgaris With 1,450-nm Diode Laser and 450-nm Blue Light. 2019. Dermatologic Surgery **Trial ID** Kwon 2019 **Country** Korea, Republic of **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	N=50 **Characteristics** **Sex** Mixed **age (mean±SD)** 21.6±7.8 **age (min/max)** 18/39 **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Mild-to-moderate acne vulgaris as defined by revised Leeds score 2-8 **Exclusion details** Pregnancy, mental illness, intake of oral isotretinoin within 3 months, and application of other oral and topical acne medications, chemical peeling, and lightbased treatments within 6 weeks	**Interventions** **Treatment duration (weeks)** 20 **Treatment duration category** 12 to <24 weeks **Treatment intensity** 3 sessions - at 4 week intervals **Number of arms** 2 **Split face design** Yes **Intervention: arm 1** sequential application of both nonablative 1,450-nm diode laser (Smoothbeam) and 450-nm blue light; For the DL mode treatment, each half of the facial area received 2 passes of the stamp mode, which comprised 4 micropulses lasting a total of 280 ms with	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; random allocation sequence created using computer-based random number generators with randomisation codes secured in a safe until all data analyses performed **2. Deviation from intervention** Some concerns; single-blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Low; less than 5% dropouts **4. Outcome measurement (efficacy)** Low; evaluator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Number included **Number randomised: arm 1** 25 **Number randomised: arm 2** 25 **Number completed: arm 1** 24 **Number completed: arm 2** 24	5 cryogen spurts interspersed lasting a total of 35 to 40 ms (Figure 1). The spot size was 6 mm. Laser energies ranged from 5 to 7 J/cm2. **Intervention: arm 2** 450-nm visible blue light; With the BL mode, treatment hand piece delivered symmetrical peak wavelengths; 450 nm for the BL. The irradiance range was 3.5 to 7.0 mW/cm2 for the BL, with the radiant fluencies during a single treatment being 0.6 to 1.2 J/cm2. **Coded intervention: arm 1** Smoothbeam + BLU-PT **Coded intervention: arm 2** BLU-PT		
Study details **Reference** Langner, A. S.-D., R.,Layton, A.A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide (Duac) and erythromycin + zinc acetate (Zineryt) in the treatment of mild to moderate facial acne vulgaris. 2007. Journal of the European Academy of Dermatology & Venereology **Trial ID** Langner 2007	N=148 **Characteristics** **Sex** Mixed **age (mean±SD)** 20.399999999999999±5.3 **age (min/max)** 12/38 **Inclusion/exclusion criteria** **Used validated acne scale** Yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Patients aged 12–39 years with mild to moderate acne	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** a ready mixed, once daily gel containing clindamycin phosphate (1%) plus benzoyl peroxide (5%)	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomised on a 1:1 ratio using computer-generated randomisation schedule with a block size of 6; methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; single-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; more than 5%

Study details	Participants	Interventions	Outcomes and results	Comments
Country Europe **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	vulgaris of the face, with at least 15 inflammatory and/or non-inflammatory lesions but no more than three nodulocystic lesions and an acne grade of less than 7 **Exclusion details** Patients who were using antiandrogen-containing contraceptives, who had received oral or topical steroids, oral or topical antibiotics, or acne treatment of any kind, including natural or artificial UV therapy, or did so at any stage of their participation in the trial were excluded as were those who had participated in any clinical trial within 30 days of recruitment into the study. Other exclusion criteria included factors that could interfere with the evaluation of study treatment (such as disease of facial skin) and those that would safeguard the subject (history of regional enteritis or ulcerative colitis or history of antibiotic-associated colitis). **Number included** **Number randomised: arm 1** 73 **Number randomised: arm 2** 75	**Intervention: arm 2** a twice daily solution of erythromycin (4%) plus zinc acetate (1.2%) **Coded intervention: arm 1** CLIND-topical + BPO-topical **Coded intervention: arm 2** ERYTH-topical + ZINC-topical		discontinued (6.8% vs 10.7%) for similar reasons; missing data imputed using last observation carried forward **4. Outcome measurement (efficacy)** Low; assessor-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 1 73 **Number completed: arm 2** 75			
Study details **Reference** Langner, A. C., A.,Goulden, V.,Ambroziak, M.A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide and adapalene in the treatment of mild to moderate facial acne vulgaris. 2008. British Journal of Dermatology **Trial ID** Langner 2008 **Country** Europe **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=130 **Characteristics** **Sex** Mixed **age (mean±SD)** 21.6±4.5999999999999996 **age (min/max)** 13/38 **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Patients aged 12–39 years with mild to moderate acne vulgaris of the face, with at least 15 inflammatory and/or non-inflammatory lesions but no more than three nodulocystic lesions and an acne grade of 2 or more, but less than 7 **Exclusion details** Patients who were using antiandrogen-containing contraceptives, who had received oral or topical steroids, oral or topical antibiotics, or acne treatment of any kind, including natural or artificial UV therapy, or did so	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** a ready-mixed once daily gel containing clindamycin phosphate 10 mg mL-1 + benzoyl peroxide 50 mg mL-1 (Duac; also known as Clindoxyl and Indoxyl **Intervention: arm 2** a once-daily gel containing adapalene 0.1% (Differin) **Coded intervention: arm 1** CLIND-topical + BPO-topical **Coded intervention: arm 2** ADAP-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomised on a 1:1 ratio using computer-generated randomisation schedule with a block size of 6; methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; single-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; more than 5% discontinued (10.8% vs 9.2%) because of non-compliance, adverse events, personal reasons, withdrawal of consent, unavailability or other reasons; missing data imputed using last observation carried forward **4. Outcome measurement (efficacy)** Low; assessor-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol

Study details	Participants	Interventions	Outcomes and results	Comments
	at any stage of their participation in the trial were excluded as were those who had participated in any clinical trial within 30 days of recruitment into the study. Other exclusion criteria included factors that could interfere with the evaluation of study treatment (such as disease of facial skin) and those that would safeguard the subject (history of regional enteritis or ulcerative colitis or history of antibiotic-associated colitis). **Number included** **Number randomised: arm 1** 65 **Number randomised: arm 2** 65 **Number completed: arm 1** 58 **Number completed: arm 2** 59			**6. Overall bias** Some concerns
Study details **Reference** Leheta, T. M.Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities. 2009. Journal of cosmetic and laser therapy **Trial ID** Leheta 2009	N=45 **Characteristics** **Sex** Mixed **age (mean±SD)** 24.1±4.1989999999999998 **age (min/max)** 18/30 **Inclusion/exclusion criteria** **Used validated acne scale** No	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Treatment intensity** 6 sessions - 1 every 2 weeks **Number of arms** 3 **Split face design** No	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; because the 3 interventions were different, blinding of participatns was not possible; not reported if ITT

Study details	Participants	Interventions	Outcomes and results	Comments
Country Egypt **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completes	**Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Age of 18 years or older, general good health, mild to moderately severe facial acne vulgaris. **Exclusion details** Pregnant or lactating females, nodulocystic acne, active infection, herpes simplex or zoster, bacterial folliculitis, use of isotretinoin in the last 12 months, history of keloid scarring, and pigmentation abnormalities in the treatment areas. **Number included** **Number randomised: arm 1** 15 **Number randomised: arm 2** 15 **Number randomised: arm 3** 15 **Number completed: arm 1** 13 **Number completed: arm 2** 13 **Number completed: arm 3** 15	**Intervention: arm 1** non-purpuric PDL treatment with the RegenLite laser, using the following laser parameters: wavelength of 585 nm, pulse duration of 350 s, spot size of 7 mm, and fl uence of 3 J/cm2 **Intervention: arm 2** 0.1% tretinoin cream each evening and 5% benzoyl peroxide gel each morning. **Intervention: arm 3** retinoic acid cream (0.025%) at bedtime for 2 weeks prior to TCA peeling. **Coded intervention: arm 1** PDL **Coded intervention: arm 2** TRET-topical + BPO-topical **Coded intervention: arm 3** TCA peel		analysis was done but it looks like it was not done (see Fig. 1) **3. Missing outcome data (efficacy)** High; more than 10% discontinued in 2 out of 3 arms because they did not receive treatment **4. Outcome measurement (efficacy)** Low; assessor-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Leyden, J. J. S., A. R.,Saatjian, G. D.,Sefton, J.Erythromycin	N=109 **Characteristics** **Sex** Mixed	**Interventions** **Treatment duration (weeks)** 12	**Results** **Treatment discontinuation for**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported

Study details	Participants	Interventions	Outcomes and results	Comments
2% gel in comparison with clindamycin phosphate 1% solution in acne vulgaris. 1987. Journal of the American Academy of Dermatology **Trial ID** Leyden 1987 **Country** United States **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	**age (mean±SD)** 17.8 **age (min/max)** 14/34 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** None **Inclusion details** At least 14 years of age and had to have a minimum of ten but no more than sixty facial papules and pustules, and no more than six facial nodular cystic lesions **Exclusion details** Regular use of oral or topical antibiotics or other effective antiacne medication (e.g., benzoyl peroxide or tretinoin) within 30 days of study entry; Use of any topical antiacne agent within 14 days of study entry; treatment with estrogens for 12 weeks or less immediately preceding study entry; or previous treatment with isotretinoin **Number included** **Number randomised: arm 1** 55 **Number randomised: arm 2** 54 **Number completed: arm 1** 52	**Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** 2% erythromycin gel **Intervention: arm 2** clindamycin phosphate 1% solution **Coded intervention: arm 1** ERYTH-topical **Coded intervention: arm 2** CLIND-topical	**any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**2. Deviation from intervention** Some concerns; single-blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 5% of participants were excluded (5.45% erythromycin group and 7.4% clindomycin group) because of treatment-unrelated protocol violations, no further details provided; facial lesions (including nodules) were counted at baseline, but analysis of nodule data was not performed because no patient had more than 2 nodules at any time during the study **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 2 50			
Study details **Reference** Leyden, J. G., G. L.Randomized facial tolerability studies comparing gel formulations of retinoids used to treat acne vulgaris. 2001. Cutis; cutaneous medicine for the practitioner **Trial ID** Leyden 2001 **Country** United States **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** ITT	N=164 **Characteristics** **Sex** Mixed **age (mean±SD)** 19±na **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** None **Inclusion details** 12 years or older with mild to moderate facial acne vulgaris (10 - 60 inflammatory lesions, 10-200 facial noninflammatory lesions, no more than 2 facial nodular cystic lesions - no more than 5mm in diameter) **Exclusion details** Treatment with systemic retinoids, acne resistant to oral antibiotics, another skin condition which may interfere with the study. Pregnant or lactating females, or those of childbearing potential not using reliable birth control methods. **Number included** **Number randomised: arm 1** 82 **Number randomised: arm 2** 82	**Interventions** **Treatment duration (weeks)** 15 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** tazarotene 1% gel on alternate evenings with vehicle gel on intervening evenings **Intervention: arm 2** adapalene 0.1% gel each evening **Coded intervention: arm 1** TAZ-topical **Coded intervention: arm 2** ADAP-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation using independent organisation to produce a computer-generated randomisation code; codes were kept in a tamper-evidence sealed envelope by the independent organisation **2. Deviation from intervention** Low; double-blinded (participants and study personnel blinded); ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; 9.75% withdrawn from both arms for similar reasons **4. Outcome measurement (efficacy)** Low; likely blinded (study sites and all those working on the study did not have access to the randomisation codes at any time during the study) **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 1 74 **Number completed: arm 2** 74			
Study details **Reference** Leyden, J. J. T., E. A.,Miller, B.,Ung, M.,Berson, D.,Lee, J.Once-daily tazarotene 0.1 % gel versus once-daily tretinoin 0.1 % microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. 2002. Cutis; cutaneous medicine for the practitioner **Trial ID** Leyden 2002 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=371 **Characteristics** **Sex** Female **age (mean±SD)** 24.9±7.09 **age (min/max)** 14/48 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** None **Inclusion details** Healthy women, at least 14 years of age, with regular menstrual cycles and moderate facial acne. Moderate facial acne was defined as a total facial count of 6 to 200 noninflammatory comedones, 10 to 75 inflammatory lesions (papules and pustules), and 5 or fewer nodules. Also required a normal Papanicolaou test result within the past 6 months or a low-grade abnormal Papanicolaou test result under medical evaluation, a negative pregnancy test result, and agreement to use a	**Interventions** **Treatment duration (weeks)** 26 **Treatment duration category** 24+ weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** tablets containing 20 g of EE and 100 g of LNG in a 28-day blister pack with 21 days of active medication followed by 7 days of placebo **Intervention: arm 2** Placebo oral **Coded intervention: arm 1** EE-oral + LNG-oral **Coded intervention: arm 2** PLC-oral	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation using blocks of 4 participants within each study site, according to a computerised randomisation schedule; medication code provided in sealed envelopes labeled according to the randomisation schedule and kept by the investigator **2. Deviation from intervention** Some concerns; double-blinded (participants blinded but not clear who else blinded); ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 30% discontinued (overall) - numbers not reported for each arm; according to the paper significantly more participants in the placebo group than in the active treatment group were lost to follow-up; last observation carried forward used **4. Outcome measurement (efficacy)** Some concerns; not clear (medication code provided in

Study details	Participants	Interventions	Outcomes and results	Comments
	nonhormonal method of contraception if at risk for pregnancy. **Exclusion details** Known contraindications to OCs; cigarette smoking in a woman aged 35 or older; use of injectable estrogens, progestogens, or androgens within the 6 months before enrollment; and use of oral or implantable hormonal contraceptives for 3 months before the study. **Number included** **Number randomised: arm 1** 185 **Number randomised: arm 2** 186 **Number completed: arm 1** na **Number completed: arm 2** na			sealed envelopes and kept by the investigator, but not clear whether kept blind until after assessment/analysis) **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Lucky, A. J., J. L.,Rodriguez, D.,Jones, T. M.,Stewart, D. M.,Tschen, E. H.,Kanof, N. B.,Miller, B. H.,Wilson, D. C.,Loven, K. H.Efficacy and tolerance of adapalene cream 0.1% compared with its cream vehicle for the treatment of acne vulgaris. 2001. Cutis; cutaneous medicine for the practitioner	N=237 **Characteristics** **Sex** Mixed **age (mean±SD)** 17.4 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** 12 to 30 years of age, with	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** adapalene cream 0.1% **Intervention: arm 2** vehicle	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; double-blinded but not clear who was blinded; ITT analysis was done **3. Missing outcome data (efficacy)** High; 10.9% discontinued from

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Lucky 2001 **Country** United States **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** na	grade 2 or 3 acne vulgaris (using the Cunliffe acne grade 1-5: 30 or more noninflammatory comedos and 10 or more inflammatory lesions), who observed a washout period of 2 weeks of other treatments. **Exclusion details** Acne conglobata, acne fulminans, secondary acne chlorine or drug induced), or severe acne that necessitated treatment with a product other than topical therapy were excluded. In addition, subjects were excluded if they required topical or systemic therapy for the treatment of conditions such as atopic dermatitis, perioral dermatitis, or rosacea, or if they were pregnant or nursing. **Number included** **Number randomised: arm 1** 119 **Number randomised: arm 2** 118 **Number completed: arm 1** 106 **Number completed: arm 2** 106	**Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** Vehicle		adapalene group and 10.17% discontinued from vehicle group; 2 participants from the adapalene group withdrew because of adverse events, but no other reasons provided **4. Outcome measurement (efficacy)** Some concerns; not clear **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Maleszka R, Turek-Urasinska K, Oremus M, Vukovic J, Barsic B.Pulsed azithromycin	N=240 **Characteristics** **Sex** mixed	**Interventions** **Treatment duration (weeks)** 12	**Results** **Treatment discontinuation for**	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; participants randomised on a 1:1 ratio and using a computer random number

Study details	Participants	Interventions	Outcomes and results	Comments
treatment is as effective and safe as 2-week longer daily doxycycline treatment of acne vulgaris: a randomized, double-blind, noninferiority study.. 2011. Skinmed **Trial ID** Maleszka 2011 **Country** Poland **Study type** RCT **Source of funding** PLIVA Croatia Ltd. **Analysis method** **Intention to treat or completers analysis** Completers	**age (mean±SD)** 20.399999999999999±5.59 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unknown, 4-point scale **Inclusion details** 14 years or older with a clinical diagnosis of moderate acne vulgaris. **Exclusion details** Patients with severe acne vulgaris, other facial dermatoses, and other diseases with acne as a part of clinical presentation, and patients with beards and moustaches, and signs of hirsutism. Women of childbearing potential were asked to use reliable methods of mechanical contraception, following negative pregnancy test before treatment. **Number included** **Number randomised: arm 1** 120 **Number randomised: arm 2** 120 **Number completed: arm 1** 109 **Number completed: arm 2** 115	**Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Azithromycin 500mg o.d. for 3 days in the first week, followed by 500-mg tablets weekly to complete 10 weeks of treatment. **Intervention: arm 2** Doxycycline (Hiramicin) 100-mg capsules twice a day on the first day of the treatment, followed by doxycycline 100-mg capsules once a day during 12 weeks of treatment **Coded intervention: arm 1** AZITH-oral **Coded intervention: arm 2** DOXY-oral	**any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	generator to select random blocks; numbers sealed in separate envelopes and centrally packed for distribution **2. Deviation from intervention** Low; double blinded (all study personnel in contact with participants and participants blinded); ITT analysis performed **3. Missing outcome data (efficacy)** Low; < 5% withdrawn from each arm in ITT analysis, >5% from each arm withdrawn from per-protocol analysis for similar reasons across groups; last observation carried forward used **4. Outcome measurement (efficacy)** Low; all study personnel in contact with participants were blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Marazzi,Clinical evaluation of Double Strength Isotrexin versus Benzamycin in the topical treatment of mild to moderate acne vulgaris. 2002a. Journal of Dermatological Treatment **Trial ID** Marazzi 2002a **Country** United Kingdom **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** na	N=188 **Characteristics** **Sex** Mixed **age (mean±SD)** 17±4.3499999999999996 **age (min/max)** 12/33 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Facial acne vulgaris having 15–100 inflammatory lesions and/or 15–100 non-inflammatory lesions, but not more than three nodulocystic lesions. **Exclusion details** - **Number included** **Number randomised: arm 1** 95 **Number randomised: arm 2** 93 **Number completed: arm 1** 74 **Number completed: arm 2** 63	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** gel containing isotretinoin 0.1%w/w and erythromycin 4.0%w/w in a vehicle of butylated hydroxytoluene, hydroxypropylcellulose and ethanol **Intervention: arm 2** comparator gel contained benzoyl peroxide 5.0%w/w and erythromycin 3.0%w/w **Coded intervention: arm 1** ISO-topical + ERYTH-topical **Coded intervention: arm 2** BPO-topical + ERYTH-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using pre-determined randomisation schedule; methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; single-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** High; 22% participants from one and 32% from the other arm discontinued because of lack of treatment efficacy, adverse events, refusal to co-operate, development of exclusion criteria and other reasons **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Milani, M. B., A.,Zavattarelli, M.Efficacy and safety of	N=60 **Characteristics** **Sex** Mixed	**Interventions** **Treatment duration (weeks)** 8	**Results** **Clinician rated improvement in**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported

Study details	Participants	Interventions	Outcomes and results	Comments
stabilised hydrogen peroxide cream (Crystacide) in mild-to-moderate acne vulgaris: A randomised, controlled trial versus benzoyl peroxide gel. 2003. Current Medical Research and Opinion **Trial ID** Milani 2003 **Country** Italy **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**age (mean±SD)** 25±6 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** None **Inclusion details** 15-35 years with mild to moderate acne vulgaris, defined as at least 10 inflammatory lesions and 10 non-inflamatory lesions, and no more than two nodulo-cystic lesions. **Exclusion details** Acne conglobata, severe acne, or otherwise requiring more than topical treatment **Number included** **Number randomised: arm 1** 30 **Number randomised: arm 2** 30 **Number completed: arm 1** 30 **Number completed: arm 2** 30	**Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Hydrogen peroxide gel (Crystacide 1%) **Intervention: arm 2** Benzoyl peroxide gel (PanOxyl 4%) **Coded intervention: arm 1** HPS-topical **Coded intervention: arm 2** BPO-topical	**acne** See supplement 4	**2. Deviation from intervention** Some concerns; single-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Low; all participants completed the trial **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Mills Jr, O. H. K., A. M.,Pochi, P.,Comite, H.Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. 1986. International Journal of Dermatology	N=50 **Characteristics** **Sex** Mixed **age (other information)** average age was 20 in the 3 trials combined	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; double-blinded but not clear who was

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Mills 1986;Trial 1 **Country** United States **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	**Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** None **Inclusion details** Mild to moderately severe inflammatory acne vulgaris of the face (minimum of 10 inflammatory lesions) **Exclusion details** - **Number included** **Number randomised: arm 1** 25 **Number randomised: arm 2** 25 **Number completed: arm 1** 25 **Number completed: arm 2** 25	**Split face design** No **Intervention: arm 1** 2.5% BPO gel **Intervention: arm 2** vehicle **Coded intervention: arm 1** BPO-topical **Coded intervention: arm 2** Vehicle	**acne** See supplement 4	blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Low; all participants appear to have competed the study **4. Outcome measurement (efficacy)** Some concerns; not clear **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Mills, O. H. B., R. S.,Kligman, A. M.,McElroy, J. A.,Di Matteo, J.A comparative study of Erycette vs Cleocin-T. 1992. Advances in Therapy **Trial ID** Mills 1992 **Country** United States **Study type** RCT	**Characteristics** **Sex** mixed **age (mean±SD)** not reported **age (min/max)** 18/30 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Good health, 18-30 years, and	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** Clindamycin phosphate 1% topical solution b.d.	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** High; single blinded (participants were not blinded); not reported if ITT analysis was done (crossover study) **3. Missing outcome data (efficacy)** Some concerns; not reported how many participants were randomised in each arm;

Study details	Participants	Interventions	Outcomes and results	Comments
Source of funding Industry funded **Analysis method** **Intention to treat or completers analysis** completers	with 10 to 50 lesions consisting of comodones, papules and pustules. **Exclusion details** - **Number included** **Number randomised: arm 1** na **Number randomised: arm 2** na **Number completed: arm 1** 59 **Number completed: arm 2** 57	**Intervention: arm 2** Erythromycin 2% topical pledgets b.d. **Coded intervention: arm 1** CLIND-topical **Coded intervention: arm 2** ERYTH-topical		overall less than 5% discontinued; no reasons given **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Mohammadi, S., Pardakhty, A., Khalili, M., Fathi, R., Rezaeizadeh, M., Farajzadeh, S., Mohebbi, A., Aflatoonian, M.Niosomal benzoyl peroxide and clindamycin lotion versus niosomal clindamycin lotion in treatment of acne vulgaris: a randomized clinical trial. 2019. Advanced Pharmaceutical Bulletin **Trial ID** Mohammadi 2019 **Country** Iran, Islamic Republic of **Study type** RCT **Source of funding** The research department in	N=110 **Characteristics** **Sex** mixed **age (mean±SD)** 19.1 **age (min/max)** 13/30 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Participants ranging from 12 to 30 years **Exclusion details** Pregnancy, lactation, history of allergy to CL or BPO, patient with history of inflammatory bowel disease, colitis,	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <26 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** niosomal CL 1% **Intervention: arm 2** niosomal combination of BPO 1% and CL 1% **Coded intervention: arm 1** CLIND-topical **Coded intervention: arm 2** BPO-topical + CLIND-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported for allocation **2. Deviation from intervention** Low; double-blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; 9% discontinued **4. Outcome measurement (efficacy)** Low; double-blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
Kerman University of Medical Sciences, Kerman, Iran. **Analysis method** **Intention to treat or completers analysis** Completers	polycystic ovary syndrome, hirsutism and patient taking neuromuscular blockers or oral anti-acne drug since 6 months ago and topical anti-acne drugs since 1 month ago **Number included** **Number randomised: arm 1** 55 **Number randomised: arm 2** 55 **Number completed: arm 1** 50 **Number completed: arm 2** 50			
Study details **Reference** Mokhtari, F. G., M.,Siadat, A. H.,Jafari-Koshki, T.,Faghihi, G.,Nilforoushzadeh, M. A.,Hosseini, S. M.,Abtahi-Naeini, B.Efficacy of intense-pulsed light therapy with topical benzoyl peroxide 5% versus benzoyl peroxide 5% alone in mild-to-moderate acne vulgaris: A randomized controlled trial. 2017. Journal of Research in Pharmacy Practice **Trial ID** Mokhtari 2017 **Country** Iran, Islamic Republic of **Study type** RCT	N=72 **Characteristics** **Sex** Mixed **age (mean±SD)** 25.6±6.05 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** Unclear **Inclusion details** Mild-to-moderate acne and Fitzpatrick skin phototype III and IV, patient preference to experience laser therapy, having no acne scar, no pregnancy or breast feeding, not receiving topical or systemic antibiotic in the last 2 weeks, not receiving systemic	**Interventions** **Treatment duration (weeks)** 13 **Treatment duration category** 12 to <24 weeks **Treatment intensity** 3 sessions **Number of arms** 2 **Split face design** No **Intervention: arm 1** benzoyl peroxide 5% with concomitant intense-pulsed light **Intervention: arm 2** BPO only **Coded intervention: arm 1** BPO-topical + IPL	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using random blocks of 2, no other methods reported **2. Deviation from intervention** High; not-blinded; it appears that ITT analysis was performed (figure 1) **3. Missing outcome data (efficacy)** High; More than 9% in one arm and 27% in the other discontinued (reasons provided) **4. Outcome measurement (efficacy)** High; not blinded **5. Selective reporting** Low; protocol registered with

Study details	Participants	Interventions	Outcomes and results	Comments
Source of funding Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	steroid and retinoid in the last 6 months, photosensitivity, no tendency to developing hypertrophic and keloid scars. **Exclusion details** Sensitivity to BP, using intervening treatments at the same time, and irregular visits or loss to follow up. **Number included** **Number randomised: arm 1** 32 **Number randomised: arm 2** 40 **Number completed: arm 1** 29 **Number completed: arm 2** 29	**Coded intervention: arm 2** BPO-topical		Iranian Registry of Clinical Trials Centre **6. Overall bias** High
Study details **Reference** Na, J. I. S., D. H.Red light phototherapy alone is effective for acne vulgaris: Randomized, single-blinded clinical trial. 2007. Dermatologic Surgery **Trial ID** Na 2007 **Country** Korea, Republic of **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or**	N=60 **Characteristics** **Sex** Mixed **age (mean±SD)** 23.6±na **age (min/max)** 19/33 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** None **Inclusion details** Mild to moderate acne **Exclusion details** Pregnancy; use of oral	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Treatment intensity** twice a day **Number of arms** 2 **Split face design** Yes **Intervention: arm 1** The irradiation source was a portable red light–emitting device, which had a wavelength of 635	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** High; single-blinded (participants not blinded); not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; 6.6% participants discontinued treatment for personal reaons; at 8 weeks after treatment had completed, 22 participants were followed up (73.3%)

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis Completers	contraceptives; and treatment with oral antibiotics, topical agents, or chemical peels during the previous 4 weeks. Subjects who had taken oral retinoids during the previous 6 months, subjects who had eye problems, or those whose acne was considered to be cystic **Number included** **Number randomised: arm 1** 30 **Number randomised: arm 2** 30 **Number completed: arm 1** 28 **Number completed: arm 2** 28	to 670nm and an irradiance of 6mW. **Intervention: arm 2** No treatment **Coded intervention: arm 1** RED **Coded intervention: arm 2** No treatment		**4. Outcome measurement (efficacy)** Low; 2 independent investigators unaware of treated side **5. Selective reporting** Some concerns; study protocol approved by University, but no other details provided **6. Overall bias** High
Study details **Reference** Nestor, M. S. S., N.,MacRi, A.,Manway, M.,Paparone, P.Efficacy and tolerability of a combined 445nm and 630nm over-the-counter light therapy mask with and without topical salicylic acid versus topical benzoyl peroxide for the treatment of mild-to-moderate acne vulgaris. 2016. Journal of clinical and aesthetic dermatology **Trial ID** Nestor 2016	N=105 **Characteristics** **Sex** Mixed **age (mean±SD)** na±na **age (min/max)** 12/35 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Healthy male and female subjects 12 to 35 years old	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** 445nm blue/630nm red light therapy mask (MASK) **Intervention: arm 2** Neutrogena® Complete Acne Therapy System Overnight Acne Control Lotion (2.5% benzoyl peroxide)	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomised in a blinded fashion, but no other methods reported **2. Deviation from intervention** Some concerns; single-blinded; ITT analysis was done **3. Missing outcome data (efficacy)** High; 12% overall discontinued (22.8% receiving MASK, 5.7% receiving BPO, 8.6% receiving MASK-SA), the authors

Study details	Participants	Interventions	Outcomes and results	Comments
Country United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** na	with Fitzpatrick Skin Types I to VI. Mild to moderate facial acne vulgaris, defined as 20 to 140 total lesions, with 10 to 90 noninflammatory and 10 to 50 inflammatory facial lesions, but no nodules or cysts (Investigator's Global Assessment Score of 2, 2.5, 3, or 3.5 using the Modified Cook's Scale) **Exclusion details** A known allergy to any ingredients in the test products; presence of severe acne or acne conglobate; pre-existing or dormant facial dermatologic conditions, such as psoriasis, rosacea, rashes, many or severe excoriations that could interfere with the outcome of the study; use of prescription topical antibiotics, such as clindamycin or topical retinoids within the past two weeks or the use of oral retinoids within the past six months; use of oral antibiotics within the past four weeks; use of topical acne medications containing BPO or salicylic acid within the past two week; excessive facial hair, including beard, mustache or goatee, or scars that could interfere with imaging or evaluations; or participation in any other	**Intervention: arm 3** Neutrogena® All-in-1 Acne Control Facial Treatment (1% salicylic acid plus retinol) and the MASK treatment **Coded intervention: arm 1** BR-LED **Coded intervention: arm 2** BPO-topical **Coded intervention: arm 3** BR-LED + SAL topical + RETINOL		reported this was mainly because of inability to attend study visits but did not provide details for each treatment arm **4. Outcome measurement (efficacy)** Low; evaluator-blinded **5. Selective reporting** Some concerns; study protocol approved by institutional review board, but no other details reported **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	clinical study during the past four weeks. **Number included** **Number randomised: arm 1** 35 **Number randomised: arm 2** 35 **Number randomised: arm 3** 35 **Number completed: arm 1** 27 **Number completed: arm 2** 33 **Number completed: arm 3** 32			
Study details **Reference** Ozolins, M. A. E., E.,Avery, P. A. J.,Cunliffe, P. W. J.,Wan Po, P. A. L.,O'Neill, P. C.,Simpson, N. B.,Walters, C. E.,Carnegie, E.,Lewis, J. B.,Dada, J.,Haynes, M.,Williams, K.,Williams, P. H. C.Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: Randomised controlled trial. 2004. Lancet **Trial ID** Ozolins 2004 **Country** United Kingdom	N=649 **Characteristics** **Sex** mixed **age (mean±SD)** 19.7±6.1 **age (min/max)** 11/42 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Mild to moderate acne vulgaris (acne grade 3·0 or less) and at least 15 inflamed and 15 non-inflamed lesions on the face **Exclusion details** Acne that was primarily	**Interventions** **Treatment duration (weeks)** 18 **Treatment duration category** 12 to <24 weeks **Number of arms** 5 **Split face design** No **Intervention: arm 1** OXYTETRA-oral 500mg b.d. + PLC-topical **Intervention: arm 2** MINO-oral 100mg + PLC-topical **Intervention: arm 3** BPO- topical 5% + PLC-oral **Intervention: arm 4** Combined formulation of BPO-	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation using a computer-generated randomisation code known only to trial co-ordinator and pharmacy staff; randomisation in blocks of 11, without stratification; treatments provided in sealed opaque boxes labelled with participant's unique identification number (see 2005 HTA report for full details) **2. Deviation from intervention** Some concerns; ITT used; the authors stated that "participants were not blinded because of the prohibitive

Study details	Participants	Interventions	Outcomes and results	Comments
Study type RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF/LOCB	truncal, nodular, comedonal, or due to secondary causes; pregnancy, breastfeeding, or intention to become pregnant; onset of acne after age 26 years; fear of developing a physical deformity; another dermatological disease of the face; significant systemic disease; previous treatment with oral isotretinoin; current acne treatment from a consultant dermatologist; interacting medication; participation in any other clinical trial within the previous 3 months; and known hypersensitivity to study medications **Number included** **Number randomised: arm 1** 131 **Number randomised: arm 2** 130 **Number randomised: arm 3** 130 **Number randomised: arm 4** 127 **Number randomised: arm 5** 131 **Number completed: arm 1** 94 **Number completed: arm 2** 90 **Number completed: arm 3** 92	topical 5%/ERYTH-topical 3%+ PLC-oral **Intervention: arm 5** BPO-topical 5% + ERYTH-topical 2% + PLC-oral **Coded intervention: arm 1** OXYTETRA-oral + PLC-topical **Coded intervention: arm 2** MINO-oral + PLC-topical **Coded intervention: arm 3** BPO-topical + PLC-oral **Coded intervention: arm 4** BPO-topical + ERYTH-topical + PLC-oral **Coded intervention: arm 5** BPO-topical + ERYTH-topical + PLC-oral		costs of manufacturing identical placebos and reformulating the active treatments to make all five interventions look the same however, it was estimated that around half of the participants were unsure of which of their treatments was active" (see 2005 HTA report for full details) **3. Missing outcome data (efficacy)** High; 27% withdrew (range 19.7% to 30.8% across treatment groups) because of loss to follow-up, unwilling/unable to attend visit, exacerbation of acne, adverse events **4. Outcome measurement (efficacy)** Low; Assessors blinded **5. Selective reporting** Low; trial included on the Cochrane skin group trials register **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 4 102 **Number completed: arm 5** 93			
Study details **Reference** Palombo-Kinne, E. S., I.,Schumacher, U.,Graser, T.Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. 2009. Contraception **Trial ID** Palombo-Kinne 2009 **Country** Europe **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOFC	N=1338 **Characteristics** **Sex** female **age (mean±SD)** 24.4±5.9 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Female patients between 16 and 45 years old with mild to moderate papulopustular acne and without contraindications to COC use. Mild to moderate facial papulopustular acne was defined as 10–50 comedones (non-inflammatory lesions), 10–50 papules and pustules together (inflammatory lesions) and not more than three small nodules (inflammatory lesions); a normal Papanicolaou test result within the past 6 months; use of a non-hormonal method of contraception for sexually active patients **Exclusion details** Presence of known	**Interventions** **Treatment duration (weeks)** 24 **Treatment duration category** 24+ weeks **Number of arms** 3 **Split face design** no **Intervention: arm 1** EE-oral 0.030mg + DNG-oral 2mg **Intervention: arm 2** CPA-oral (2mg) + EE-oral (0.035mg) **Intervention: arm 3** PLC-oral **Coded intervention: arm 1** EE-oral + DNG-oral **Coded intervention: arm 2** CPA-oral + EE-oral **Coded intervention: arm 3** PLC-oral	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomised on a 2:2:1 ratio, but no other methods reported **2. Deviation from intervention** Low; ITT used; double blinded (double-dummy approach used to maintain participant blinding; not clear who else blinded) **3. Missing outcome data (efficacy)** Low; loss to follow-up or withdrawals (reasons provided): 5.3% vs 4.7% vs 8% **4. Outcome measurement (efficacy)** Some concerns; Trial was double blind, but not clear who else was blinded in addition to participants **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	contraindications to OCs; smoking, if age at inclusion is N30 years; pregnancy and lactation (at least three regular cycles were to elapse before start of treatment); and a body mass index N30 kg/m2. Dermatological exclusion criteria were as follows: other forms of acne and atopy and intake of preparations with known or suspected acne-inducing effects (e.g., vitamins B, anabolics, corticoids). **Number included** **Number randomised: arm 1** 530 **Number randomised: arm 2** 541 **Number randomised: arm 3** 267 **Number completed: arm 1** 497 **Number completed: arm 2** 512 **Number completed: arm 3** 243			
Study details **Reference** Papageorgiou, P. K., A.,Chu, A.Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris. 2000a. British Journal of Dermatology	N=107 **Characteristics** **Sex** mixed **age (mean±SD)** 25.01±na **Inclusion/exclusion criteria** **Used validated acne scale** no	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Treatment intensity** 84 sessions as irradiation carried out daily for 15 minutes	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using a computerised randomisation list; methods not reported for allocation concealment **2. Deviation from intervention**

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Papageorgiou 2000a **Country** United Kingdom **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	**Acne scale** Unclear **Inclusion details** Mild to moderate acne, age ranging from 14 to 50 years, otherwise healthy **Exclusion details** Patients who were pregnant, on oral contraceptives, had taken oral antibiotics during the previous 2 weeks, and patients whose acne was assessed as very mild (with fewer than five inflammatory lesions) or severe (cystic) **Number included** **Number randomised: arm 1** 27 **Number randomised: arm 2** 30 **Number randomised: arm 3** 25 **Number randomised: arm 4** 25 **Number completed: arm 1** 23 **Number completed: arm 2** 25 **Number completed: arm 3** 21 **Number completed: arm 4** 22	**Number of arms** 4 **Split face design** no **Intervention: arm 1** BLU-PT 415nm **Intervention: arm 2** BR-LED 415 and 660nm **Intervention: arm 3** White light control **Intervention: arm 4** BPO-topical 5% **Coded intervention: arm 1** BLU-PT **Coded intervention: arm 2** BR-LED **Coded intervention: arm 3** PLC-physical **Coded intervention: arm 4** BPO-topical		Some concerns; Not blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; 23% withdrawals or loss to follow-up - main reason in the phototherapy groups was non-compliance on using the light boxes, but no other reasons reported; 9/107 stopped treatment for efficacy reasons (unclear from which treatment arms) **4. Outcome measurement (efficacy)** Low; Assessors blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Papageorgiou, P. P. C., A. C.Chloroxylenol and zinc oxide	N=45	**Interventions** **Treatment duration (weeks)** 8	**Results** **Treatment discontinuation for**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; Medication dispensed in identical

Study details	Participants	Interventions	Outcomes and results	Comments
containing cream (Nels cream) vs. 5% benzoyl peroxide cream in the treatment of acne vulgaris. A double-blind, randomized, controlled trial. 2000b. Clinical and Experimental Dermatology **Trial ID** Papageorgiou 2000b **Country** United Kingdom **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	**Characteristics** **Sex** mixed **age (mean±SD)** 27.73±na **age (min/max)** 14/50 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear **Inclusion details** Age ranging from 14 to 50 years, with grade I acne severity and a minimum of five inflammatory lesions on the face. **Exclusion details** Severe nodulocystic acne requiring oral treatment; any acne therapy, systemic or topical, for 2 weeks prior to the entering the study; the use of any antibiotics during the study; the use of oestrogens; or pregnancy **Number included** **Number randomised: arm 1** 15 **Number randomised: arm 2** 15 **Number randomised: arm 3** 15 **Number completed: arm 1** 13	**Treatment duration category** 6 to <12 weeks **Number of arms** 3 **Split face design** no **Intervention: arm 1** Nels Cream (chloroxylenol + zinc oxide) b.d. **Intervention: arm 2** Vehicle b.d. **Intervention: arm 3** BPO-topical 5% b.d. **Coded intervention: arm 1** NELS-topical **Coded intervention: arm 2** Vehicle **Coded intervention: arm 3** BPO-topical	**any reason** See supplement 4	containers no other methods reported **2. Deviation from intervention** Some concerns; double blind (but not stated who exactly was blinded); not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; 10% dropped out voluntarily or were lost to follow-up; 2 participants discontinued due to flare-up of their acne, but not clear in which group **4. Outcome measurement (efficacy)** Some concerns; double blind (but not stated who exactly was blinded) **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 2 15 **Number completed: arm 3** 13			
Study details **Reference** Pazoki-Toroudi, H. N.-K., M.,Tabatabaie, H.,Ajami, M.,Habibey, R.,Shizarpour, M.,Babakoohi, S.,Rahshenas, M.,Firooz, A.Combination of azelaic acid 5% and erythromycin 2% in the treatment of acne vulgaris. 2010. Journal of Dermatological Treatment **Trial ID** Pazoki-Toroudi 2010 **Country** Iran, Islamic Republic of **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**Characteristics** **Sex** mixed **age (mean±SD)** 20.53±2.44 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Age between 14 and 40 years, mild-to-moderate forms of acne vulgaris with at least 10 inflammatory lesions on the face (with a maximum of three nodules) **Exclusion details** Patients with other types of acne such as acne conglobata, acne fulminans and acne secondary to pregnancy or lactation; those suffering from other skin diseases such as psoriasis, dermatitis, and papulopustular rosacea, which affect the treatment course; patients with a history of hepatic or kidney disease, allergic drug reaction, malnutrition, or those receiving	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 4 **Split face design** no **Intervention: arm 1** Azelaic acid 5% gel **Intervention: arm 2** Erythromycin 2% gel **Intervention: arm 3** Azelaic acid 5% + Erythromycin 2% gel **Intervention: arm 4** Placebo **Coded intervention: arm 1** AZE-topical **Coded intervention: arm 2** ERYTH-topical **Coded intervention: arm 3** AZE-topical+ERYTH-topical **Coded intervention: arm 4** PLC-topical	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; Methods not reported **2. Deviation from intervention** High; double blind (participants and dermatologists); no ITT (placebo group changed to routine treatment after 4 weeks) **3. Missing outcome data (efficacy)** High; 16.5% non-placebo participants discontinued because of loss to follow-up - unclear which treatment arm and unclear for placebo group **4. Outcome measurement (efficacy)** High; placebo group outcomes not measured after 4 weeks; dermatologist blinded **5. Selective reporting** High; Not reported whether there was a pre-registered protocol; unclear why placebo group changed to routine treatment, whether this was pre-specified or because of worsening of participant symptoms

Study details	Participants	Interventions	Outcomes and results	Comments
	topical or systemic anti-acne antibiotic therapy within 45 days or isotretinoin within 6 months before the beginning of the study; in addition, anyone taking drugs such as theophyllin, phenytoin, barbiturates, carbamazepine, cyclosporine, warfarin, ergotamine and triazolam within 1 week before the beginning of the study. **Number included** **Number randomised: arm 1** na **Number randomised: arm 2** na **Number randomised: arm 3** na **Number randomised: arm 4** 20 **Number completed: arm 1** 35 **Number completed: arm 2** 31 **Number completed: arm 3** 40 **Number completed: arm 4** 20			**6. Overall bias** High
Study details **Reference** Pazoki-Toroudi, H. N., M. A.,Ajami, M.,Jaffary, F.,Aboutaleb, N.,Nassiri-Kashani, M.,Firooz, A.Combination of azelaic acid	N=150 **Characteristics** **Sex** mixed **age (mean±SD)** 22.66±2.4	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; Methods not reported **2. Deviation from intervention** Some concerns; double blind

Study details	Participants	Interventions	Outcomes and results	Comments
5% and clindamycin 2% for the treatment of acne vulgaris. 2011. Cutaneous and Ocular Toxicology **Trial ID** Pazoki-Toroudi 2011 **Country** Iran, Islamic Republic of **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Age between 14 and 40 years, mild-to-moderate forms of acne vulgaris with at least 10 inflammatory lesions on the face . **Exclusion details** Nodulocystic lesions (>3), Other types of acne such as acne conglubata or fulminans and acne secondary to pregnancy or lactation, Other skin diseases such as psoriasis, dermatitis, or papulopustular rosacea that affect the therapeutic course, History of hepatic or kidney disease, Malnutrition, Topical antiacne therapy or systemic therapy with antibiotics 45 days before the beginning of the study, History of allergic reaction to prescribed drugs, Taking drugs such as theophyllin, phenytoin, barbiturates, carbamazepine, cyclosporine, warfarin, ergotamine, and triazolam within 1 week before beginning the study, and Pregnant or lactating patients.	**Split face design** no **Intervention: arm 1** Azelaic acid 5% gel **Intervention: arm 2** Clindamycin 2% gel **Intervention: arm 3** Azelaic acid + Clindamycin gel **Coded intervention: arm 1** AZE-topical **Coded intervention: arm 2** CLIND-topical **Coded intervention: arm 3** AZE-topical+CLIND-topical	**acne** See supplement 4	(participants and dermatologists); no ITT **3. Missing outcome data (efficacy)** High; 16% discontinued (similar across treatment arms); 2 patients for lack of efficacy in AA group, other reasons not reported **4. Outcome measurement (efficacy)** Low; dermatologist blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number included **Number randomised: arm 1** 50 **Number randomised: arm 2** 50 **Number randomised: arm 3** 50 **Number completed: arm 1** 45 **Number completed: arm 2** 43 **Number completed: arm 3** 44			
Study details **Reference** Poli, F. R., V.,Lauze, C.,Adhoute, H.,Morinet, P.Efficacy and safety of 0.1% retinaldehyde/ 6% glycolic acid (diacneal) for mild to moderate acne vulgaris. A multicentre, double-blind, randomized, vehicle-controlled trial. 2005. Dermatology (basel, switzerland) **Trial ID** Poli 2005 **Country** France **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or**	N=79 **Characteristics** **Sex** mixed **age (mean±SD)** 18.649999999999999±4.24 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Greasy or normal or combination skin type, with phototypes II–IV, presenting with inflammatory (7–15 lesions) and retentional (15–30 lesions) mild to moderate acne vulgaris **Exclusion details** Patients presenting with a	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** Diacneal (0.1% retinaldehyde and 6% glycolic acid) **Intervention: arm 2** Vehicle **Coded intervention: arm 1** DIACNEAL topical **Coded intervention: arm 2** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; Methods not reported **2. Deviation from intervention** Some concerns; double blind but not clear who blinded; around 10% temporary discontinuation of treatment in active arm **3. Missing outcome data (efficacy)** High; discontinuation 30% - Unclear how many due to efficacy. Not all randomised patients included in ITT. **4. Outcome measurement (efficacy)** Some concerns; not clear **5. Selective reporting** Some concerns; Not reported

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis ITT **Method of ITT imputation** LOFC	beard, suffering from nodulocystic lesions or secondary acne (occupational, cosmetic or drug induced) or severe acne that required an additional therapy were not included. In addition, subjects could not be included if they suffered from systemic disease, had potential allergy or required topical or systemic therapy that might interfere with the study as well as pregnant or nursing females or subjects under oral contraception lasting for less than 3 months or including cyproterone acetate. **Number included** **Number randomised: arm 1** 42 **Number randomised: arm 2** 39 **Number completed: arm 1** 32 **Number completed: arm 2** 29			whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Rademaker, M. W., J. M.,Birchall, N. M.Isotretinoin 5 mg daily for low-grade adult acne vulgaris - A placebo-controlled, randomized double-blind study. 2014. Journal of the European Academy of Dermatology and Venereology	N=58 **Characteristics** **Sex** mixed **age (mean±SD)** 38.049999999999997±7.49 **age (min/max)** 25/55	**Interventions** **Treatment duration (weeks)** 16 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; study centres randomised independently using a computer-generated randomisation schedule, no other methods reported **2. Deviation from intervention** High; double-blinded for group

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Rademaker 2014 **Country** New Zealand **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOFC	**Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** 25–55 years of age, with low-grade adult acne - defined as three or more acne lesions/ month on the face, for at least the last 3 months **Exclusion details** Any patients with acne greater than grade 2, by the Modified Leeds Acne Assessment scale. Pregnancy (or unwilling to adopt contraception), breast-feeding, any significant systemic illness, BMI over 35, or any systemic agent likely to influence the patient's acne (including systemic glucocorticoids or antibiotics). Patients were not allowed any topical or systemic anti-acne products in the preceding 4 weeks, or during the study period. Oestrogen and/or progesterone therapy (including levonorgestrel-releasing intrauterine device) was acceptable, but only if on a stable dose for at least 6 months preceding the start of the study. Patients were excluded if they had been on a	**Intervention: arm 1** 5mg isotretinoin once daily **Intervention: arm 2** No treatment for 16 weeks **Coded intervention: arm 1** ISO<120.Daily<0.5 **Coded intervention: arm 2** PLC-oral		1 (isotretinoin), double-blinded then open label for group 2 (placebo then active treatment); placebo and isotretinoin capsules similar in smell, taste and appearance; protocol deviations reported (n=12, unclear whether similar across treatment groups); ITT analysis was done **3. Missing outcome data (efficacy)** High; around 25% discontinued but not clear how many from which group; not clear how many were randomised to each group; last observation carried forward used to impute data **4. Outcome measurement (efficacy)** Low; all data processed and analysed by an independent organisation; to ensure assessor blinding to adverse events, assessments were performed by a study nurse separately **5. Selective reporting** Some concerns; registered with the Australia/New Zealand Clinical Trials Registry (retrospectively due to an administrative error) **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	systemic retinoid in the preceding 6 months. **Number included** **Number randomised: arm 1** 29 **Number randomised: arm 2** 29 **Number completed: arm 1** 29 **Number completed: arm 2** 29			
Study details **Reference** Ragab, Magdy A., Hussein, Tarek M., Salem, Mona A.Photodynamic therapy using 5-aminolevulinic acid and intense pulsed light against intense pulsed light alone in the treatment of acne vulgaris. 2014. Journal of the Egyptian Womenâ<U+0080><U+0099>s Dermatologic Society **Trial ID** Ragab 2014 **Country** Egypt **Study type** RCT **Source of funding** No funding sources **Analysis method** **Intention to treat or completers analysis** completers	N=25 **Characteristics** **Sex** mixed **age (mean±SD)** 19.4 **age (min/max)** 14/39 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Evaluator's Global Severity Scale (EGSS) **Inclusion details** Participants aged 14 years or over.Participants with mild to moderate acne vulgaris; determined by Evaluator Global Severity score.Score of 2 or 3 on scale before treatment **Exclusion details** Therapy with oral isotretinoin in	**Interventions** **Treatment duration (weeks)** 2 **Treatment duration category** 0 to <6 weeks **Treatment intensity** 2 sessions **Number of arms** 2 **Split face design** No **Intervention: arm 1** PDT using 5-aminolevulinic acid (ALA) with intense pulsed light (IPL) **Intervention: arm 2** IPL alone **Coded intervention: arm 1** 5ALA-IPL-PDT **Coded intervention: arm 2** IPL	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported for allocation **2. Deviation from intervention** Some concerns; not reported if participants were blinded **3. Missing outcome data (efficacy)** Low; all participants completed the study **4. Outcome measurement (efficacy)** Some concerns; not reportedif/who was blinded; it mentioned only that the evaluation of efficacy was based on photographs taken before the first treatment and at follow-up visits. **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol

Study details	Participants	Interventions	Outcomes and results	Comments
	the past 6 months, the use of topical or systemic antibiotics 2 weeks before the study, photosensitive dermatoses, pregnancy, or lactation **Number included** **Number randomised: arm 1** 15 **Number randomised: arm 2** 10 **Number completed: arm 1** 15 **Number completed: arm 2** 10			**6. Overall bias** Some concerns
Study details **Reference** Rao, G. R. G., S.,Dhurat, R.,Sharma, A.,Dongre, P.,Baliga, V. P.Efficacy, safety, and tolerability of microsphere adapalene vs. conventional adapalene for acne vulgaris. 2009. International Journal of Dermatology **Trial ID** Rao 2009 **Country** India **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	N=175 **Characteristics** **Sex** mixed **age (mean±SD)** 18.7 **age (min/max)** 12/34 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Aged between 12–40 years were with mild to moderate facial acne vulgaris - a minimum of 20 inflammatory (mean range at baseline 20–50) and 20 noninflammatory (mean range at baseline 20–	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** microsphere adapalene 0.1% gel O.D. **Intervention: arm 2** adapalene 0.1% gel o.d. **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** ADAP-topical	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using a computer generated randomisation list in a 1:1 ratio and kept blinded to those involved in the clinical trial (but methods not reported for allocation concealment); differences in age between groups at baseline **2. Deviation from intervention** Some concerns; not clear if participants were blinded; treatment packaged in identical tubes and dispensed by a third party; it appears that ITT analysis was not done **3. Missing outcome data (efficacy)** High; more than 10%

Study details	Participants	Interventions	Outcomes and results	Comments
	100) lesions, otherwise in good health. Female patients had to be post-menopausal for 1 year, sterile or using birth control for > 6 months. Patients with any skin phototypewere included in the study provided the degree of skin pigmentation did not interferewith the test site evaluation. **Exclusion details** Patients who were pregnant or breast-feeding, those with an abnormal skin hyper-pigmentation or a history of skin disease that could confound site analysis (such as atopic dermatitis, psoriasis), a history of known sensitivity to Adapalene or other ingredients of the formulation, other skin care products, topical medications, latex or any other specific kinds of tape, or to any metal especially aluminium used in Finn chambers. Concomitant treatment with topical or systemic corticosteroids, immunosuppressants (cyclophosphamide, azathioprine, etc.) and ultraviolet B or PUVA therapy were also grounds for exclusion. Any dermatological disorder or personal appearance issue which, in the investigator's opinion, could			discontinued in both arms; no reasons reported (although difference in discontinuations because of adverse events: n=8 receiving conventional adapalene vs n=0 receiving microsphere adapalene) **4. Outcome measurement (efficacy)** Low; assessor-blinded **5. Selective reporting** Some concerns; approval of the clinical trial protocol given by institutional review board, but no other details reported **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	interfere with the accurate evaluation of the subject, men with facial hair that would interfere with the assessments, patients with facial nodules or cysts, those with drug – induced or severe acne, such as acne conglobata or fulminans, or those who had taken systemic retinoids within the previous 6–12 months, those who had taken systemic antibacterial agents or other anti-acne treatments within 2–6 weeks of commencement of the trial. **Number included** **Number randomised: arm 1** 88 **Number randomised: arm 2** 87 **Number completed: arm 1** 79 **Number completed: arm 2** 75			
Study details **Reference** Redmond, G. P. O., W. H.,Lippman, J. S.,Kafrissen, M. E.,Jones, T. M.,Jorizzo, J. L.Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: A randomized, placebo-controlled trial. 1997. Obstetrics and Gynecology	N=227 **Characteristics** **Sex** women **age (mean±SD)** 28.4 **age (min/max)** 15/49 **Inclusion/exclusion criteria** **Used validated acne scale** no	**Interventions** **Treatment duration (weeks)** 26 **Treatment duration category** 24+ weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** Ethinyl estradiol	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation using computer-generated randomisation schedule which was stored securely by Pharmaceutical company; study treatments packaged in individual, sealed, participant numbered boxes according to randomisation schedule and forwarded to investigators

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Redmond 1997 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOFC	**Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Female with six to 100 cornedones (noninflammatory lesions), ten to 50 inflammatory lesions (papules or pustules), and fewer than five nodules **Exclusion details** Systemic retinoids, systemic antimicrobials, and topical acne treatments were not allowed within 6 months, 1 month, and 2 weeks, respectively, of enrollment. **Number included** **Number randomised: arm 1** 114 **Number randomised: arm 2** 113 **Number completed: arm 1** 84 **Number completed: arm 2** 80	0.035mg+norgestimate 0.18mg (week 1), 0.215mg (week 2), 0.250mg (week 3) **Intervention: arm 2** Placebo **Coded intervention: arm 1** EE-oral+NGM-oral **Coded intervention: arm 2** PLC-oral		**2. Deviation from intervention** High; double-blinded ("Investigators, study staff, subjects, and data analysts remained blinded to treatment"); ITT analysis was done but some outcome data reported only as per protocol analysis; major protocol violations reported **3. Missing outcome data (efficacy)** High; 77.5% participants completed the study; 11% in active group and 4.4% in placebo group discontinued because of adverse events; 3.4% in the active group and 0% in the placebo group discontinued because of exacerbation of acne **4. Outcome measurement (efficacy)** Low; evaluator blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Rizer, R. L. S., J. L.,Whiting, D.,Bucko, A.,Shavin, J.,Jarratt, M.Clindamycin phosphate 1%	N=667 **Characteristics** **Sex** mixed	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported

Study details	Participants	Interventions	Outcomes and results	Comments
gel in acne vulgaris. 2001. Advances in Therapy **Trial ID** Rizer 2001 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOFC	**age (mean±SD)** 19.4 **age (min/max)** 12/51 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Acne Vulgaris **Exclusion details** - **Number included** **Number randomised: arm 1** 168 **Number randomised: arm 2** 84 **Number randomised: arm 3** 166 **Number randomised: arm 4** 84 **Number randomised: arm 5** 165 **Number completed: arm 1** 146 **Number completed: arm 2** 71 **Number completed: arm 3** 146 **Number completed: arm 4** na **Number completed: arm 5** na	**Number of arms** 5 **Split face design** no **Intervention: arm 1** 1% Clindagel QD (water based formulation) **Intervention: arm 2** Vehicle QD **Intervention: arm 3** Clindagel BID **Intervention: arm 4** Vehicle BID **Intervention: arm 5** Cleocin T BID (gel based formulation) **Coded intervention: arm 1** CLIND-topical **Coded intervention: arm 2** Vehicle **Coded intervention: arm 3** CLIND-topical **Coded intervention: arm 4** Vehicle **Coded intervention: arm 5** CLIND-topical	**Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**2. Deviation from intervention** Some concerns; not reported if participants were blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; more than 10% discontinued (12.1% to 15.5% across 5 treatment arms); 4 participants discontinued because of adverse events, but no other reasons provided; last observation carried forward used **4. Outcome measurement (efficacy)** Low; evaluator-blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Rosen, M. P. B., D. M.,Nagamani, M.A randomized controlled trial of second- versus third-generation oral contraceptives in the treatment of acne vulgaris. 2003. American Journal of Obstetrics and Gynecology **Trial ID** Rosen 2003 **Country** United States **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	N=34 **Characteristics** **Sex** female **age (mean±SD)** 34.049999999999997±7.16 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Premenopausal women aged 18 to 46 years. Facial acne evidence by clinical examination. **Exclusion details** Participants were excluded if workup tests suggested an androgen-secreting ovarian tumor (testosterone >200 ng/dL), congenital adrenal hyperplasia (17-hydroxyprogesterone >2 ng/mL), or Cushing syndrome. Those receiving oral contraceptives within 2 months of enrollment or who used long-acting progestins within 6 months of enrollment were also excluded. **Number included** **Number randomised: arm 1** 17 **Number randomised: arm 2** 17	**Interventions** **Treatment duration (weeks)** 36 **Treatment duration category** 24+ weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** 0.3 mg of ethinyl estradiol (EE)/0.15 mg of levonorgestrel **Intervention: arm 2** 0.3 mg of EE/0.15 mg of desogestrel **Coded intervention: arm 1** EE-oral + LNG-oral **Coded intervention: arm 2** EE-oral + DSG-oral	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using block ramdomistion (provided by Pharmacy), no other methods reported **2. Deviation from intervention** Some concerns; participants were blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; one arm more than 50% lost to follow-up, the other - more than 40%; 1 participants per arm due to side effects **4. Outcome measurement (efficacy)** Low; investigators were blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 1 9 **Number completed: arm 2** 7			
Study details **Reference** Sadick, N. L., Z.,Laver, L.Treatment of mild to moderate acne vulgaris using a combined light and heat energy device: Home-use clinical study. 2010b. Lasers in Surgery and Medicine **Trial ID** Sadick 2010b **Country** Israel **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	N=63 **Characteristics** **Sex** mixed **age (mean±SD)** 23.6 **age (min/max)** 14/47 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** At least 14 years old, at least four inflamed, facial, acne lesions **Exclusion details** On any other acne treatment regimen, other exclusion criteria unstated **Number included** **Number randomised: arm 1** 31 **Number randomised: arm 2** 32 **Number completed: arm 1** 29 **Number completed: arm 2** 32	**Interventions** **Treatment duration (weeks)** 0.57 **Treatment duration category** 0 to <6 weeks **Treatment intensity** 8 sessions (2 per day for 4 days) **Number of arms** 2 **Split face design** no **Intervention: arm 1** no!no! Skin device (broad spectrum light of 450-2000nm, 6 J/cm-2) **Intervention: arm 2** Placebo **Coded intervention: arm 1** no!no! **Coded intervention: arm 2** PLC-physical	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported; active treatment arm had higher percentage of pustules and lower percentage of papules at baseline **2. Deviation from intervention** Some concerns; double-blinded (observer unblinded, participants appear to have been blinded); unclear how well the placebo device matched the active one; ITT analysis performed **3. Missing outcome data (efficacy)** Some concerns; 6.45% discontinued in the active treatment arm, all participants completed placebo treatment (not because of adverse events, but reasons not provided); for time-to-event analyses, participants were censored **4. Outcome measurement (efficacy)** Low; Assessors blinded **5. Selective reporting** Some concerns; Not reported

Study details	Participants	Interventions	Outcomes and results	Comments
				whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Sagi, E. V., D.,Shemer, A.,Laver, Z.,Amichi, B.,Shiri, J.,Zuckerman, F.,Oren, I.,Friedman, R.,David, M.Topical treatment of acne vulgaris with a combination of erythromycin 2% plus bifonazole 1% once daily compared to erythromycin 2% alone twice daily: A randomized, double-blind, controlled, clinical study. 2000. Journal of Dermatological Treatment **Trial ID** Sagi 2000 **Country** Israel **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	N=207 **Characteristics** **Sex** mixed **age (mean±SD)** 20.3 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Cook **Inclusion details** Aged 16–25 years, suffering from mild to moderate facial acne, Cook's grade > 3, with 10–30 in□ amed papules and pustules (but no cystsaged 16–25 years, suffering from mild to moderate facial acne, Cook's grade > 3, with 10–30 inflamed papules and pustules (but no cysts) **Exclusion details** Prior use of either oral or topical anti-acne medication within 30 days of the study entry; use of oral contraceptives 12 weeks preceding entry; previous treatmentwith medications known to affect acne directly or indirectly, such as retinoids,	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** 2.3% erythromycin (w/v) **Intervention: arm 2** 2.3% erythromycin (w/v) + 1% bifonazole **Coded intervention: arm 1** ERYTH-topical **Coded intervention: arm 2** ERYTH-topical+BIFON-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; double-blinded (participants each received 2 bottles, one coded for morning and one for evening application; not clear who else blinded); not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; more than 20% discontinued in each arm (most were lost to follow up); not clear how many were randomised to each arm **4. Outcome measurement (efficacy)** Some concerns; not clear **5. Selective reporting** Some concerns; authors reported that the study protocol was based on accepted methodology, but not reported whether there was a pre-registered protocol

Study details	Participants	Interventions	Outcomes and results	Comments
	antiepileptics, antituberculosis, vitamins B6 and B12, and drugs containing iodides or bromides. Also pregnant and lactating women. **Number included** **Number randomised: arm 1** 106 **Number randomised: arm 2** 101 **Number completed: arm 1** 83 **Number completed: arm 2** 74			**6. Overall bias** High
Study details **Reference** Schaller, M., Sebastian, M., Rees, C., Seidel, D., Hennig, M.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. 2016. Journal of the european academy of dermatology and venereology. 30 (6) (pp 966-973), 2016. Date of publication: 2016. **Trial ID** Schaller 2016 **Country** Germany	N=217 **Characteristics** **Sex** mixed **age (mean±SD)** 20.1 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Static Global Assessment (ISGA)/Investigator's global severity Assessment **Inclusion details** 12–45 years old, having facial acne vulgaris (defined as having 17–60 inflammatory lesions [papules and pustules], =1 facial nodular cystic lesion, 20–125 non-inflammatory facial lesions and an	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** Benzoyl peroxide 3% + clindamycin 1% QD **Intervention: arm 2** Azelaic acid 20% BID **Coded intervention: arm 1** BPO-topical+CLIND-topical **Coded intervention: arm 2** AZE-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation on a 1:1 ratio using computer-generated schedule, no other methods reported **2. Deviation from intervention** Some concerns; single-blinded (participants, site staff responsible for dispensing treatment and individuals involved in study conduct were not blinded to treatment); ITT and modified ITT analyses were done **3. Missing outcome data (efficacy)** Some concerns; 3.7% vs 6.4% discontinued (reasons provided)

Study details	Participants	Interventions	Outcomes and results	Comments
Study type RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOFC	Investigator's Static Global Assessment [ISGA] score of 'mild' or 'moderate'). **Exclusion details** Being pregnant (or at risk of becoming pregnant), breastfeeding, a history of non-acne facial disease or severe systemic disease, having received medications that could interfere with the evaluation of the study treatments within the 6 months pre-study (antibiotics, corticosteroids, retinoids), facial procedures within the last month, or known hypersensitivity or allergy to active constituents of the study drugs. **Number included** **Number randomised: arm 1** 108 **Number randomised: arm 2** 109 **Number completed: arm 1** 104 **Number completed: arm 2** 102			**4. Outcome measurement (efficacy)** Low; assessor-blinded **5. Selective reporting** Low; registered on clincial trials **6. Overall bias** Some concerns
Study details **Reference** Seaton, E. D. C., A.,Mouser, P. E.,Grace, I.,Clement, R. M.,Chu, A. C.Pulsed-dye laser treatment for inflammatory	N=41 **Characteristics** **Sex** mixed **age (min/max)** 18/45	**Interventions** **Treatment intensity** 1 session **Number of arms** 2 **Split face design** no	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in**	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation using computer-generated sequence; allocations contained in opaque, sequentially-numbered, sealed envelopes and concealed from

Study details	Participants	Interventions	Outcomes and results	Comments
acne vulgaris: Randomised controlled trial. 2003. Lancet **Trial ID** Seaton 2003 **Country** United Kingdom **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOFC	**age (other information)** median (IQR) in PDL group: 26 (23-32); in PLC 31 (20-36) **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Aged between 18 and 45 years with mild-to-moderate facial inflammatory acne defined as the presence of at least ten acne papules or pustules between the brow and jawline and an acne severity score of between 2 and 7 on the Leeds revised acne grading system. **Exclusion details** Washout periods for previous treatments were 4 weeks for oral antibiotics, 12 weeks for cyproterone acetatecontaining contraceptives, 52 weeks for oral isotretinoin, and 2 weeks for topical treatments. Acne treatments were not allowed during the study. **Number included** **Number randomised: arm 1** 31 **Number randomised: arm 2** 10 **Number completed: arm 1** 27	**Intervention: arm 1** Pulsed dye laser **Intervention: arm 2** Sham laser **Coded intervention: arm 1** PDL **Coded intervention: arm 2** PLC-physical	**acne** See supplement 4	participants and assessorrs - only known to investigator providing treatment; some differences in baseline characteristics, but not considered excessive **2. Deviation from intervention** Some concerns; double-blinded (participants and assessors blinded); ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; 12.9% discontinued from laser treatment (change of residence or need for antibiotic treatment for acne), 10% discontinuation in sham treatment due to dissatisfaction with clinical response **4. Outcome measurement (efficacy)** Low; assessor blinded **5. Selective reporting** High; local ethics committee approved protocol, but no further details provided; some results reported only at 12 weeks after treatment (not at other visits, i.e. 2, 4, 8 weeks) **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 2 9			
Study details **Reference** Shalita, A. R,. Smith E.B., Bauer ETopical Erythromycin v Clindamycin Therapy for Acne. A Multicenter, Double-blind Comparison. 1984. Arch Dermatol **Trial ID** Shalita 1984 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	N=178 **Characteristics** **Sex** mixed **age (mean±SD)** 22.7±na **age (min/max)** 12/39 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Moderate acne vulgaris of the face,defined as at least ten papules or pustules and at least five open or closed comedones. **Exclusion details** Patients with a known hypersensitivity to any ingredient of the products to be used, pregnant patients, or those contemplating pregnancy were excluded. **Number included** **Number randomised: arm 1** 88 **Number randomised: arm 2** 90	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <26 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** topical 1.5% erythromycin solution **Intervention: arm 2** topical 1% clindamycin phosphate solution **Coded intervention: arm 1** ERYTH-topical **Coded intervention: arm 2** CLIND-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; treatments assigned at equal frequencies in blocks of four; methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; double-blinded; it appears that participants were blinded, but not clearly stated (treatments provided in identical bottles labeled with patient details); not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; Less than 5% and less than 10% discontinued in both arms; 1 only due to side effects **4. Outcome measurement (efficacy)** Some concerns; not clear who blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 1 74 **Number completed: arm 2** 80			
Study details **Reference** Shalita, A. R. C., D. K.,Griffith, R. F.,Herbert, A. A.,Hickman, J. G.,Maloney, J. M.,Miller, B. H.,Tschen, E. H.,Chandraratna, R. A.,Gibson, J. R.,et al.,Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. 1999. Cutis; cutaneous medicine for the practitioner **Trial ID** Shalita 1999 **Country** United States **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** completers	N=446 **Characteristics** **Sex** mixed **age (mean±SD)** 20.8 **age (min/max)** 14/44 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** 14 years or older with mild to moderate facial acne vulgaris defined as 10 to 60 inflammatory lesions, 25 to 200 noninflammatory lesions, and six or less nodular cystic lesions. **Exclusion details** Acne that is known to be resistant to anti-biotics, pregnant, nursing, or of childbaring potential but not using reliable contraception. Also no antibiotics or systemic anti-acne medication within 4 weeks, or 2 weeks for topical therapy, or systemic retinoinds or estrogens within 12 weeks.	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** Topical tazarotene 0.1% o.d. **Intervention: arm 2** Topical tazarotene 0.05% o.d. **Intervention: arm 3** Topical vehicle o.d. **Coded intervention: arm 1** TAZ-topical **Coded intervention: arm 2** TAZ-topical **Coded intervention: arm 3** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; double-blinded (not reported if participants were blinded); unclear if ITT analysis was done **3. Missing outcome data (efficacy)** High; 25% lost to follow up overall (reasons included protocol deviations, loss to follow-up or use of concomitant medication; adverse events or lack of efficacy; unclear how many discontinued from each treatment arm and for what reasons); last observation carried forward conducted on treatment-related adverse events over time **4. Outcome measurement (efficacy)** Some concerns; blinding not reported **5. Selective reporting** Some concerns; Not reported

Study details	Participants	Interventions	Outcomes and results	Comments
	Number included **Number randomised: arm 1** 150 **Number randomised: arm 2** 148 **Number randomised: arm 3** 148 **Number completed: arm 1** 122 **Number completed: arm 2** 124 **Number completed: arm 3** 129			whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Shalita, A. M., B.,Menter, A.,Abramovits, W.,Loven, K.,Kakita, L.Tazarotene cream versus adapalene cream in the treatment of facial acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. 2005. Journal of drugs in dermatology : JDD **Trial ID** Shalita 2005 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or**	N=1026 **Characteristics** **Sex** mixed **age (mean±SD)** 18.89±6.39 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Static Global Assessment (ISGA)/Investigator's global severity Assessment **Inclusion details** 12 years of age or older with mild to moderate facial acne vulgaris and an Investigator's Static Global Assessment (ISGA) score of 2 or greater at baseline. Also a minimum of 17 but no more than 40 facial inflammatory lesions, including	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 4 **Split face design** no **Intervention: arm 1** Clindamycin foam o.d. **Intervention: arm 2** Vehicle foam o.d. **Intervention: arm 3** Clindamycin gel 1% o.d. **Intervention: arm 4** Vehicle gel o.d. **Coded intervention: arm 1** CLIND-topical **Coded intervention: arm 2** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation in a 3:1:3:1 ratio and stratified by study site; randomisation codes were sealed and only revealed in emergency **2. Deviation from intervention** Some concerns; authors reported that the study was double-blinded, but not clear who else blinded other than investigators (participants and co-ordinators not blinded); ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; around 10% participants lost to follow up overall (10.9% vs 10.1% vs 11.8% vs 11.7%)

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis ITT **Method of ITT imputation** na	nasal lesions, and a minimum of 20, but no more than 150 facial non-inflammatory lesions, excluding nasal lesions. **Exclusion details** Any active nodulo-cystic lesions and those who had used topical or systemic treatment within 4 weeks prior to study entrance. **Number included** **Number randomised: arm 1** 386 **Number randomised: arm 2** 127 **Number randomised: arm 3** 385 **Number randomised: arm 4** 128 **Number completed: arm 1** 344 **Number completed: arm 2** 112 **Number completed: arm 3** 346 **Number completed: arm 4** 113	**Coded intervention: arm 3** CLIND-topical **Coded intervention: arm 4** Vehicle		**4. Outcome measurement (efficacy)** Low; evaluator blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Shwetha, H. G., A.,Revathi, T. N.A comparative study of efficacy and safety of combination of topical 1% clindamycin and 0.1% adapalene with 1%	N=120 **Characteristics** **Sex** mixed **age (mean±SD)** 18.03±1.85	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation list using table of random numbers; methods not reported for allocation concealment

Study details	Participants	Interventions	Outcomes and results	Comments
clindamycin and 2.5% benzoyl peroxide in mild to moderate acne at a tertiary care hospital. 2014. Journal of Chemical and Pharmaceutical Research **Trial ID** Shwetha 2014 **Country** India **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**age (min/max)** 12/25 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Indian Grading Scale **Inclusion details** Mild to moderate acne on face as per Indian Acne Alliance Grading for Severity of acne, aged between 12 to 25 years **Exclusion details** Other variants of acne, drug induced acne, pregnant and lactating mothers and those with history of hypersensitivity to any component of the drug **Number included** **Number randomised: arm 1** 60 **Number randomised: arm 2** 60 **Number completed: arm 1** 59 **Number completed: arm 2** 58	**Split face design** no **Intervention: arm 1** topical 1% clindamycin + 0.1% adapalene **Intervention: arm 2** topical 1% clindamycin + 2.5% benzoyl peroxide **Coded intervention: arm 1** CLIND-topical+ADAP-topical **Coded intervention: arm 2** CLIND-topical+BPO-topical	**acne** See supplement 4	**2. Deviation from intervention** Some concerns; not reported if participants were blinded; not clear whether ITT analysis was done **3. Missing outcome data (efficacy)** Low; <5% lost to follow up **4. Outcome measurement (efficacy)** Some concerns; blinding not reported **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Smith, E. B. P., R. S.,McCabe, J. M.,Becker, L. E.Benzoyl peroxide lotion (20 percent) in acne. 1980b. Cutis **Trial ID** Smith 1980b	N=59 **Characteristics** **Sex** mixed **age (mean±SD)** 22.55 **age (min/max)** 18/30	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; double-blinded (participants blinded); not clear if ITT done

Study details	Participants	Interventions	Outcomes and results	Comments
Country United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** At least ten inflammatory papules and/or pustules and no more than three nodulocystic lesions on the face, otherwise in good health **Exclusion details** Not topical medication for acne during the week before the study, and no oral antibioti cs, oral contraceptives, or systemic corticosteroids for one month before the study began. Also no pregnant women or subjects with a history of hypersensitivity to benzoyl peroxide **Number included** **Number randomised: arm 1** 29 **Number randomised: arm 2** 30 **Number completed: arm 1** 25 **Number completed: arm 2** 26	**Split face design** no **Intervention: arm 1** 20% Benzoyl-peroxide b.d. **Intervention: arm 2** Vehicle b.d. **Coded intervention: arm 1** BPO-topical **Coded intervention: arm 2** Vehicle		**3. Missing outcome data (efficacy)** Some concerns; 13.8% vs 13.3% discontinued (reasons not reported) **4. Outcome measurement (efficacy)** Low; evaluator blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Smith, S. R. K., S.A study of 5.5% benzoyl peroxide	N=48 **Characteristics** **Sex** mixed	**Interventions** **Treatment duration (weeks)** 12	**Results** **Treatment discontinuation for**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported

Study details	Participants	Interventions	Outcomes and results	Comments
microsphere cream versus 6% benzoyl peroxide gel in the treatment of acne vulgaris. 2006. Cosmetic Dermatology **Trial ID** Smith 2006 **Country** United States **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**age (mean±SD)** 17.1 **age (min/max)** 12/37 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Mild to moderate facial acne vulgaris, 12 years of age or older, had 20 to 50 papules and pustules, 20 to 60 open and closed comedones (excluding those on the nose), and no more than 1 nodule in the facial treatment area **Exclusion details** Used topical antibiotics within 2 weeks; topical retinoids within 12 weeks; light treatment, photodynamic therapy, or chemical peels within 8 weeks; oral antibiotics within 4 weeks; oral antiandrogens within 8 weeks; or oral retinoids within 12 months of study commencement **Number included** **Number randomised: arm 1** 24 **Number randomised: arm 2** 24	**Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** NeoBenz (5.5% benzoyl peroxide microsphere cream) b.d. **Intervention: arm 2** Triaz (6% benzoyl peroxide gel) b.d. **Coded intervention: arm 1** BPO-topical **Coded intervention: arm 2** BPO-topical	**any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4	**2. Deviation from intervention** Some concerns; participants were blinded; not reported if ITT was done **3. Missing outcome data (efficacy)** Some concerns; around 10% participants lost to follow up overall (1 participant withdrew because of irritation, 3 for administrative reasons) **4. Outcome measurement (efficacy)** Low; evaluator blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 1 24 **Number completed: arm 2** 20			
Study details **Reference** Sommer, S. B., R.,Cunliffe, W. J.,Holland, D.,Holland, K. T.,Naags, H.Investigation of the mechanism of action of 2% fusidic acid lotion in the treatment of acne vulgaris. 1997. Clinical and Experimental Dermatology **Trial ID** Sommer 1997 **Country** United Kingdom **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	N=56 **Characteristics** **Sex** mixed **age (mean±SD)** 18.8±1.05 **age (min/max)** 17/22 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Aged 12-25 years with predominantly mild to moderate facial acne vulgaris, and between 15 and 75 inflamed papules and pustules, and off of anti-acne treatment for one month **Exclusion details** Other significant facial dermatoses such as seborrhoeic eczema or rosacea. Also patients who had received oral isotretinoin in the previous 12 months, and patients who had been on an oral contraceptive pill for less	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** Fucidin lotion (fusidic acid) **Intervention: arm 2** Vehicle (Fucidin base) **Coded intervention: arm 1** FCA-topical **Coded intervention: arm 2** Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; Methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; double-blind, but not clear who blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; around 10% participants lost to follow up overall (1 participant from each group withdrew because of inconvenience in attending; the remainder withdrew for unknown reasons) **4. Outcome measurement (efficacy)** Some concerns; not clear who was blinded; **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol; treatment appears to have been for 12 weeks (visits at baseline, 1, 4, 9 and 12 weeks), but outcomes presented at 0, 2, 4,

Study details	Participants	Interventions	Outcomes and results	Comments
	than 3 months, and patients taking the Dianette. **Number included** **Number randomised: arm 1** 28 **Number randomised: arm 2** 28 **Number completed: arm 1** 25 **Number completed: arm 2** 27			6, 8, 10, 12, 14 weeks and end of treatment **6. Overall bias** High
Study details **Reference** Stinco, G. B., G.,Trotter, D.,Pillon, B.,Patrone, P.Relationship between sebostatic activity, tolerability and efficacy of three topical drugs to treat mild to moderate acne. 2007. Journal of the European Academy of Dermatology and Venereology **Trial ID** Stinco 2007 **Country** Italy **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	N=65 **Characteristics** **Sex** mixed **age (mean±SD)** 18.25 **age (min/max)** 12/24 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Mild or moderate comedonic or papulopustular acne, localized on the face. each patients had a minimum of 20 facial non-inflammatory lesions (open and closed comedones) and 10 inflamed lesions. Also required to be in good health and have not received any oral	**Interventions** **Treatment duration (weeks)** 8 **Treatment duration category** 6 to <12 weeks **Number of arms** 3 **Split face design** no **Intervention: arm 1** Azelaic acid o.d. **Intervention: arm 2** Benzoyl peroxide o.d. **Intervention: arm 3** Adapalene o.d. **Coded intervention: arm 1** AZE-topical **Coded intervention: arm 2** BPO-topical **Coded intervention: arm 3** ADAP-topical	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported; 20 volunteers also recruited for control group (no details provided) **2. Deviation from intervention** Some concerns; not clear if participants were blinded; not reported if ITT was done **3. Missing outcome data (efficacy)** Some concerns; 4% (azelaic acid) vs 10% (BPO) vs 5% (adapalne) vs 20% (control) participants lost to follow up overall **4. Outcome measurement (efficacy)** Some concerns; blinding not reported **5. Selective reporting** Some concerns; Not reported whether there was a pre-

Study details	Participants	Interventions	Outcomes and results	Comments
	or topical anti-acne therapy in the 8 weeks prior the study. **Exclusion details** Subjects over the age of 24, patients who were taking systemic drugs of any type of treatment **Number included** **Number randomised: arm 1** 25 **Number randomised: arm 2** 20 **Number randomised: arm 3** 20 **Number completed: arm 1** 24 **Number completed: arm 2** 18 **Number completed: arm 3** 19			registered protocol; no outcome data reported on control group **6. Overall bias** High
Study details **Reference** Stoughton, R. B. L., J. J.Efficacy of 4 percent chlorhexidine gluconate skin cleanser in the treatment of acne vulgaris. 1987. Cutis **Trial ID** Stoughton 1987 **Country** United States **Study type** RCT **Source of funding** Unstated	N=50 **Characteristics** **Sex** mixed **age (other information)** no information on age given other than inclusion criteria of 12-35 years **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, lesion type x severity scale 0-100	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** Benzoyl peroxide b.d. **Intervention: arm 2** Chlorhexidine gluconate b.d. **Coded intervention: arm 1** BPO-topical	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; Methods not reported **2. Deviation from intervention** High; 2 of 3 studies were reported to be double-blind, but not clear if participants were blinded; it does not appear that ITT was performed (participants omitted from statistical analysis for various reasons) **3. Missing outcome data (efficacy)**

Study details	Participants	Interventions	Outcomes and results	Comments
Analysis method **Intention to treat or completers analysis** Completers	**Inclusion details** Patients between the ages of twelve and thirty-five with acne and a minimum of ten erythematous facial papules and pustules **Exclusion details** Chronic illness or skin disease other than acne vulgaris (eg, acne conglobata), severe acne that would require more than topical therapy, systemic treatment with antibiotics or other therapy for acne within one month before entering the study, and pregnancy. **Number included** **Number randomised: arm 1** 25 **Number randomised: arm 2** 25 **Number completed: arm 1** 24 **Number completed: arm 2** 23	**Coded intervention: arm 2** CHLOR-topical		High; 3/50 participants in the active-control study did not complete the study and 3 from the 2 vehicle studies; the authors also reported that 17/110 participants did not complete the vehicle studies **4. Outcome measurement (efficacy)** Some concerns; evaluator blinded (not clear whether this was the case for all 3 studies) **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol; data evaluated at 0, 2, 4, 8 and 12 weeks, but only reported for 8 and 12 weeks (the authors stated that assessments at week 8 and beyond are considered the most valid indicators of efficacy) **6. Overall bias** High
Study details **Reference** Strauss, J. S. S., A. M.Acne treatment with topical erythromycin and zinc: effect of Propionibacterium acnes and free fatty acid composition. 1984b. Journal of the American Academy of Dermatology	N=22 **Characteristics** **Sex** mixed **age (min/max)** 13/35 **Inclusion/exclusion criteria** **Used validated acne scale** no	**Interventions** **Treatment duration (weeks)** 10 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** no	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using a computer-generated random number list; methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; double-blind, but not clear if participants

Study details	Participants	Interventions	Outcomes and results	Comments
Trial ID Strauss 1984b **Country** United States **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	**Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Aged between 13 and 35 years of age with mild-to-moderate ache vulgaris. Each volunteer had to have P. acnes bacterial counts greater than 10 and free fatty acids greater than 8% of the skin surface lipids in two baseline determinations. **Exclusion details** Treatment with oral antibiotics or had any topical therapy for at least 4 weeks before entry into the study. Patients with known allergic reactions to the contents of the test product were excluded, as were women who were pregnant, lactating, or taking oral contraceptives. Patients were not allowed to take zinc-containing products for at least 4 weeks. **Number included** **Number randomised: arm 1** 12 **Number randomised: arm 2** 10 **Number completed: arm 1** 11 **Number completed: arm 2** 10	**Intervention: arm 1** 4% erythromycin solution containing 1.2% zinc acetate **Intervention: arm 2** Vehicle **Coded intervention: arm 1** ERYTH -topical+ ZINC-topical **Coded intervention: arm 2** Vehicle		were blinded; not reported if ITT was done **3. Missing outcome data (efficacy)** Low; <5% participants withdrew **4. Outcome measurement (efficacy)** Some concerns; blinding not reported **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Swinyer, L. J. B., M. D.,Swinyer, T. A.,Mills, O. H., Jr.A comparative study of benzoyl peroxide and clindamycin phosphate for treating acne vulgaris. 1988. British Journal of Dermatology **Trial ID** Swinyer 1988 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	N=60 **Characteristics** **Sex** mixed **age (mean±SD)** 19.8 **age (min/max)** 16/25 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Aged 16 to 25 with acne vulgaris grades I and II. More than 20 total facial lesions but no nodular-cystic lesions **Exclusion details** Had not received systemic or topical antibiotic treament in the past 7 days, or had treatment from a dermatologist in the past month, and no underlying disease or dermataological conditions. **Number included** **Number randomised: arm 1** 30 **Number randomised: arm 2** 30 **Number completed: arm 1** 30 **Number completed: arm 2** 30	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** Benzac W5 (5% benzoyl peroxide gel) b.d. **Intervention: arm 2** Cleocin T (1% clindamycin phosphate solution) b.d. **Coded intervention: arm 1** BPO-topical **Coded intervention: arm 2** CLIND-topical	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; participants randomised using a randomised set of numbers, no other methods reported **2. Deviation from intervention** Some concerns; participants were not blinded; not reported if ITT was done **3. Missing outcome data (efficacy)** Low; <5% withdrawals (5% vs 2.4% vs 2.5%); voluntary withdrawal due to number of follow-up visits **4. Outcome measurement (efficacy)** Low; evaluator blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Tan, J. B., R.,Gratton, D.,Kerrouche, N.,Canosa, J. M.The safety and efficacy of four different fixed combination regimens of adapalene 0.1%/benzoyl peroxide 2.5% gel for the treatment of acne vulgaris: results from a randomised controlled study. 2018. European Journal of Dermatology **Trial ID** Tan 2018 **Country** Canada **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	N=123 **Characteristics** **Sex** mixed **age (mean±SD)** 20.56±6.43 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** Aged between 12 and 35 years of age with mildto- moderate facial acne vulgaris, assessed using the Investigator Global Assessment Scale (IGA of 2 or 3 on a scale from 0=clear to 5=very severe) with a minimum of 10 inflammatory lesions, 10 to 100 non-inflammatory lesions, and no more than one nodule or cyst on the face, as well as Phototype of I to IV on the Fitzpatrick scale **Exclusion details** - **Number included** **Number randomised: arm 1** 32 **Number randomised: arm 2** 29 **Number randomised: arm 3** 32	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 4 **Split face design** no **Intervention: arm 1** A/BPO-3h: adapalene 0.1% + benzoyl peroxide 2.5% - daily for 3h **Intervention: arm 2** A/BPO-moisturizer: adapalene 0.1% + benzoyl peroxide 2.5%- daily overnight with moisturizer **Intervention: arm 3** A/BPO-EoN: adapalene 0.1% + benzoyl peroxide 2.5%- every other night **Intervention: arm 4** A/BPO-EN: adapalene 0.1% + benzoyl peroxide 2.5%- - daily overnight **Coded intervention: arm 1** ADAP-topical+BPO-topical **Coded intervention: arm 2** ADAP-topical+BPO-topical **Coded intervention: arm 3** ADAP-topical+BPO-topical **Coded intervention: arm 4** ADAP-topical+BPO-topical	**Results** **Treatment discontinuation due to side effects** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation on 1:1:1:1 ratio, no other methods reported **2. Deviation from intervention** Some concerns; single-blinded (not clear if participants were blinded); not reported if ITT was done **3. Missing outcome data (efficacy)** High; 15% participants lost to follow up overall; discontinuations due to adverse events reported (3.4% vs 3.1% vs 10%), no other reasons stated **4. Outcome measurement (efficacy)** Some concerns; blinding not reported **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 4 30 **Number completed: arm 1** na **Number completed: arm 2** na **Number completed: arm 3** na **Number completed: arm 4** na			
Study details **Reference** Thiboutot, D. G., M. H.,Jarratt, M. T.,Kang, S.,Kaplan, D. L.,Millikan, L.,Wolfe, J.,Loesche, C.,Baker, M.Randomized controlled trial of the tolerability, safety, and efficacy of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. 2001. Cutis; cutaneous medicine for the practitioner **Trial ID** Thiboutot 2001a **Country** United States **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** ITT	N=168 **Characteristics** **Sex** mixed **age (min/max)** 12/35 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Between 12 and 35 years of age, with mild or moderate facial acne vulgaris (global facial grades 1-5, according to Cunliffe acne grades7), inflammatory lesion counts (papules and pustules) between 10 and 40 inclusive, and a minimum of 20 and a maximum of 125 noninflammatory lesions (open and closed comedos). **Exclusion details** Patients with acne conglobata,	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** Adapalene gel 0.1% **Intervention: arm 2** Tretinoin gel 0.025% **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** TRET-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; treatments randomised into blocks with each block assigned to each study site and participants assigned a unique number in sequential order **2. Deviation from intervention** Some concerns; participants blinded (treatments packaged with blinded labeling in identical tubes); unclear if ITT analysis performed **3. Missing outcome data (efficacy)** Low; <5% loss to follow-up or withdrawals **4. Outcome measurement (efficacy)** Low; investigator-blinded (treatments packaged with blinded labeling in identical tubes)

Study details	Participants	Interventions	Outcomes and results	Comments
Method of ITT imputation WOCF	acne fulminans, secondary acne, or severe acne requiring more than topical treatment were excluded from the study, as were patients with underlying diseases or other dermatologie conditions that required the use of interfering topical or systemic therapy. In addition, no patients had received topical treatment before the study with preparations including alcohol (1 day); corticosteroids on facial area, antibiotics, anti-inflammatory drugs, or retinoids (2 weeks); or any other topical acne treatments (1 week). Patients who had received systemic treatment with corticosteroids or antibiotics (excluding penicillins) during the 4 weeks before study entry or other systemic acne treatments (including isotretinoin) for the previous 3 months, also were excluded. Pregnant or nursing women, those planning a pregnancy, or patients who had participated in another clinical trial in the preceding 30 days were excluded. In addition, patients with known sensitivities to study medication, those with a beard or other facial hair, or those having any other condition that			**5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	could interfere with the evaluation were excluded from the study. **Number included** **Number randomised: arm 1** 84 **Number randomised: arm 2** 84 **Number completed: arm 1** na **Number completed: arm 2** na			
Study details **Reference** Thiboutot, D. P., D. M.,Egan, N.,Flores, J.,Herndon, J. H.,Kanof, N. B.,Kempers, S. E.,Maddin, S.,Poulin, Y. P.,Wilson, D. C.,et al.,Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. 2006. Journal of the american academy of dermatology **Trial ID** Thiboutot 2006 **Country** North America **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or**	N=653 **Characteristics** **Sex** mixed **age (mean±SD)** 18.2±6.14 **age (median)** 16 **age (min/max)** 12/52 **age (other information)** 12-17, n=419; 18-64, n=234. Data for each group also reported **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** 12 years or older, with 20 to 100 noninflammatory facial lesions, 20 to 50 inflammatory	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** No **Intervention: arm 1** ADAP 0.3% gel **Intervention: arm 2** ADAP 0.1% gel **Intervention: arm 3** Vehicle gel **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** ADAP-topical **Coded intervention: arm 3** Vehicle	**Results** **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation on 2:2:1 ratio and remained blinded to study personnel; medication was packaged in identical tubes and dispensed by a third party **2. Deviation from intervention** Low; participants blinded; ITT analysis performed **3. Missing outcome data (efficacy)** Some concerns; participants discontinued: 13.6% vs 8.75% vs 11.7%; mainly due to patient request or loss to follow-up; last observation carried forward **4. Outcome measurement (efficacy)** Low; investigator-blinded

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis ITT **Method of ITT imputation** not reported	facial lesions, and no nodules or cysts **Exclusion details** Patients with severe acne requiring isotretinoin therapy or other dermatologic conditions requiring interfering treatment. Women were excluded if they were pregnant, nursing, or planning a pregnancy as were men with facial hair that would interfere with the assessments **Number included** **Number randomised: arm 1** 258 **Number randomised: arm 2** 261 **Number randomised: arm 3** 134 **Number completed: arm 1** 227 **Number completed: arm 2** 240 **Number completed: arm 3** 120			**5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Thiboutot, D. M. W., J.,Bucko, A.,Eichenfield, L.,Jones, T.,Clark, S.,Liu, Y.,Graeber, M.,Kang, S.Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: Results of a multicenter, randomized double-blind, controlled study.	N=512 **Characteristics** **Sex** mixed **age (mean±SD)** 16.399999999999999 **age (min/max)** 12/56	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 4 **Split face design** No	**Results** **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomised on 2:2:2:1 ratio; medication was packaged in identical tubes and dispensed by a third party **2. Deviation from intervention** Low; participants blinded; ITT analysis performed

Study details	Participants	Interventions	Outcomes and results	Comments
2007. Journal of the American Academy of Dermatology **Trial ID** Thiboutot 2007 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	**Number included** **Number randomised: arm 1** 149 **Number randomised: arm 2** 148 **Number randomised: arm 3** 149 **Number randomised: arm 4** 71 **Number completed: arm 1** 139 **Number completed: arm 2** 131 **Number completed: arm 3** 139 **Number completed: arm 4** 63 **Inclusion/exclusion criteria** **Inclusion details** 12 years of age or older, with 30 to 100 noninflammatory facial lesions, 20 to 50 inflammatory facial lesions, and no nodules or cysts **Exclusion details** Subjects with severe acne requiring isotretinoin therapy or other dermatologic conditions requiring interfering treatment. Women were excluded if they were pregnant, nursing, or planning a pregnancy as were men with facial hair that would interfere with the assessments.	**Intervention: arm 1** ADAP 0.1%/BPO 2.5% gel **Intervention: arm 2** ADAP 0.1% gel **Intervention: arm 3** BPO 2.5% gel **Intervention: arm 4** Vehicle gel **Coded intervention: arm 1** ADAP-topical + BPO-topical **Coded intervention: arm 2** ADAP-topical **Coded intervention: arm 3** BPO-topical **Coded intervention: arm 4** Vehicle		**3. Missing outcome data (efficacy)** Some concerns; more than 5% discontinued (6.7% vs 11.5% vs 6.7% vs 11.3%; mainly due to patient request); last observation carried forward **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
Study details **Reference** Thiboutot, D. E., L.,Shalita, A.,Del Rosso, J. Q.,Swinyer, L.,Tanghetti, E.,Tschen, E.,Parr, L.A 3-step acne system containing solubilized benzoyl peroxide versus clindamycin-benzoyl peroxide. 2009. Cutis; cutaneous medicine for the practitioner **Trial ID** Thiboutot 2009 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	N=139 **Characteristics** **Sex** mixed **age (mean±SD)** 20 **age (min/max)** 12.4/45.7 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Aged 12 to 45 years with mild to moderate facial acne vulgaris (10–100 noninflammatory lesions; 17–60 inflammatory lesions; =2 nodulocystic lesions on the face, excluding the nose). Females of childbearing potential were required to have a negative urine pregnancy test result and to use an acceptable method of contraception throughout the study. **Exclusion details** Using other medicated products on their face or had used a medicated facial cleanser in the preceding week; a topical a-hydroxy acid or antiacne medication in the	**Interventions** **Treatment duration (weeks)** 10 **Treatment duration category** 6 to <12 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** Salicylic acid cleanser 2% BID + salicylic acid toner 2% QD + solubilized BPO gel 5% BID **Intervention: arm 2** Control cleanser BID + Clindamycin 1%-benzoyl peroxide gel 5% BID **Coded intervention: arm 1** SAL topical +BPO-topical **Coded intervention: arm 2** CLIND-topical+BPO-topical	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomised on a 1:1 ratio; no other methods reported **2. Deviation from intervention** Some concerns; not clear if participants were blinded; not reported if ITT was done **3. Missing outcome data (efficacy)** Some concerns; 8% discontinued (8.6% clindamycin-BPO vs 7.2% 3-step acne system); reasons provided **4. Outcome measurement (efficacy)** Low; investigator or expert grader blinded (except for participant grading on burning/stinging and itching) **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	preceding 2 weeks; a topical retinoid, topical or systemic antibiotic, or topical or systemic steroid in the preceding 4 weeks; estrogen/ birth control pills for less than 3 months immediately before the baseline visit; or systemic retinoids in the preceding 6 months. Other exclusion criteria included participation in an investigational study in the preceding 30 days; having received a facial cosmetic procedure (eg, laser resurfacing, chemical peel, dermabrasion) in the preceding 6 months; allergy to BPO, clindamycin, lincomycin, salicylic acid, sunscreens, or substances to be used in the study; uncontrolled systemic disease; infection with human immunodeficiency virus; a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis; a beard or sideburns that could interfere with study evaluations; and pregnancy, breastfeeding, or planning of a pregnancy during the study. **Number included** **Number randomised: arm 1** 69 **Number randomised: arm 2** 70			

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 1 64 **Number completed: arm 2** 64			
Study details **Reference** Thielitz, A. L., A.,Wiede, A.,Kropf, S.,Papakonstantinou, E.,Gollnick, H.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. 2015. Journal of the European Academy of Dermatology and Venereology **Trial ID** Thielitz 2015 **Country** Germany **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=55 **Characteristics** **Sex** female **age (mean±SD)** 29.17±6.96 **Inclusion/exclusion criteria** **Used validated acne scale** yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Female patients with mild-to-moderate acne including 'late-type acne', aged 18–45 years. Acne global severity grades 2–4 (mild – moderate – moderately severe), according to a modified Investigator's Static Global Assessment (ISGA) and 2–7, according to the Leeds Revised Acne Grading Scale (LRAGS, a pictural acne grading system) corresponding to mild (2–3) and moderate (4–7) forms. **Exclusion details** More than one nodule, pregnancy or breast-feeding, planned pregnancy, known hypersensitivity to any of the study products or the	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** no **Intervention: arm 1** Azelaic acid 15% for 9 months (results reported for treatment phase only, 12 weeks) **Intervention: arm 2** Azelaic acid 15% for 3 months, followed by 6 months observation (results reported for treatment phase only, 12 weeks) **Intervention: arm 3** Adapalene gel 0.1% for 9 months (results reported for treatment phase only, 12 weeks) **Coded intervention: arm 1** AZE-topical **Coded intervention: arm 2** AZE-topical **Coded intervention: arm 3** ADAP-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation using software RITA on 1:1:1 ratio using minimisation method of Pocock and Simon and stratification for age and severity classification at study entry; methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; it appears that participants may not have been blinded (participants instructed not to discuss treatment and potential side-effects with investigators); ITT analysis was done **3. Missing outcome data (efficacy)** High; 31% lost to follow up **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	medication with a systemic retinoid within the past 6 months before study inclusion. Patients were not allowed to take any other topical or systemic anti-acne medication including systemic oral corticosteroids in the preceding 2 weeks, or during the study period. Females of childbearing potential using effective contraception methods must have been taking the same type of birth control for at least 6 months prior to entering **Number included** **Number randomised: arm 1** 17 **Number randomised: arm 2** 19 **Number randomised: arm 3** 19 **Number completed: arm 1** 11 **Number completed: arm 2** 16 **Number completed: arm 3** 11			
Study details **Reference** Thorneycroft, I. H. G., H.,Schellschmidt, I.Superiority of a combined contraceptive containing drospirenone to a triphasic preparation	N=1154 **Characteristics** **Sex** female **age (mean±SD)** 24.05±5.8	**Interventions** **Treatment duration (weeks)** 24 **Treatment duration category** 24+ weeks **Number of arms** 2	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation in 1:1 ratio using computer-generated randomisation list; methods not reported for allocation concealment

Study details	Participants	Interventions	Outcomes and results	Comments
containing norgestimate in acne treatment. 2004. Cutis **Trial ID** Thorneycroft 2004 **Country** Germany **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Otherwise healthy female subjects ranging in age from 15 to 40 years without contraindications for combined oral contraceptive use with mild to moderate acne vulgaris, having 6 to 100 comedones (noninflammatory lesions), 10 to 50 papules or pustules together, and not more than 5 nodules on the face (inflammatory lesions). Normal gynecologic examination and cervical smear within the last 6 months; negative pregnancy test; 3 spontaneous withdrawal bleedings following delivery, abortion, or lactation; and avoidance of comedogenic cosmetics or sunscreens, sex hormone preparations, and antiacne therapy **Exclusion details** Subjects older than 30 years who smoked and those who were pregnant or lactating, acne comedonica or nodulocystic/conglobate acne; acne with multiple large nodes,	**Split face design** no **Intervention: arm 1** 30micrograms ethinyl estradiol + 3milligrams drospirenone **Intervention: arm 2** 35micrograms ethinyl estradiol + 0.18, 0.215, 0.25mg norgestimate **Coded intervention: arm 1** EE-oral + DROS-oral **Coded intervention: arm 2** EE-oral+NGM-oral	**due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**2. Deviation from intervention** Some concerns; double-blind but not clear if participants were blinded; full analysis set included, but unclear whether this was ITT analysis **3. Missing outcome data (efficacy)** Some concerns; discontinuations 6.2% vs 7% due to adverse events, other reasons, withdrawal of consent, protocol deviation, or lack of efficacy (similar across trials) **4. Outcome measurement (efficacy)** Some concerns; blinding not reported **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	cysts, fistular comedones, or abscessing fistular ducts; previous acne treatment failure with (antiandrogenic) sex hormone preparations given for at least 3 months; and the need for other medication with known acne-inducing effects, such as lithium, vitamin B1, or corticoids. **Number included** **Number randomised: arm 1** 568 **Number randomised: arm 2** 586 **Number completed: arm 1** 533 **Number completed: arm 2** 545			
Study details **Reference** Tirado-Sanchez, A. P.-O., R. M.Efficacy and tolerance of superoxidized solution in the treatment of mild to moderate inflammatory acne. A double-blinded, placebo- controlled, parallel-group, randomized, clinical trial. 2009. Journal of Dermatological Treatment **Trial ID** Tirado-Sanchez 2009 **Country** Mexico **Study type** RCT	N=87 **Characteristics** **Sex** mixed **age (mean±SD)** 18.6 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear, type of lesion x counts scale **Inclusion details** Mild to moderate inflammatory acne, meaning 10–50 inflammatory lesions (papules	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 3 **Split face design** no **Intervention: arm 1** Superoxidised solution (an electrochemically processed aqueous solution manufactured from pure water and sodium chloride) **Intervention: arm 2** Benzoyl peroxide 5% gel	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Low; randomisation using balanced blocks method, followed computer-generated random numbers and assigned to participants by one investigator not assessing outcomes **2. Deviation from intervention** Some concerns; double-blinded but not clear if participants were blinded; not reported if ITT was done **3. Missing outcome data (efficacy)**

Study details	Participants	Interventions	Outcomes and results	Comments
Source of funding Not industry funded **Analysis method** **Intention to treat or completers analysis** Completers	and pustules) with an absence of nodulocystic lesions **Exclusion details** No other inflammatory cutaneous disease could be present on the face. Patients were not to have used any other topical treatment for 14 days, systemic antibiotics for 30 days, or systemic retinoid for at least 6 months prior to the start of treatment. **Number included** **Number randomised: arm 1** 39 **Number randomised: arm 2** 24 **Number randomised: arm 3** 24 **Number completed: arm 1** 39 **Number completed: arm 2** 24 **Number completed: arm 3** 22	**Intervention: arm 3** Placebo **Coded intervention: arm 1** SOS-topical **Coded intervention: arm 2** BPO-topical **Coded intervention: arm 3** PLC-topical		Low; <5% loss to follow-up or withdrawals **4. Outcome measurement (efficacy)** Low; investigator-blinded (assessment performed by second investigator not involved in dispensing treatment) **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns
Study details **Reference** Tirado-Sanchez, A. E., Y. S.,Ponce-Olivera, R. M.,Bonifaz, A.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	N=131 **Characteristics** **Sex** mixed **age (mean±SD)** 20±6.15 **Inclusion/exclusion criteria** **Used validated acne scale** no	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 4 **Split face design** no	**Results** **Treatment discontinuation for any reason** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention** Some concerns; double-blinded but not clear if participants were blinded; not reported if ITT was done

Study details	Participants	Interventions	Outcomes and results	Comments
on Mexican patients (skin type III-IV). 2013. Journal of Cosmetic Dermatology **Trial ID** Tirado-Sanchez 2013 **Country** Mexico **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	**Acne scale** Unclear, type of lesion x counts scale **Inclusion details** 18 years or older with at least ten noninflammatory acne lesions and <30 inflammatory lesions on the entire face. Patients with childbearing potential were required to use birth control and to have a negative pregnancy test result at the beginning of the study **Exclusion details** Patients who had received topical treatment within 1 week prior to inclusion or systemic anti-acne drugs within 2 weeks beforehand were excluded from the study, as were those treated with systemic retinoids within 3 months prior to inclusion or those patients having any concomitant skin conditions on the study area, which could interfere with the study results **Number included** **Number randomised: arm 1** 43 **Number randomised: arm 2** 43	**Intervention: arm 1** Adapalene 0.1% gel **Intervention: arm 2** Adapalene 0,3% gel **Intervention: arm 3** Tretinoin 0.05% gel **Intervention: arm 4** Placebo gel **Coded intervention: arm 1** ADAP-topical **Coded intervention: arm 2** ADAP-topical **Coded intervention: arm 3** TRET-topical **Coded intervention: arm 4** PLC-topical		**3. Missing outcome data (efficacy)** Low; <5% loss to follow-up or withdrawals **4. Outcome measurement (efficacy)** Some concerns; blinding not reported **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 3 45 **Number randomised: arm 4** 40 **Number completed: arm 1** 42 **Number completed: arm 2** 42 **Number completed: arm 3** 43 **Number completed: arm 4** 37			
Study details **Reference** Tong, D. P., W.,Barnetson, R. S. C.Evaluation of 0.75% metronidazole gel in acne - A double-blind study. 1994. Clinical and Experimental Dermatology **Trial ID** Tong 1994 **Country** Australia **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** Completers	N=96 **Characteristics** **Sex** mixed **age (mean±SD)** 20.7±4.5 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Leeds Grading Scale, Cunliffe **Inclusion details** Healthy, non-institutionalized patients free of intercurrent disease and over 12 years old, with a minimum of six and maximum of 50 inflammatory papules, and no more rhan six nodulocystic lesions. **Exclusion details** if patients had received ultraviolet therapy 2 weeks before the trial; or if 4 weeks	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** no **Intervention: arm 1** Metronizadole 0.75% **Intervention: arm 2** Placebo **Coded intervention: arm 1** MET-topical **Coded intervention: arm 2** PLC-topical	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; unclear randomisation process; treatments provided in identical tubes and both placed in iindividually numbered, identical boxes **2. Deviation from intervention** Some concerns; participants were blinded; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Low; <5% loss to follow-up or withdrawals **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol

Study details	Participants	Interventions	Outcomes and results	Comments
	prior to the trial they had had a systemic illness, antibiotics (topical or systemic), topical acne treatments, or vitamin A therapy; or if in the 3 months preceding rhey had taken isotretinoin, anti-androgens, corticosteroids, anticoagulants or oestrogen-based contraceptives. Other exclusion criteria were known drug allergies, alcohol and recreational drug abuse, pregnancy and lactation. Finally, those patients with beards, excessive facial hair, skin conditions or increased pigmentation which precluded accurate evaluation of rheir acne were also excluded **Number included** **Number randomised: arm 1** 48 **Number randomised: arm 2** 48 **Number completed: arm 1** 46 **Number completed: arm 2** 47			**6. Overall bias** Some concerns
Study details **Reference** van Vloten, W. A. v. H., C. W.,van Zuuren, E. J.,Gerlinger, C.,Heithecker, R.The effect of 2 combined oral Contraceptives containing either drospirenone or	N=125 **Characteristics** **Sex** female **age (mean±SD)** 22.89±3.76	**Interventions** **Treatment duration (weeks)** 36 **Treatment duration category** 26+ weeks **Number of arms** 2	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation**	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation on a 2:1 ratio; no other methods reported **2. Deviation from intervention** Some concerns; double-blind,

Study details	Participants	Interventions	Outcomes and results	Comments
cyproterone acetate on acne and seborrhea. 2002. Cutis; cutaneous medicine for the practitioner **Trial ID** van Vloten 2002 **Country** Europe **Study type** RCT **Source of funding** Unstated **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** na	**Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** None **Inclusion details** Women aged 16 to 35 years (30 years for smokers), otherwise healthy with mild-to-moderate facial acne (comedones, papules, pustules, nodules <0.5 cm), who had minor occurrence of seborrhea and/or hair growth on the upper lip, chin and chest. At least 8 papulopustular lesions on the face. **Exclusion details** Pregnancy, lactation, contraindication to oral contraceptive use, obesity (>20% normal weight), Pap smear >CII, genital infection and use of parenteral depot contraceptives in the last 6 months. Presence of multiple large nodes, cysts, fistular comedos of abscessing fistular ducts. Previous unsucessful treatment with antiandrogenic hormone treatments, treatment with isotretinoin within the last year. **Number included** **Number randomised: arm 1** 82	**Split face design** No **Intervention: arm 1** 30 micrograms EE and 3 mg DRSP (Yasmin) **Intervention: arm 2** 35 micrograms EE and 2 mg CPA (Diane 35) **Coded intervention: arm 1** EE-oral + DROS-oral **Coded intervention: arm 2** CPA-oral + EE-oral	**due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	but not reported who was blinded; ITT analysis was done **3. Missing outcome data (efficacy)** High; more than 5% discontinued due to side effects in one arm (9.3%); second treatment arm, 11% discontinued due to withdrawal of consent, protocol violations, railure to attend clinic, not taken treatment **4. Outcome measurement (efficacy)** Some concerns; not reported who was blinded **5. Selective reporting** Some concerns; not reported whether there was a pre-registered protocol; treatment appears to have been for 9 cycles and outcomes reported, but the authors also mention a follow-up period but no further details **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number randomised: arm 2 43 **Number completed: arm 1** 68 **Number completed: arm 2** 38			
Study details **Reference** Wiegell, S. R. W., H. C.Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: A blinded, randomized, controlled trial. 2006b. British Journal of Dermatology **Trial ID** Wiegell 2006b **Country** Denmark **Study type** RCT **Source of funding** Not industry funded **Analysis method** **Intention to treat or completers analysis** completers	N=36 **Characteristics** **Sex** mixed **age (mean±SD)** 23.387096774193548±5 **Number included** **Number randomised: arm 1** 21 **Number randomised: arm 2** 15 **Number completed: arm 1** 12 **Number completed: arm 2** 11 **Inclusion/exclusion criteria** **Inclusion details** 18 years or older with general good health and more than 12 inflammatory acne lesions in the face **Exclusion details** Patients with skin type VI (black skin) and pregnant or lactating woman were excluded. The patients had to have no history of oral retinoid use within 1 year of study entry, no systemic antibiotics	**Interventions** **Treatment intensity** Total 2 sessions, once every 2 weeks. Endpoint is 2 wks after last session (4 wks data) **Number of arms** 2 **Split face design** No **Intervention: arm 1** MAL 2g RED-PDT **Intervention: arm 2** No treatment **Coded intervention: arm 1** MAL-RED-PDT **Coded intervention: arm 2** No treatment	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation on 4:3 ratio; no othe rmethods reported **2. Deviation from intervention** Some concerns; participants were instructed not to reveal to blinded dermatologist whether they had been treated or not; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** High; around 37% participants were lost to follow up in treatment arm (due to pain during first treatment; side effects; dissatisfaction with response) and 1% in control arm (due to military service); reasons for withdrawal were not comparable between the arms **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; protocol

Study details	Participants	Interventions	Outcomes and results	Comments
	within 1 month and no topical acne treatment within 2 weeks.			approved by Ethics Committee, but no further details provided **6. Overall bias** High
Study details **Reference** Wolf, J. E., Jr.,Kaplan, D.,Kraus, S. J.,Loven, K. H.,Rist, T.,Swinyer, L. J.,Baker, M. D.,Liu, Y. S.,Czernielewski, J.Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. 2003. Journal of the American Academy of Dermatology **Trial ID** Wolf 2003 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	N=249 **Characteristics** **Sex** Mixed **age (mean±SD)** 18.3±7.06 **age (min/max)** 12/53 **Inclusion/exclusion criteria** **Used validated acne scale** Yes **Acne scale** Leeds Revised Grading Scale **Inclusion details** Patients with mild to moderate acne vulgaris, at least 12 years of age, and had a global severity grade ranging from 2 to 8, according to the Leeds Revised Acne Grading System. They had 10 to 50 inflammatory facial lesions (no more than 3 nodules or cysts) and 20 to 150 noninflammatory facial lesions. **Exclusion details** Acne conglobata, acne fulminans, secondary acne, severe acne, or other dermatologic conditions requiring systemic treatment.	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** adapalene gel 0.1% plus clindamycin phosphate lotion 1% b.d. **Intervention: arm 2** clindamycin plus vehicle b.d. **Coded intervention: arm 1** ADAP-topical +CLIND-topical **Coded intervention: arm 2** CLIND-topical + Vehicle	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation on a 1:1 ratio, no other methods reported **2. Deviation from intervention** Some concerns; not reported if participants were blinded; ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; over 10% discontinued in both arms - reasons similar between arms; last observation carried forward **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; protocol approved by Institutional Review Board, but no further details provided **6. Overall bias** Some concerns

Study details	Participants	Interventions	Outcomes and results	Comments
	Women were excluded if they were pregnant, planning a pregnancy or nursing. Men with beards were excluded if these were likely to cause interference with study assessments. **Number included** **Number randomised: arm 1** 125 **Number randomised: arm 2** 124 **Number completed: arm 1** 107 **Number completed: arm 2** 110			
Study details **Reference** Xu, J. H. L., Q. J.,Huang, J. H.,Hao, F.,Sun, Q. N.,Fang, H.,Gu, J.,Dong, X. Q.,Zheng, J.,Luo, D.,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. 2016. Journal of the european academy of dermatology and venereology : JEADV **Trial ID** Xu 2016	N=1016 **Characteristics** **Sex** Mixed **age (mean±SD)** 23.3±4.5 **Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** Investigator's Static Global Assessment (ISGA)/Investigator's global severity Assessment **Inclusion details** Aged 12–45 years (inclusive) diagnosed with mild to moderate acne, with at least 17, but not more than 60 facial inflammatory lesions (papules	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks **Number of arms** 2 **Split face design** No **Intervention: arm 1** topical clindamycin 1%/benzoyl peroxide 5% once-daily gel **Intervention: arm 2** clindamycin 1% twice-daily gel **Coded intervention: arm 1** CLIND-topical + BPO-topical **Coded intervention: arm 2** CLIND-topical	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation on a 1:1 ratio using comput-ergenerated randomisation schedule; Methods not reported for allocation concealment **2. Deviation from intervention** Some concerns; participants and perosnnel do not appear to have been blinded; ITT analysis was done **3. Missing outcome data (efficacy)** High; around 14% participants discontinued; higher rate for adverse events in clindamycin combination (2.4%) vs

Study details	Participants	Interventions	Outcomes and results	Comments
Country China **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** ITT **Method of ITT imputation** LOCF	plus pustules), at least 20 but not more than 125 facial non-inflammatory lesions (open and closed comedones), no more than 1 facial nodular lesion with no cystic lesions, and who had a baseline Investigator's Static Global Assessment (ISGA) score of 2 or 3 **Exclusion details** Cystic acne lesions, acne conglobata, acne fulminans or secondary acne (e.g. chloracne or druginduced acne) were excluded from the study. Women of childbearing potential had to use medically acceptable method of contraception during the study; pregnant and lactating women **Number included** **Number randomised: arm 1** 500 **Number randomised: arm 2** 516 **Number completed: arm 1** 430 **Number completed: arm 2** 445			clincamycin alone (0.8%); last observation carried forward used **4. Outcome measurement (efficacy)** Low; assessor-blinded **5. Selective reporting** Low; registered on clinical trials.gov **6. Overall bias** High
Study details **Reference** Yentzer, B. A. A., R. A.,Fountain, J. M.,Clark, A. R.,Taylor, S. L.,Fleischer, A. B.,Feldman, S. R.Simplifying regimens promotes greater	N=26 **Characteristics** **Sex** Mixed **age (mean±SD)** na±na	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <24 weeks	**Results** **Treatment discontinuation for any reason** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; methods not reported **2. Deviation from intervention**

Study details	Participants	Interventions	Outcomes and results	Comments
adherence and outcomes with topical acne medications: a randomized controlled trial. 2010. Cutis; cutaneous medicine for the practitioner **Trial ID** Yentzer 2010 **Country** United States **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** Investigator's Global Assessment scale (IGA) **Inclusion details** 12 years and older with an investigator global assessment (IGA) of mild to moderate acne vulgaris (score of 2 or 3) **Exclusion details** Pregnant or planning to become pregnant; breastfeeding; using oral retinoids within 2 months of enrollment; or using topical retinoids, oral antibiotics, nicotinamide, oral steroids, or any other medication determined to have potentially confounding effects on the results of the study within 1 month prior to the start of the trial. Also use of topical medications for acne, such as cosmetics containing retinol, within 2 weeks prior to study entry; any skin condition or disease requiring concurrent therapy or confounding evaluation; history of hypersensitivity to the medications or their components; facial skin cancer or actinic keratoses; use of photosensitizing agents; use of	**Number of arms** 2 **Split face design** No **Intervention: arm 1** once daily application of clindamycin phosphate 1.2%–tretinoin 0.025% gel combination product **Intervention: arm 2** separate daily applications of clindamycin phosphate gel 1% and tretinoin cream 0.025% (C gel 1 T cream) for a total of 2 applications daily. **Coded intervention: arm 1** CLIND-topical + TRET-topical **Coded intervention: arm 2** CLIND-topical + TRET-topical	**Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	Some concerns; single blinded; not reported if ITT was done **3. Missing outcome data (efficacy)** High; withdrawal were not comparable between the groups (30.8% vs 7.7%) **4. Outcome measurement (efficacy)** Low; investigator-blinded **5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	isotretinoin in the last 6 months; use of chemical peels, microdermabrasion, or laser resurfacing within 3 months of study entry; Crohn disease; ulcerative colitis; or colitis with prior antibiotic use. **Number included** **Number randomised: arm 1** 13 **Number randomised: arm 2** 13 **Number completed: arm 1** 9 **Number completed: arm 2** 12			
Study details **Reference** Zayed, A. A., Sobhi, R. M., El Aguizy, R. M. S., Sabry, D., Mahmoud, S. B.Sequential peeling as a monotherapy for treatment of milder forms of acne vulgaris. 2019. Journal of Cosmetic Dermatology. **Trial ID** Zayed 2019 **Country** Egypt **Study type** RCT **Source of funding** No funding sources **Analysis method** **Intention to treat or**	N=45 **Characteristics** **Sex** female **age (mean±SD)** 20.23±3 **age (min/max)** 16/30 **Inclusion/exclusion criteria** **Used validated acne scale** no **Acne scale** Unclear **Inclusion details** Mild to moderate acne vulgaris (active lesions).Skin phototypes III and IV.No topical or systemic treatment for the preceding 1	**Interventions** **Treatment duration (weeks)** 12 **Treatment duration category** 12 to <26 weeks **Treatment intensity** Sequential peeling with GLY & SAL every 2 weeks for 3 months (6 sessions) **Number of arms** 3 **Split face design** no **Intervention: arm 1** Sequential peeling sessions with 70% Glycolic Acid kept for 3 minutes followed by 20% Salicylic Acid once every 2 weeks for 3 months	**Results** **Treatment discontinuation for any reason** See supplement 4 **Treatment discontinuation due to side effects** See supplement 4 **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation method unclear, allocation concealed using closed envelopes **2. Deviation from intervention** Some concerns; not reported if participants were blinded; not reported in ITT analysis was done **3. Missing outcome data (efficacy)** High; 13% discontinued; reasons provided **4. Outcome measurement (efficacy)** Some concerns; blinding not reported

Study details	Participants	Interventions	Outcomes and results	Comments
completers analysis completers	month.Having realistic expectations **Exclusion details** Severe acne vulgaris, acne conglobata and acne fulminans, steroid induced acne, hormonal acne.Pregnancy and breast feeding.History of atopic dermatitis, psoriasis, irritant contact dermatitis, photosensitivity, keloids, history of salicylism, immunocompromised patients, open wounds, and active herpes simplex infection **Number included** **Number randomised: arm 1** 15 **Number randomised: arm 2** 15 **Number randomised: arm 3** 15 **Number completed: arm 1** 14 **Number completed: arm 2** 13 **Number completed: arm 3** 12	**Intervention: arm 2** A combination of sequential peeling sessions and oral doxycycline, 100 mg twice/day for 1 month and then 100 mg/day for 2 months. **Intervention: arm 3** Oral doxycycline for 3 months **Coded intervention: arm 1** GLY peel + SAL peel **Coded intervention: arm 2** GLY peel + SAL peel + DOXY-oral **Coded intervention: arm 3** DOXY-oral		**5. Selective reporting** Some concerns; Not reported whether there was a pre-registered protocol **6. Overall bias** High
Study details **Reference** Zheng, Y. Y., S.,Xia, Y.,Chen, J.,Ye, C.,Zeng, Q.,Lai, W.Efficacy and safety of 2% supramolecular salicylic acid compared with 5% benzoyl	N=68 **Characteristics** **Sex** Mixed **age (mean±SD)** 26±na	**Interventions** **Treatment duration (weeks)** 6 **Treatment duration category** 6 to <12 weeks **Number of arms** 2	**Results** **Clinician rated improvement in acne** See supplement 4	**Cochrane RoB Tool v2.0** **1. Randomisation** Some concerns; randomisation list generated by statistician using softare; methods not reported for allocation concealment

Study details	Participants	Interventions	Outcomes and results	Comments
peroxide/0.1% adapalene in the acne treatment: a randomized, split-face, open-label, single-center study. 2019. Cutaneous and ocular toxicology **Trial ID** Zheng 2019 **Country** China **Study type** RCT **Source of funding** Industry funded **Analysis method** **Intention to treat or completers analysis** Completers	**Inclusion/exclusion criteria** **Used validated acne scale** No **Acne scale** Pillsbury **Inclusion details** Mild to moderate acne, age range of 18–35 years. The severity of acne was classified as mild (grade I), moderate (grade II and III), and severe (grade IV) according to the Pillsbury grading system. Patients with grade I–III acne were enrolled in this clinical trial. **Exclusion details** Pregnancy and lactation, a history of photoallergy, a history of solar exposure within one week, active facial herpes simplex, planning to have children, scar diathesis, allergy to SA or similar ingredients, consumed antibiotics, hormonal drugs, isotretinoin, or photoallergic drugs within the last two weeks, diabetes mellitus, organ defects of the heart, lung, liver and kidney, and neurological or psychiatric disorders. **Number included** **Number randomised: arm 1** 34 **Number randomised: arm 2** 34	**Split face design** yes **Intervention: arm 1** 0.01% adapalene plus 5% benzoyl peroxide **Intervention: arm 2** 2% supramolecular salicylic acid **Coded intervention: arm 1** ADAP-topical + BPO-topical **Coded intervention: arm 2** SAL topical		**2. Deviation from intervention** High; open-labeled; according to the paper "The funder, investigators, patients, and research staff remained masked to the randomisation list but were not masked to treatment"; not reported if ITT analysis was done **3. Missing outcome data (efficacy)** Some concerns; more than 5% discontinued (due to side effects) **4. Outcome measurement (efficacy)** High; open-labeled **5. Selective reporting** Some concerns; study protocol approved by Ethics Committee, but no other details provided **6. Overall bias** High

Study details	Participants	Interventions	Outcomes and results	Comments
	Number completed: arm 1 31 **Number completed: arm 2** 31			

5ALA-IPL-PDT: 5-aminolevulinic acid using intense pulsed light; ADAP: adapalene; AZE: azelaic acid; AZITH: azithromycin; BLU-PT: blue light; BPO: benzoyl peroxide; BR-LED: blue + red light; CHLOR: chlorhexidine gluconate; CLIND: clindamycin; CMA: chlormadinone acetate; CPA: co-cyprindiol; DAPS: dapsone; DNG: dienogest; DOXY: doxycycline; DROS: drospirenone; EE: ethinylestradiol; ERYTH: erythromycin; FCA: fusidic acid; GLY: glycolic acid; HPS: hydrogen peroxide; IPL: intense pulsed light; ISO: isotretinoin; IQR: interquartile range; ITT: intension to treat; LEVA: levamisole; LNG: levonorgestrel; LOCB: last observation carried backward; LOCF: last observation carried forward; MAND: mandelic; MET: metronidazole; MINO: minocycline; NGM: norgestimate; OXYTETRA: oxytetracycline; PDL: pulsed dye laser; PDT: photochemical therapy; PHY: phytic acid; PLC: placebo; RCT: randomised controlled trial; RoB: risk of bias; SAL: salicylic acid; SD: standard deviation; TAZ: tazarotene; TRET: tretinoin.

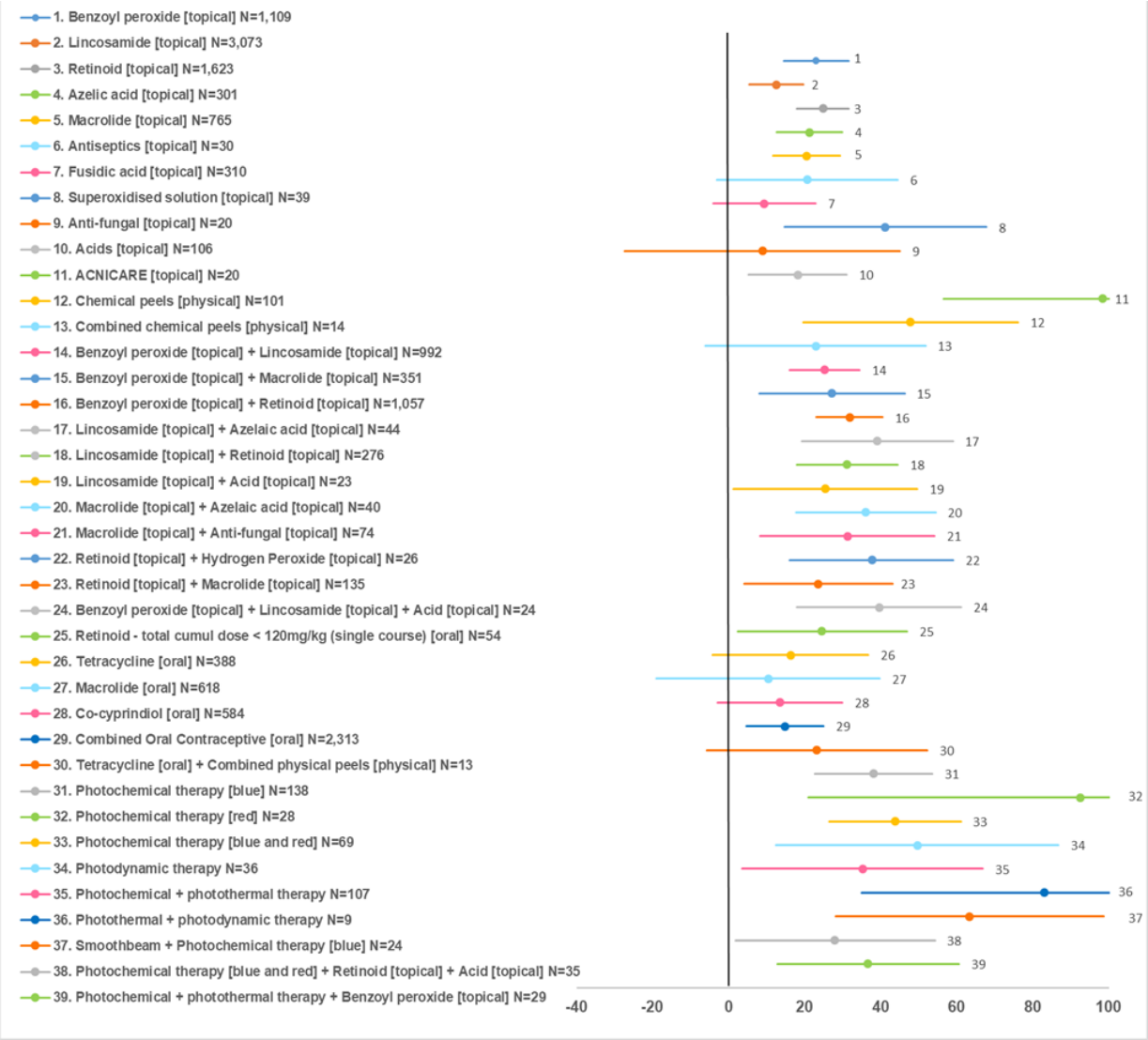
Appendix E – Network Meta-analysis results

Network meta-analysis results for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Efficacy: % change in total acne lesion count from baseline

Base-case analysis

Figure 5. NMA treatment efficacy in people with mild to moderate acne: base-case forest plots, treatment class effects vs placebo



All treatment class effects versus placebo (N=2698). Results expressed as mean difference in % change from baseline; values on the right side of vertical axis indicate higher effect compared with placebo.

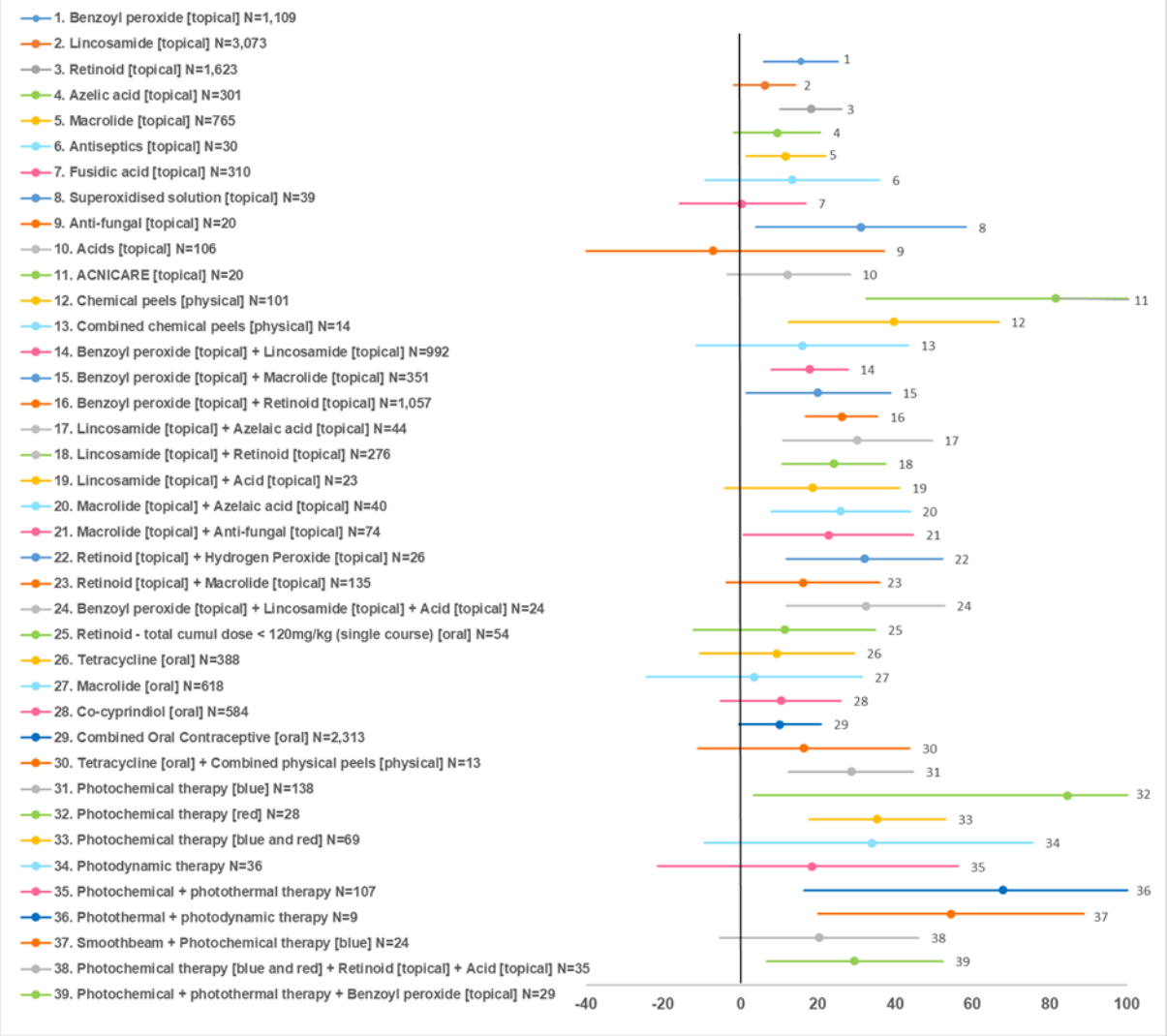
Table 8. NMA treatment efficacy in people with mild to moderate acne: base-case treatment class effects vs placebo & rankings

Class	N	Effect vs placebo (mean, 95% CrI)	Rank, females (mean, 95% CrI)	Rank, males (mean, 95% CrI)
ACNICARE [topical]	20	98.43 (56.59 to 147.20)	2.05 (1 to 5)	2.05 (1 to 5)
Photothermal + photodynamic therapy	9	82.96 (35.10 to 129.90)	3.37 (1 to 13)	3.36 (1 to 13)
Photochemical therapy [red]	28	92.59 (21.00 to 164.60)	3.87 (1 to 27)	3.84 (1 to 27)
Smoothbeam + Photochemical therapy [blue]	24	63.39 (28.11 to 98.57)	5.67 (1 to 20)	5.66 (1 to 20)
Chemical peels [physical]	101	47.88 (19.73 to 76.10)	9.63 (3 to 29)	9.59 (3 to 28)
Photodynamic therapy	36	49.72 (12.46 to 86.70)	10.15 (3 to 34)	10.07 (3 to 33)
Photochemical therapy [blue and red]	69	43.78 (26.46 to 61.11)	10.19 (4 to 21)	10.18 (4 to 21)
Superoxidised solution [topical]	39	41.09 (14.66 to 67.84)	12.89 (3 to 33)	12.81 (3 to 32)
Benzoyl peroxide [topical] + Lincosamide [topical] + Other acid [topical]	24	39.58 (17.88 to 61.17)	13.04 (4 to 31)	12.99 (4 to 30)
Azelaic acid [topical] + Lincosamide [topical]	44	39.16 (19.23 to 59.00)	13.13 (4 to 30)	13.09 (4 to 29)
Photochemical therapy [blue]	138	38.09 (22.75 to 53.63)	13.26 (6 to 25)	13.24 (6 to 25)
Retinoid [topical] + Hydrogen Peroxide [topical]	26	37.67 (16.09 to 59.16)	14.26 (4 to 32)	14.19 (4 to 32)
Azelaic acid [topical] + Macrolide [topical]	40	36.04 (17.72 to 54.44)	14.98 (5 to 31)	14.92 (5 to 30)
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	29	36.56 (12.77 to 60.66)	15.23 (4 to 34)	15.12 (4 to 33)
Photochemical + photothermal therapy	107	35.27 (3.62 to 66.86)	17.17 (5 to 38)	16.94 (5 to 37)
Benzoyl peroxide [topical] + Retinoid [topical]	1057	31.81 (22.99 to 40.55)	17.40 (10 to 26)	17.36 (10 to 26)
Lincosamide [topical] + Retinoid [topical]	276	31.26 (17.91 to 44.51)	18.08 (8 to 31)	18.01 (8 to 30)
Macrolide [topical] + Anti-fungal [topical]	74	31.33 (8.38 to 54.21)	18.83 (5 to 37)	18.63 (5 to 36)
Benzoyl peroxide [topical] + Macrolide [topical]	351	27.33 (8.20 to 46.29)	21.59 (8 to 36)	21.32 (8 to 34)
Retinoid [topical] + Other acid [topical] + Photochemical therapy [blue and red]	35	27.98 (1.84 to 54.28)	21.63 (6 to 39)	21.27 (6 to 37)
Lincosamide [topical] + Other acid [topical]	23	25.52 (1.37 to 49.60)	23.39 (7 to 39)	22.98 (7 to 38)
No treatment	39	25.07 (-32.23 to 81.90)	23.45 (4 to 41)	22.74 (4 to 39)
Benzoyl peroxide [topical] + Lincosamide [topical]	992	25.28 (16.06 to 34.46)	23.50 (15 to 33)	23.32 (15 to 32)
Retinoid [topical]	1623	24.82 (17.90 to 31.67)	23.90 (16 to 32)	23.75 (16 to 31)
Retinoid - total cumulative dose < 120mg/kg (single course) [oral]	54	24.51 (2.35 to 47.01)	24.27 (8 to 39)	23.84 (8 to 37)
Tetracycline [oral] + Combined chemical peels [physical]	13	23.25 (-5.69 to 52.28)	24.82 (6 to 40)	24.25 (6 to 38)
Retinoid [topical] + Macrolide [topical]	135	23.58 (4.06 to 43.19)	24.95 (10 to 39)	24.51 (10 to 37)
Combined chemical peels [physical]	14	22.89 (-6.10 to 51.79)	25.09 (6 to 40)	24.51 (6 to 38)
Benzoyl peroxide [topical]	1109	23.03 (14.47 to 31.59)	25.79 (18 to 33)	25.53 (18 to 33)
Antiseptics [topical]	30	20.69 (-3.12 to 44.54)	27.10 (9 to 40)	26.46 (9 to 38)
Azelaic acid [topical]	301	21.26 (12.57 to 29.88)	27.46 (18 to 36)	27.09 (18 to 35)
Macrolide [topical]	765	20.45 (11.72 to 29.26)	28.24 (19 to 36)	27.81 (19 to 35)
Other acid [topical]	106	18.21 (5.29 to 31.04)	29.84 (17 to 39)	29.18 (17 to 37)
Tetracycline [oral]	388	16.43 (-4.11 to 36.79)	30.75 (15 to 40)	29.90 (15 to 38)
Combined Oral Contraceptive [oral]	2313	14.75 (4.74 to 24.94)	32.75 (22 to 39)	Not relevant
Anti-fungal [topical]	20	8.93 (-27.32 to 45.06)	32.77 (9 to 41)	31.56 (9 to 39)
Co-cyprindiol [oral]	584	13.48 (-2.87 to 29.95)	32.92 (18 to 40)	Not relevant
Macrolide [oral]	618	10.45 (-19.04 to 39.80)	33.30 (12 to 41)	32.12 (12 to 39)
Lincosamide [topical]	3073	12.60 (5.55 to 19.65)	34.70 (28 to 39)	33.52 (28 to 37)
Fusidic acid [topical]	310	9.32 (-4.06 to 22.88)	35.82 (25 to 41)	34.43 (25 to 39)
Placebo	2698	Reference	39.80 (37 to 41)	37.85 (35 to 39)

Classes ordered by mean rank for females (rank=1 indicates highest efficacy)
Effects with 95% CrI crossing the no effect line and respective classes are shown in red. CrI: credible intervals

Bias-adjusted analysis

Figure 6. NMA treatment efficacy in people with mild to moderate acne: bias-adjusted forest plots, treatment class effects vs placebo



All treatment class effects versus placebo (N=2698). Results expressed as mean difference in % change from baseline; values on the right side of vertical axis indicate higher effect compared with placebo.

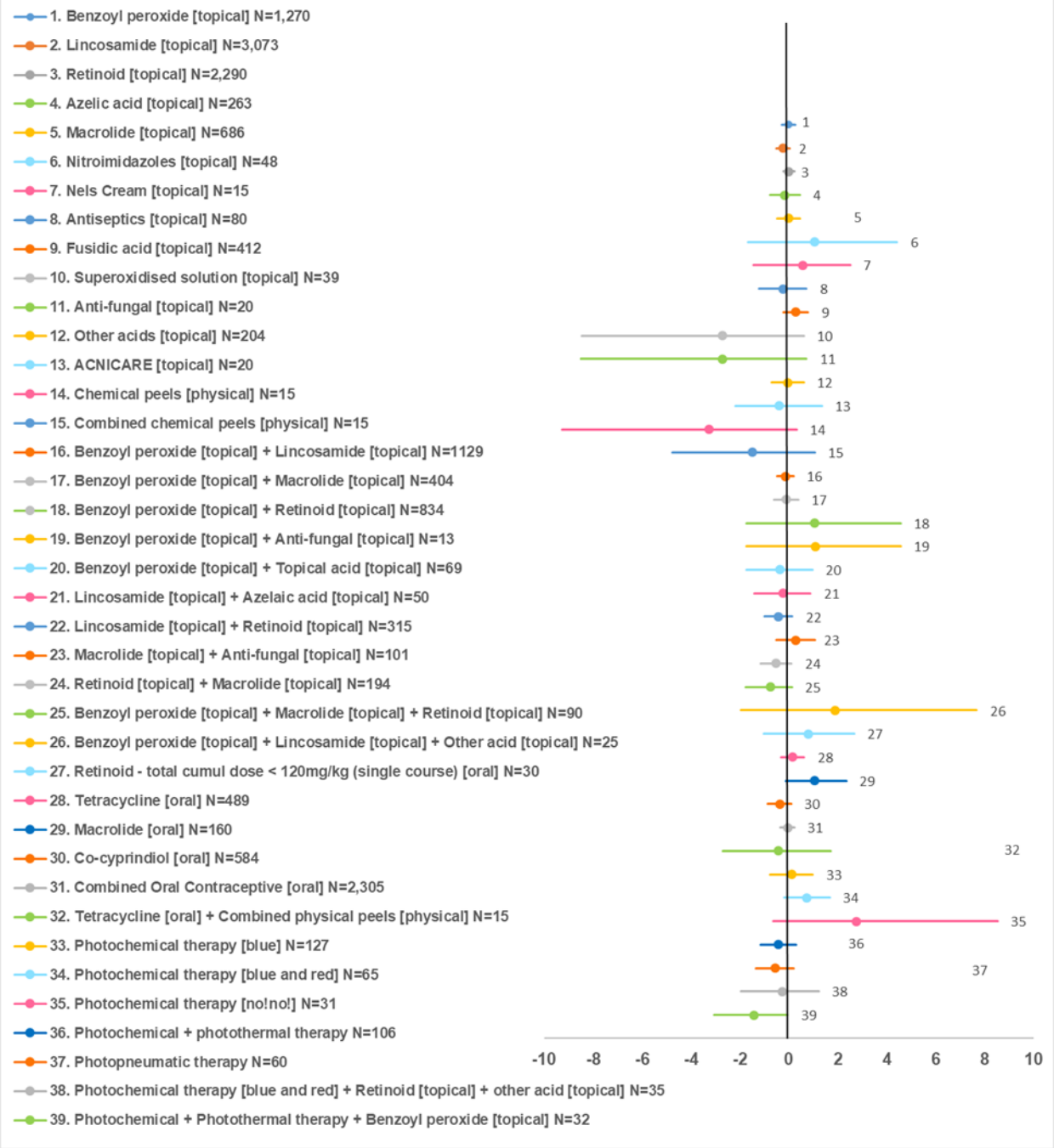
Table 9. NMA treatment efficacy in people with mild to moderate acne: bias-adjusted treatment class effects vs placebo & rankings

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 to 135.70)	2.73 (1 to 10)	2.72 (1 to 10)
Photothermal + photodynamic therapy	9	67.87 (16.51 to 118.00)	4.30 (1 to 22)	4.27 (1 to 22)
Photochemical therapy [red]	28	84.57 (3.34 to 163.80)	4.34 (1 to 35)	4.26 (1 to 33)
Smoothbeam + Photochemical therapy [blue]	24	54.34 (19.99 to 88.78)	5.51 (1 to 20)	5.49 (1 to 20)
Chemical peels [physical]	101	39.70 (12.54 to 66.78)	9.23 (2 to 28)	9.18 (2 to 27)
Photochemical therapy [blue and red]	69	35.36 (17.75 to 53.08)	10.05 (4 to 21)	10.03 (4 to 21)
Benzoyl peroxide [topical] + Lincosamide [topical] + Other acid [topical]	24	32.37 (11.97 to 52.76)	12.13 (4 to 28)	12.06 (4 to 28)
Retinoid [topical] + Hydrogen Peroxide [topical]	26	32.16 (11.94 to 52.16)	12.27 (4 to 29)	12.20 (4 to 28)
Azelaic acid [topical] + Lincosamide [topical]	44	30.24 (10.97 to 49.54)	13.38 (4 to 29)	13.29 (4 to 29)
Superoxidised solution [topical]	39	31.07 (3.94 to 58.38)	13.93 (3 to 35)	13.76 (3 to 34)
Photodynamic therapy	36	33.95 (-9.34 to 75.64)	14.03 (3 to 39)	13.74 (3 to 37)
Photochemical therapy [blue]	138	28.58 (12.55 to 44.72)	14.14 (6 to 27)	14.06 (6 to 26)
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	29	29.37 (6.81 to 52.22)	14.38 (4 to 33)	14.24 (4 to 32)
Benzoyl peroxide [topical] + Retinoid [topical]	1057	26.16 (16.75 to 35.36)	15.44 (8 to 24)	15.39 (8 to 24)
Azelaic acid [topical] + Macrolide [topical]	40	25.92 (7.96 to 43.87)	16.31 (6 to 32)	16.16 (6 to 31)
Lincosamide [topical] + Retinoid [topical]	276	24.23 (10.84 to 37.51)	17.22 (8 to 29)	17.08 (8 to 28)
No treatment	39	29.88 (-36.27 to 93.56)	17.83 (2 to 41)	17.28 (2 to 39)
Macrolide [topical] + Anti-fungal [topical]	74	22.77 (0.74 to 44.65)	19.18 (5 to 37)	18.85 (5 to 35)
Benzoyl peroxide [topical] + Macrolide [topical]	351	20.14 (1.44 to 38.73)	21.00 (8 to 35)	20.62 (8 to 34)
Retinoid [topical] + Other acid [topical] + Photochemical therapy [blue and red]	35	20.26 (-5.28 to 45.98)	21.49 (6 to 39)	21.00 (6 to 38)
Lincosamide [topical] + Other acid [topical]	23	18.67 (-4.10 to 41.07)	22.61 (7 to 39)	22.09 (7 to 37)
Retinoid [topical]	1623	18.27 (10.28 to 26.14)	22.71 (15 to 31)	22.43 (15 to 30)
Photochemical + photothermal therapy	107	18.42 (-21.39 to 56.29)	23.02 (5 to 41)	22.34 (5 to 39)
Benzoyl peroxide [topical] + Lincosamide [topical]	992	17.91 (8.01 to 27.73)	23.14 (15 to 32)	22.80 (15 to 31)
Tetracycline [oral] + Combined chemical peels [physical]	13	16.44 (-10.96 to 43.82)	24.17 (6 to 40)	23.49 (6 to 38)
Combined chemical peels [physical]	14	16.06 (-11.37 to 43.40)	24.49 (6 to 40)	23.78 (6 to 38)
Retinoid [topical] + Macrolide [topical]	135	16.19 (-3.65 to 35.89)	24.67 (9 to 39)	24.05 (9 to 37)
Benzoyl peroxide [topical]	1109	15.60 (6.02 to 25.11)	25.53 (18 to 33)	25.04 (18 to 32)
Antiseptics [topical]	30	13.41 (-9.20 to 36.05)	26.94 (9 to 40)	26.12 (9 to 38)
Other acid [topical]	106	12.28 (-3.38 to 28.30)	28.27 (14 to 39)	27.42 (13 to 37)
Retinoid - total cumulative dose < 120mg/kg (single course) [oral]	54	11.40 (-12.13 to 34.87)	28.50 (10 to 41)	27.56 (10 to 39)
Macrolide [topical]	765	11.71 (1.50 to 21.87)	29.19 (20 to 36)	28.34 (20 to 35)
Co-cyprindiol [oral]	584	10.49 (-5.10 to 26.01)	29.65 (14 to 40)	Not relevant
Combined Oral Contraceptive [oral]	2313	10.18 (-0.47 to 20.85)	30.36 (19 to 38)	Not relevant
Tetracycline [oral]	388	9.41 (-10.54 to 29.32)	30.54 (15 to 40)	29.48 (15 to 38)
Azelaic acid [topical]	301	9.54 (-1.83 to 20.59)	31.15 (22 to 38)	30.08 (21 to 37)
Macrolide [oral]	618	3.54 (-24.34 to 31.38)	33.35 (13 to 41)	32.00 (13 to 39)
Lincosamide [topical]	3073	6.28 (-1.67 to 14.18)	34.02 (27 to 39)	32.59 (26 to 37)
Anti-fungal [topical]	20	-7.12 (-51.55 to 37.13)	35.37 (8 to 41)	33.81 (8 to 39)
Fusidic acid [topical]	310	0.34 (-15.84 to 16.89)	36.65 (25 to 41)	34.97 (25 to 39)
Placebo	2698	Reference	37.80 (33 to 41)	35.93 (31 to 39)

Classes ordered by mean rank for females (rank=1 indicates highest efficacy)
Effects with 95% CrI crossing the no effect line and respective classes are shown in red. CrI: credible intervals

Acceptability: treatment discontinuation for any reason

Figure 7. NMA treatment discontinuation for any reason in people with mild to moderate acne: base-case forest plots, treatment class effects vs placebo



All treatment class effects versus placebo (N=2893). Results expressed as log-odds ratios; values on the left side of vertical axis indicate lower discontinuation for any reason compared with placebo.

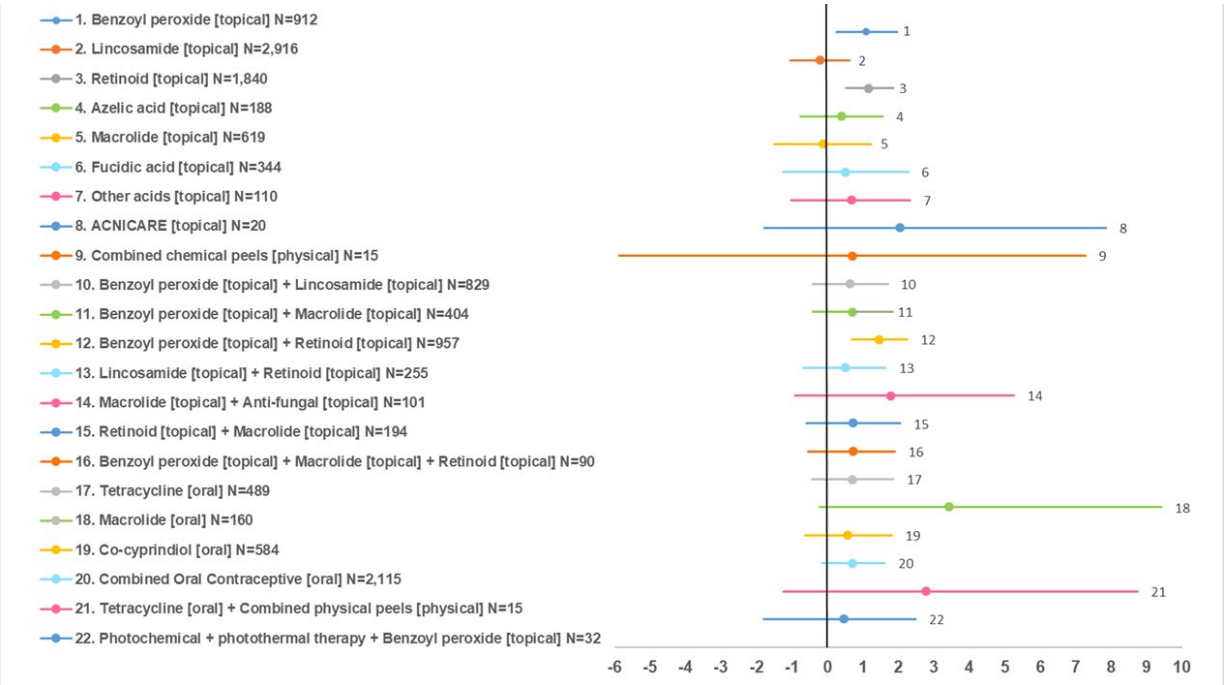
Table 10. NMA treatment discontinuation for any reason in people with mild to moderate acne: base-case treatment class effects vs placebo & rankings

Class	N	logOR vs placebo (mean, 95% CrI)	Rank, females (mean, 95% CrI)	Rank, males (mean, 95% CrI)
Chemical peel [physical]	15	-3.27 (-9.28 to 0.32)	4.25 (1 to 31)	4.13 (1 to 29)
Superoxidised solution [topical]	39	-2.72 (-8.47 to 0.60)	5.85 (1 to 34)	5.65 (1 to 32)
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	32	-1.44 (-3.05 to -0.05)	6.00 (1 to 22)	5.88 (1 to 20)
Anti-fungal [topical]	20	-2.72 (-8.50 to 0.72)	6.05 (1 to 35)	5.84 (1 to 33)
Combined chemical peels [physical]	15	-1.49 (-4.78 to 1.07)	9.39 (1 to 36)	9.01 (1 to 34)
Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical]	90	-0.76 (-1.77 to 0.13)	10.13 (3 to 28)	9.81 (3 to 26)
Photopneumatic therapy	60	-0.58 (-1.36 to 0.18)	12.00 (4 to 30)	11.56 (4 to 28)
Retinoid [topical] + Macrolide [topical]	194	-0.53 (-1.17 to 0.11)	12.05 (5 to 26)	11.59 (5 to 24)
Lincosamide [topical] + Retinoid [topical]	315	-0.42 (-1.00 to 0.14)	13.78 (6 to 28)	13.19 (6 to 27)
Photochemical + photothermal therapy	106	-0.44 (-1.17 to 0.28)	14.18 (5 to 31)	13.57 (5 to 29)
Co-cyprindiol [oral]	584	-0.38 (-0.86 to 0.09)	14.39 (6 to 28)	Not relevant
Lincosamide [topical]	3073	-0.25 (-0.51 to 0.02)	16.67 (10 to 25)	15.81 (10 to 23)
Benzoyl peroxide [topical] + Topical acid [topical]	69	-0.36 (-1.73 to 0.97)	17.04 (3 to 36)	16.19 (3 to 34)
ACNICARE [physical]	20	-0.39 (-2.21 to 1.34)	17.26 (3 to 38)	16.41 (3 to 36)
Tetracycline [oral] + Combined chemical peels [physical]	15	-0.42 (-2.72 to 1.72)	17.56 (2 to 38)	16.69 (2 to 36)
Antiseptics [topical]	80	-0.25 (-1.23 to 0.72)	18.30 (5 to 35)	17.35 (5 to 33)
Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red]	35	-0.27 (-1.96 to 1.23)	18.83 (3 to 37)	17.85 (3 to 35)
Lincosamide [topical] + Azelaic acid [topical]	50	-0.23 (-1.40 to 0.88)	18.87 (4 to 36)	17.88 (4 to 34)
Benzoyl peroxide [topical] + Lincosamide [topical]	1129	-0.16 (-0.49 to 0.18)	19.48 (11 to 29)	18.37 (11 to 28)
Benzoyl peroxide [topical] + Retinoid [topical]	834	-0.15 (-0.45 to 0.15)	19.51 (11 to 29)	18.38 (11 to 27)
Azelaic acid [topical]	263	-0.16 (-0.78 to 0.44)	19.61 (8 to 33)	18.52 (7 to 31)
Benzoyl peroxide [topical] + Macrolide [topical]	404	-0.12 (-0.61 to 0.38)	20.56 (10 to 32)	19.36 (10 to 30)
Combined Oral Contraceptive [oral]	2305	-0.06 (-0.35 to 0.23)	22.28 (13 to 32)	Not relevant
Topical acid [topical]	204	-0.04 (-0.69 to 0.60)	22.44 (8 to 35)	21.12 (8 to 33)
Macrolide [topical]	686	-0.02 (-0.47 to 0.44)	23.20 (12 to 32)	21.77 (11 to 31)
Benzoyl peroxide [topical]	1270	-0.01 (-0.29 to 0.26)	23.70 (15 to 31)	22.20 (15 to 29)
Retinoid [topical]	2290	0.00 (-0.23 to 0.22)	24.24 (16 to 31)	22.70 (15 to 30)
Placebo	2893	Reference	24.40 (18 to 31)	22.80 (16 to 29)
Photochemical therapy [blue]	127	0.11 (-0.77 to 0.98)	25.15 (8 to 36)	23.67 (8 to 34)
Tetracycline [oral]	489	0.16 (-0.31 to 0.63)	27.67 (16 to 35)	25.94 (15 to 33)
Macrolide [topical] + Anti-fungal [topical]	101	0.26 (-0.53 to 1.06)	28.28 (11 to 37)	26.60 (11 to 35)
Nels Cream [topical]	15	0.56 (-1.45 to 2.50)	28.66 (4 to 39)	27.09 (4 to 37)
Fusidic acid [topical]	412	0.27 (-0.24 to 0.77)	29.64 (18 to 36)	27.81 (17 to 34)
Nitroimidazoles [topical]	48	1.03 (-1.68 to 4.42)	30.12 (4 to 40)	28.52 (4 to 38)
Benzoyl peroxide [topical] + Anti-fungal [topical]	13	1.08 (-1.75 to 4.58)	30.20 (4 to 40)	28.60 (4 to 38)
Retinoid - total cumulative dose < 120mg/kg (single course) [oral]	30	0.78 (-1.03 to 2.68)	30.95 (6 to 40)	29.25 (6 to 38)
Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical]	25	1.88 (-1.95 to 7.68)	31.93 (3 to 40)	30.28 (3 to 38)
Photochemical therapy [blue and red]	65	0.73 (-0.19 to 1.66)	33.67 (19 to 39)	31.74 (18 to 37)
Macrolide [oral]	160	1.06 (-0.13 to 2.35)	35.24 (21 to 40)	33.29 (20 to 38)
Photochemical therapy [no!no!]	31	2.74 (-0.65 to 8.54)	36.47 (10 to 40)	34.58 (9 to 38)

Classes ordered by mean rank for females (rank=1 indicates lowest risk of discontinuation for any reason)
Effects with 95% CrI NOT crossing the no effect line and respective classes are shown in red.
CrI: credible intervals; OR: odds ratio

Tolerability: treatment discontinuation due to side effects

Figure 8. NMA treatment discontinuation due to side effects in people with mild to moderate acne: base-case forest plots, treatment class effects vs placebo



All treatment class effects versus placebo (N=2024). Results expressed as log-odds ratios; values on the left side of vertical axis indicate lower discontinuation due to side effects compared with placebo.

Table 11. NMA treatment discontinuation due to side effects in people with mild to moderate acne: base-case treatment class effects vs placebo & rankings

Class	N	logOR vs placebo (mean, 95% CrI)	Rank, females (mean, 95% CrI)	Rank, males (mean, 95% CrI)
Lincosamide [topical]	2916	-0.22 (-1.05 to 0.63)	3.97 (1 to 10)	3.76 (1 to 9)
Placebo	2024	Reference	5.19 (1 to 11)	4.96 (1 to 10)
Macrolide [topical]	619	-0.12 (-1.49 to 1.23)	5.19 (1 to 15)	4.80 (1 to 14)
Azelaic acid [topical]	188	0.39 (-0.77 to 1.56)	8.93 (1 to 20)	8.18 (1 to 18)
Lincosamide [topical] + Retinoid [topical]	255	0.51 (-0.68 to 1.64)	9.86 (2 to 19)	8.99 (2 to 17)
Fusidic acid [topical]	344	0.50 (-1.25 to 2.28)	10.01 (1 to 21)	9.12 (1 to 19)
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	32	0.46 (-1.80 to 2.48)	10.04 (1 to 22)	9.14 (1 to 20)
Co-cyprindiol [oral]	584	0.58 (-0.63 to 1.81)	10.54 (1 to 21)	Not relevant
Benzoyl peroxide [topical] + Lincosamide [topical]	829	0.63 (-0.41 to 1.70)	11.03 (3 to 20)	10.04 (3 to 18)
Topical acid [topical]	110	0.68 (-1.01 to 2.33)	11.38 (1 to 22)	10.34 (1 to 20)
Combined chemical peels [physical]	15	0.70 (-5.88 to 7.27)	11.41 (1 to 23)	10.39 (1 to 21)
Tetracycline [oral]	489	0.71 (-0.43 to 1.86)	11.48 (4 to 19)	10.42 (3 to 17)
Benzoyl peroxide [topical] + Macrolide [topical]	404	0.71 (-0.41 to 1.83)	11.52 (4 to 19)	10.45 (3 to 17)
Combined Oral Contraceptive [oral]	2115	0.70 (-0.15 to 1.63)	11.65 (3 to 20)	Not relevant
Retinoid [topical] + Macrolide [topical]	194	0.73 (-0.59 to 2.06)	11.79 (2 to 21)	10.71 (2 to 19)
Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical]	90	0.73 (-0.55 to 1.91)	11.82 (2 to 21)	10.72 (2 to 19)
Benzoyl peroxide [topical]	912	1.11 (0.25 to 1.96)	15.52 (9 to 20)	14.03 (8 to 19)
ACNICARE [physical]	20	2.03 (-1.78 to 7.85)	15.58 (1 to 23)	14.18 (1 to 21)
Retinoid [topical]	1840	1.16 (0.51 to 1.85)	15.98 (10 to 21)	14.39 (9 to 19)
Macrolide [topical] + Anti-fungal [topical]	101	1.78 (-0.91 to 5.26)	16.51 (2 to 23)	15.00 (2 to 21)
Tetracycline [oral] + Combined chemical peels [physical]	15	2.77 (-1.25 to 8.75)	18.16 (2 to 23)	16.54 (2 to 21)
Benzoyl peroxide [topical] + Retinoid [topical]	957	1.46 (0.69 to 2.26)	18.34 (12 to 22)	16.56 (11 to 20)
Macrolide [oral]	160	3.43 (-0.23 to 9.42)	20.09 (4 to 23)	18.28 (4 to 21)

Classes ordered by mean rank for females (rank=1 indicates lowest risk of discontinuation due to side effects)
Effects with 95% CrI NOT crossing the no effect line and respective classes are shown in red.
CrI: credible intervals; OR: odds ratio

Appendix F – GRADE tables

GRADE tables for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

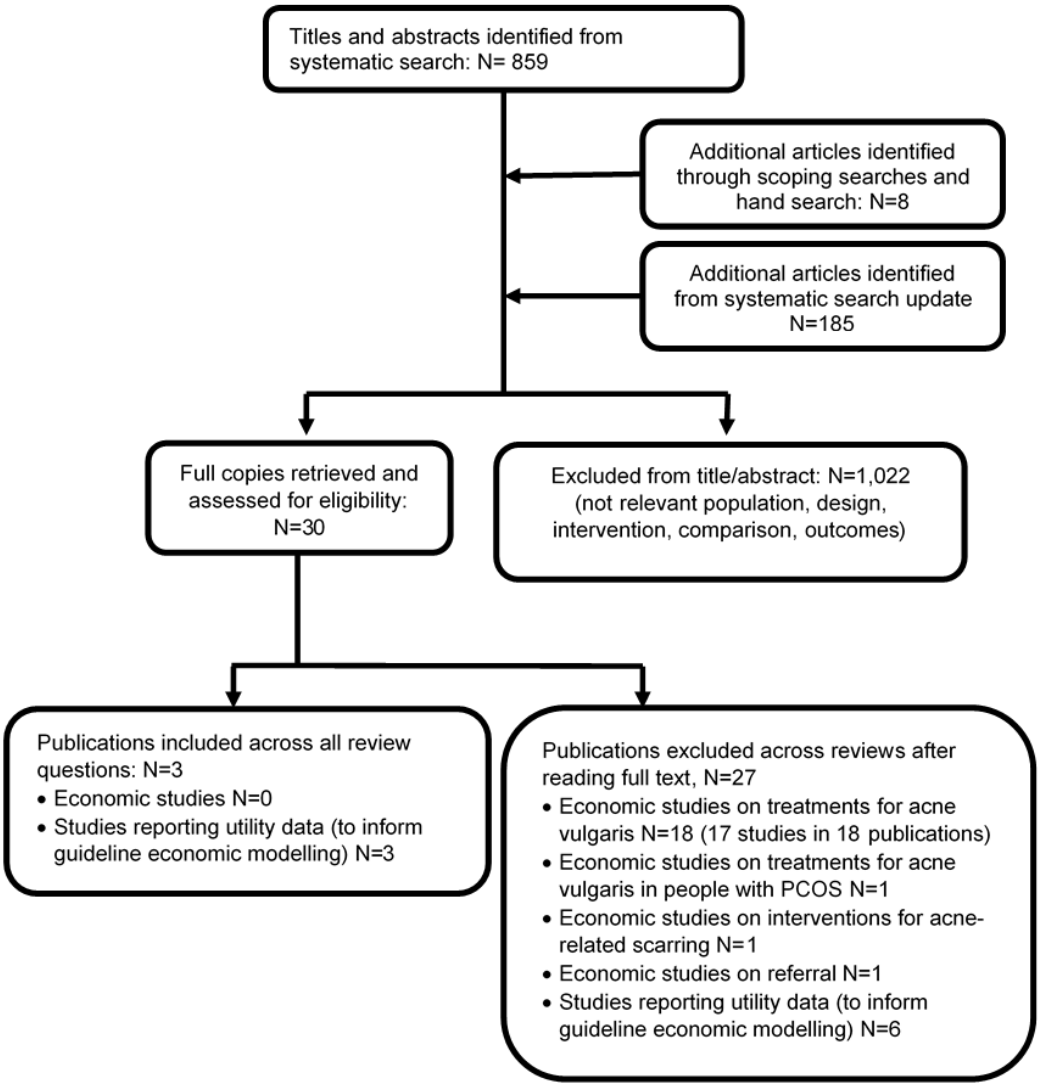
GRADE was not undertaken for this review question. Instead, threshold analysis was conducted as an alternative to GRADE, to test the robustness of treatment recommendations based on the NMA, to potential biases or sampling variation in the included evidence. Methods and results of threshold analysis are presented in appendix N.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

A global health economics search was undertaken for all areas covered in the guideline. Figure 9 shows the flow diagram of the selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data.

Figure 9. Flow diagram of selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data



Appendix H – Economic evidence tables

Economic evidence tables for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profile for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Table 12: Economic evidence profile for topical, oral and physical treatments for people with mild to moderate acne vulgaris

Economic evidence profile: topical, oral and physical treatments for people with mild to moderate acne vulgaris							
Study & country	**Limitations**	**Applicability**	**Other comment**	**Incremental cost vs GP care[1]**	**Incremental QALY vs GP care**	**NMB (£)[1]**	**Uncertainty[1]**
Guideline economic analysis UK	Minor limitations [2]	Partially applicable[3]	Outcome: QALY Data taken from bias-adjusted NMA on efficacy Step-wise approach: most cost-effective treatment is omitted at each step & prob of cost-effectiveness of next most cost-effective treatment is re-calculated	ADAP top £24 BPO top -£1 ERYTH top £18 BPO+ADAP top £25 BPO+CLIND top £27 BPO+ERYTH top £22 CLIND+TRET top £17 AZEL+CLIND top £14 AZEL+ERYTH top £21 ERYTH+BIF top £30 SAL peel £520 PCT blue £372 PCT blue & red £330	ADAP top 0.014 BPO top 0.012 ERYTH top 0.009 BPO+ADAP top 0.022 BPO+CLIND top 0.014 BPO+ERYTH top 0.017 CLIND+TRET top 0.021 AZEL+CLIND top 0.029 AZEL+ERYTH top 0.023 ERYTH+BIF top 0.020 SAL peel 0.042 PCT blue 0.030 PCT blue&red 0.040	AZEL+CLIND top £17,262 AZEL+CLIND top £17,262 PCT blue & red £17,162 AZEL+ERYTH top £17,149 BPO+ADAP top £17,124 CLIND+TRET top £17,104 ERYTH+BIF top £17,062 SAL peel £17,027 BPO+ERYTH top £17,016 ADAP top £16,956 BPO+CLIND top £16,955 BPO top £16,936 PCT blue £16,930 ERYTH top £16,858 GP care £16,701	Prob of cost effectiveness at WTP £20,000 /QALY (step-wise approach): AZEL + CLIND top 0.31; PCT blue & red 0.19; AZEL + ERYTH top 0.23; BPO + ADAP top 0.18; CLIND + TRET top 0.25; ERYTH + BIF top 0.29; SAL peel 0.36; BPO + ERYTH top 0.39; ADAP top 0.24; BPO + CLIND top 0.36; BPO top 0.45; PCT blue 0.55; ERYTH top 0.97; GP care 1.00

1. Costs expressed in 2019 GBP
2. Decision-analytic model (decision-tree); time horizon 1 year; relative effects based on guideline systematic review and NMA; baseline effects & other clinical input parameters derived from published literature and the committee's expert advice; resource use based on RCT data & other published literature supplemented by the committee's expert advice; national unit costs used; PSA conducted; CEAF presented
3. UK study; NHS & PSS perspective; QALY estimates based on the committee's expert opinion due to lack of relevant data of adequate quality
ADAP: adapalene; AZEL: azelaic acid; BIF: bifonazole; BPO: benzoyl peroxide; CLIND: clindamycin; ERYTH: erythromycin; PCT: photochemical therapy; prob: probability; SAL: salicylic acid; top: topical; TRET: tretinoin; WTP: willingness to pay

Appendix J – Economic analysis

Economic analysis for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Introduction – objective of economic modelling

The choice of treatment for people with mild to moderate acne was identified by the committee and the guideline health economist as an area with potentially major resource implications. The review of economic evidence identified no studies meeting inclusion criteria that could inform recommendations; however, there is a solid clinical evidence base that can inform primary economic modelling. An economic model was therefore developed to assess the relative cost effectiveness of treatments for people with mild to moderate acne in England.

Economic modelling methods

Population

The study population of the economic model comprised people with mild to moderate acne who present to primary care services, although they may be subsequently referred to a specialist dermatology setting.

Separate analyses were undertaken for males and females, in order to consider only suitable interventions for each sex (i.e. hormonal contraceptives were included only in analysis for females).

Interventions assessed

The range of treatments assessed in the economic analysis was determined by the availability of relevant clinical data included in the guideline systematic review of topical, oral and physical treatments for people with mild to moderate acne. Network meta-analysis (NMA) was employed for synthesis of the available efficacy data. Details of the NMA are provided in appendix M.

Based on the advice of the committee, only treatment classes with evidence of effect versus placebo with at least 40 observations each across the RCTs included in the NMA of efficacy were considered in the economic analysis, as this was deemed as the minimum amount of evidence that could suggest that a treatment may be effective and potentially cost-effective. A treatment class demonstrated evidence of effect if the 95% credible intervals [CrI] of its effect versus placebo did not cross the line of no effect.

One intervention was selected as a representative from each treatment class; this was necessary only for costing purposes, as there was no adequate evidence to estimate individual treatment effects within each treatment class. The criteria for selecting interventions to represent each treatment class were the intervention availability and usage in the UK and other practicalities of use (e.g. a combination of topical treatments available in a single formulation was preferred to combinations that are only available as separate formulations); the evidence base for each intervention within class; the risk of side effects of individual interventions within a class; and, for pharmacological treatments, the drug acquisition cost (drugs with lower acquisition costs were preferred).

Based on the above criteria, the following treatment classes and interventions were considered in the base-case economic analysis of treatments for people with mild to moderate acne:

- Topical retinoids: adapalene
- Benzoyl peroxide (topical treatment, own class)
- Azelaic acid (topical treatment, own class)
- Other acids: topical salicylic acid
- Topical lincosamides: topical clindamycin
- Topical macrolides: topical erythromycin
- Benzoyl peroxide + topical retinoid (adapalene)
- Benzoyl peroxide + topical lincosamide (clindamycin)
- Benzoyl peroxide + topical macrolide (erythromycin)
- Topical retinoid (tretinoin) + topical lincosamide (clindamycin)
- Topical retinoid (tretinoin) + topical macrolide (erythromycin)
- Azelaic acid + topical lincosamide (clindamycin)
- Azelaic acid + topical macrolide (erythromycin)
- Topical macrolide (erythromycin) + topical anti-fungal (bifonazole)
- Oral isotretinoin - total cumulative dose < 120mg/kg (single course)
- Combined oral contraceptive: ethinylestradiol + norgestimate
- Chemical peels: salicylic acid peel
- Photochemical therapy (blue light)
- Photochemical therapy (blue and red light)
- Photochemical and photothermal therapy
- GP care, comprising GP consultations without provision of any pharmacological or physical treatment, reflecting the placebo node of the network.

However, a bias-adjusted NMA on the efficacy outcome suggested evidence of bias; following bias-adjustment, a number of treatment classes did not show evidence of effect versus placebo anymore. Therefore, a bias-adjusted economic analysis was conducted, which utilised efficacy data from the respective bias-adjusted NMA and included the following treatment classes and interventions that retained evidence of effect versus placebo following bias-adjustment:

- Topical retinoids: adapalene
- Benzoyl peroxide (topical treatment, own class)
- Topical macrolides: topical erythromycin
- Benzoyl peroxide + topical retinoid (adapalene)
- Benzoyl peroxide + topical lincosamide (clindamycin)
- Benzoyl peroxide + topical macrolide (erythromycin)
- Topical retinoid (tretinoin) + topical lincosamide (clindamycin)
- Azelaic acid + topical lincosamide (clindamycin)
- Azelaic acid + topical macrolide (erythromycin)
- Topical macrolide (erythromycin) + topical anti-fungal (bifonazole)
- Chemical peels: salicylic acid peel
- Photochemical therapy (blue light)
- GP care (reflecting placebo).

Model structure

A decision-analytic model in the form of a decision-tree was constructed using Microsoft Office Excel 2016. The model estimated the total costs and benefits associated with provision of effective treatment options for people with mild to moderate acne. The structure of the model, which aimed to simulate the course of acne and relevant clinical practice in the UK, was also driven by the availability of clinical data.

According to the model structure, hypothetical cohorts of people with mild to moderate acne were initiated on each of the treatment options assessed and followed for one year (52 weeks). People within each cohort might receive a full course of treatment, or they might discontinue treatment due to intolerable side effects or any other reason. Those who discontinued received 'average acne care', comprising a mixture of care that is anticipated to be currently received by people with acne in the NHS. Following treatment, people in each cohort experienced a percentage change in their total acne lesion count (between start and end of treatment), which, for every person in each cohort, corresponded to a level of perceived acne symptom improvement: 'excellent', 'good', 'moderate' or no improvement. By the end of one year, those who experienced excellent, good or moderate improvement might relapse and return to their initial state of mild to moderate acne, otherwise they remained at the same level of improvement. Those who experienced no improvement remained in the state of no improvement until the model endpoint.

Treatment effects (i.e. % change in total acne lesion count from baseline, % CFB) that informed the model were obtained, where possible, from intention to treat (ITT) analysis reported in relevant RCTs for each treatment, usually with last observation carried forward (LOCF). This means that, for every treatment option, the model utilised data on effects that were applicable to all people in the cohort initiating this particular treatment option, whether they completed a full course of treatment or not. Therefore, in each cohort, treatment efficacy (% CFB) and associated 'acne symptom status' (i.e. excellent, good, moderate or no improvement) at end of treatment was independent of 'treatment status' (i.e. completion of a full course of treatment or early discontinuation) and therefore these two parameters were modelled separately.

A full course of any drug treatment considered in the model other than oral isotretinoin, and also a full course of a 'GP care' lasted 3 months (13 weeks). Acne symptom status at end of these treatment options was measured at this point. People who completed a full course of any of these treatments and who experienced excellent or good improvement received another 3 months (13 weeks) of their initial treatment as maintenance, i.e. between 3 and 6 months in the model. Those who completed a full course of treatment but experienced moderate improvement either continued their initial treatment as maintenance (33%), or moved to average acne care (66%) for the next 3 months (13 weeks, 3-6 months in the model). 'Average acne care' comprises a mixture of care that is anticipated to be currently received by people with acne in the NHS. Those who completed a full course of treatment but experienced no improvement moved to 'average acne care' between 3 and 6 months in the model (13 weeks). All people were assumed to retain their acne status achieved at the end of treatment (i.e. at 3 months) between 3 and 6 months in the model.

A full course of oral isotretinoin lasted 6 months (26 weeks). Acne symptom status at end of treatment with oral isotretinoin was measured at this point. People who completed a full course of oral isotretinoin did not receive further maintenance treatment.

A full course of chemical peels (physical treatment) lasted 3 months (13 weeks). Acne symptom status at end of treatment with chemical peels was measured at this point. People who completed a full course of chemical peels received average acne care between 3 and 6 months in the model, either as maintenance treatment (if initial treatment was successful) or as alternative treatment (if initial treatment was not successful). All people were assumed to retain their acne status achieved at the end of treatment (i.e. at 3 months) between 3 and 6 months in the model.

A full course of any light therapy (physical treatments) was assumed to last approximately 2 months (8 weeks). Acne symptom status at the end of light therapy was measured at this point. People who completed a full course of light therapy received average acne care between 2 and 6 months in the model, either as maintenance treatment (if initial treatment was successful) or as alternative treatment (if initial treatment was not successful). All people were assumed to retain their acne status achieved at the end of treatment (i.e. at 2 months) between 2 and 6 months in the model.

Treatment discontinuation was assumed to occur after 25% of the time of a full course of treatment (i.e. at 6.5 weeks if they were initiated on oral isotretinoin, at 3 weeks if they were initiated on any other pharmacological treatment option or chemical peels or GP care, and 2 weeks if they were initiated on light therapy). From the point of treatment discontinuation and up to 6 months in the model, they were assumed to receive average acne care.

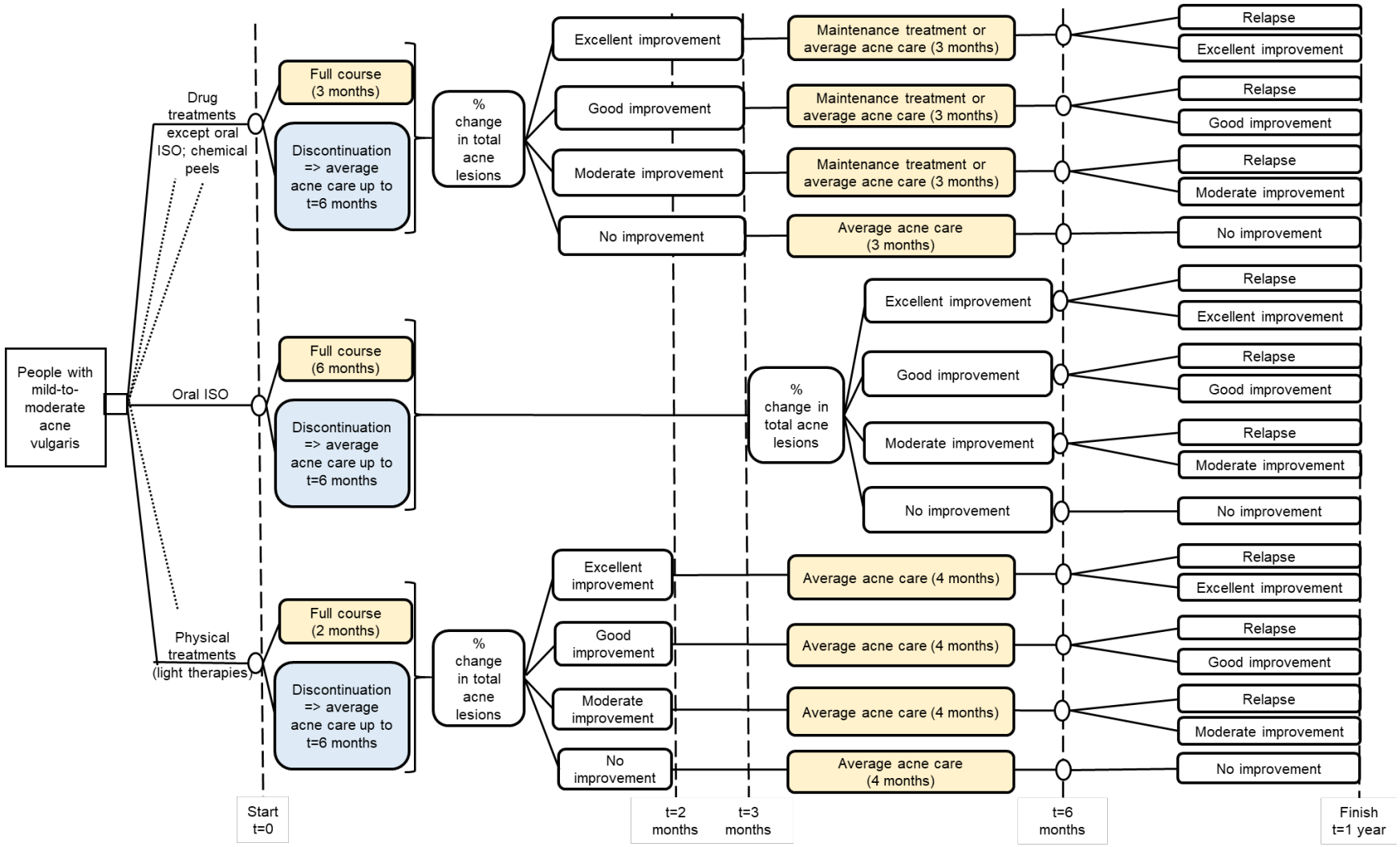
During the last 6 months (26 weeks) of the model, 70% of people who relapsed after excellent or good improvement, 70% of people with moderate improvement (regardless of whether they relapse or not) and 70% of people with no improvement received average acne care. For people with excellent or good improvement who received average acne care only if they relapsed, average acne care costs were applied only over 3 months within this period, as relapse was assumed to occur on average in the middle of the 6-month period. For people with moderate or no improvement who received average acne care during this period, average acne care costs were applied over the whole period of the last 6 months in the model.

People who discontinued treatment due to intolerable side effects experienced a reduction in their health-related quality of life (HRQoL), assumed to last over the period they received treatment and up to the point of discontinuation, plus 2 weeks after treatment discontinuation.

The one-year time horizon of the analysis was considered to be long enough to capture longer-term costs and effects of treatment, beyond treatment endpoint, without significant extrapolation and assumptions around the course of mild to moderate acne.

The structure of the economic model for treatments for people with mild to moderate acne is shown in Figure 10.

Figure 10. Schematic diagram of the economic model structure: interventions for the treatment of people with mild to moderate acne



Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and personal social services (PSS), as recommended by NICE (NICE, 2014). Costs consisted of intervention costs (healthcare professional time including follow-up, drug acquisition, laboratory testing and procedures related to physical interventions, as relevant), and costs incurred by people with acne who discontinued treatment before completion of a course, those who did not respond adequately to treatment, and those who relapsed following treatment. The cost year was 2019.

The measure of outcome was the Quality Adjusted Life Year (QALY), which incorporated utilities associated with the levels of acne improvement following treatment, as well as utility decrements due to intolerable side effects of treatment (that led to early discontinuation). The likelihood of a person having excellent or good improvement at the end of the model (i.e. at 1 year after treatment initiation) was a secondary outcome.

Relative effects on efficacy, acceptability and tolerability and methods of evidence synthesis

Relative effects on efficacy (expressed as difference in % CFB of total lesion count between pairs of treatments), acceptability (discontinuation for any reason, expressed in the form of log-odds ratios [LORs] between pairs of treatments) and tolerability (discontinuation due to intolerable side effects, also expressed in the form of LORs between pairs of treatments) for all treatment classes considered in the economic modelling were derived from the respective NMAs of treatments for people with mild to moderate acne that were undertaken for this guideline. Details on the methods and results of the NMAs, which were conducted in WinBUGS 1.4.3 (Lunn 2000; Spiegelhalter 2003) for discontinuation data and OpenBUGS 3.2.3 (https://www.openbugs.net) for efficacy data are provided in appendix M. For the economic analysis the first 100,000 iterations undertaken in WinBUGS were discarded and another 300,000 were run, thinned by 30, so as to obtain 10,000 iterations that populated the economic model.

Relative effects were combined with respective ‘baseline’ absolute effect data for each outcome, in order to estimate the absolute effects (absolute % CFB of total lesion count and absolute risks of discontinuation for any reason and due to side effects) of each treatment class in people with mild to moderate acne. Topical retinoids (adapalene) was the treatment selected to serve as baseline, as explained in the next section.

For some treatment classes considered in the economic analysis, relative effects on discontinuation (for any reason and/or due to side effects) were not available. In such cases, the class ‘borrowed’ the relative effect of another class of a similar type and with an anticipated similar effect. For some classes with no relevant data for which a similar type of class was not available (i.e. oral isotretinoin and light therapies for the outcome of discontinuation due to side effects), the estimated average absolute risk of discontinuation due to side effects of all treatments included in the economic analysis was used.

For all three outcomes, NMA models which adjusted for bias in the included evidence were fitted (details are provided in appendix M). According to these analyses, there was no indication of bias for the outcomes of discontinuation for any reason and discontinuation due to side effects. However, for the outcome of efficacy, evidence of small-study bias was identified. Bias-adjusted efficacy data derived from these models were therefore utilised in a bias-adjusted economic analysis. This analysis, as explained above, included only treatment classes that retained evidence of effect versus placebo following bias-adjustment.

The results of the NMAs that were used to populate the economic model for people with mild to moderate acne are provided in Table 13.

Table 13. Results of the guideline NMA utilised in the economic analysis: efficacy, discontinuation for any reason and discontinuation due to side effects of all treatments versus topical retinoids (adapalene) in people with mild to moderate acne

Treatment class and intervention	Relative effects versus topical retinoids (adapalene) [mean, 95% CrI]			
	Efficacy (difference in % CFB): base-case analysis	Efficacy (difference in % CFB): bias-adjusted analysis	Discontinuation for any reason (LOR)	Discontinuation due to side effects (LOR)
GP care	-24.83 (-31.81 to -17.87)	-18.50 (-26.58 to -10.47)	0.00 (-0.23 to 0.23)	-1.16 (-1.86 to -0.51)
Benzoyl peroxide	-1.82 (-10.81 to 7.09)	-2.66 (-11.14 to 5.97)	-0.01 (-0.31 to 0.28)	-0.06 (-0.86 to 0.70)
Azelaic acid	-3.60 (-13.63 to 6.57)	Not considered	-0.16 (-0.77 to 0.46)	-0.78 (-1.98 to 0.41)
Other topical acids: topical salicylic acid	-6.55 (-20.46 to 7.39)	Not considered	-0.04 (-0.73 to 0.64)	-0.49 (-2.25 to 1.23)
Topical lincosamides: topical clindamycin	-12.28 (-21.23 to -3.23)	Not considered	-0.25 (-0.54 to 0.06)	-1.38 (-2.24 to -0.52)
Topical macrolides: topical erythromycin	-4.41 (-14.63 to 5.91)	-6.65 (-16.69 to 3.70)	-0.02 (-0.49 to 0.46)	-1.29 (-2.67 to 0.07)
Benzoyl peroxide + topical retinoid (adapalene)	6.99 (-2.21 to 16.20)	7.86 (-1.26 to 16.50)	-0.14 (-0.46 to 0.16)	0.30 (-0.35 to 0.95)
Benzoyl peroxide + topical lincosamide (clindamycin)	0.39 (-9.57 to 10.34)	-0.40 (-9.71 to 8.98)	-0.16 (-0.50 to 0.20)	-0.53 (-1.52 to 0.46)
Benzoyl peroxide + topical macrolide (erythromycin)	2.39 (-17.13 to 22.13)	1.63 (-16.67 to 19.90)	-0.12 (-0.63 to 0.40)	-0.45 (-1.53 to 0.65)
Topical retinoid (tretinoin) + topical lincosamide (clindamycin)	6.40 (-7.85 to 20.63)	5.91 (-7.28 to 19.09)	-0.42 (-0.99 to 0.15)	-0.66 (-1.78 to 0.38)
Topical retinoid (tretinoin) + topical macrolide (erythromycin)	-1.32 (-22.19 to 19.35)	Not considered	-0.52 (-1.19 to 0.13)	-0.43 (-1.74 to 0.88)
Azelaic acid + topical lincosamide (clindamycin)	14.21 (-6.68 to 34.67)	11.88 (-7.43 to 30.86)	-0.23 (-1.44 to 0.90)	Borrowed from azelaic acid
Azelaic acid + topical macrolide (erythromycin)	11.09 (-7.57 to 30.41)	7.58 (-10.36 to 24.97)	Borrowed from azelaic acid + topical lincosamide	Borrowed from azelaic acid
Topical macrolide (erythromycin) + topical anti-fungal (bifonazole)	6.39 (-17.33 to 29.81)	4.29 (-17.70 to 26.05)	0.27 (-0.54 to 1.06)	0.65 (-2.06 to 4.14)
Oral isotretinoin - total cumulative dose <120mg/kg (single course)	-0.22 (-22.99 to 22.39)	Not considered	0.77 (-1.03 to 2.70)	Absolute risk assumed to be equal to the average risk of all

Treatment class and intervention	Relative effects versus topical retinoids (adapalene) [mean, 95% CrI]			
	Efficacy (difference in % CFB): base-case analysis	Efficacy (difference in % CFB): bias-adjusted analysis	Discontinuation for any reason (LOR)	Discontinuation due to side effects (LOR)
				treatments included in the analysis
Combined oral contraceptive: ethinylestradiol + norgestimate	-9.98 (-22.09 to 2.46)	Not considered	-0.06 (-0.43 to 0.31)	-0.47 (-1.55 to 0.66)
Chemical peels: salicylic acid peel	23.04 (-5.10 to 51.25)	21.44 (-4.93 to 47.82)	-3.28 (-9.30 to 0.31)	Borrowed from combined chemical peels: -0.43 (-7.17 to 6.22)
Photochemical therapy (blue light)	13.31 (-2.49 to 29.21)	10.34 (-5.07 to 26.20)	0.11 (-0.77 to 0.98)	Absolute risk of each class assumed to be equal to the average risk of all treatments included in the analysis
Photochemical therapy (blue and red light)	18.95 (1.18 to 36.89)	17.06 (-0.03 to 34.53)	0.73 (-0.21 to 1.68)	
Photochemical and photothermal therapy	10.82 (-21.47 to 43.94)	Not considered	-0.44 (-1.22 to 0.32)	
Topical retinoid: adapalene	Reference	Reference	Reference	Reference
CFB: change from baseline; CrI: credible intervals; cumul: cumulative; LOR: log-odds ratio				

Baseline parameters in people with mild to moderate acne

'Baseline' (b) absolute effect data for each outcome (i.e. efficacy, discontinuation for any reason and discontinuation due to side effects) need to be combined with respective relative effects obtained from the guideline NMAs in order to estimate absolute effects for every treatment (t) considered in the economic analysis:

$$\text{Absolute effect}_{[t]} = \text{absolute effect}_{[b]} + \text{relative effect}_{[t\text{-}b]}$$

Any treatment included in the NMA can serve as baseline treatment, including placebo (reflecting GP care in the model). The selection of a treatment to serve as baseline depends on the availability of good quality data on its absolute treatment effects. Absolute treatment effects depend on epidemiological and prognostic factors and need to be representative of the study population under conditions of routine care (i.e. of people with mild to moderate acne receiving care in England).

Ideally, baseline absolute treatment effects should be obtained from routinely collected UK data, such as those derived from large naturalistic studies, national surveys or administrative databases, which reflect routine care (rather than trial conditions). If UK data are not available, non-UK data from similar settings regarding the epidemiology of acne and routine clinical practice may be used. Alternatively, if no suitable data are available, absolute effects from one or more RCTs of good quality, with participants and settings that are representative of the model population, could be used (Dias 2011).

Baseline efficacy

Baseline data on efficacy (% CFB) were derived from large RCT trials included in the respective NMA for people with mild to moderate acne, as no relevant observational data were possible to identify. Adapalene 0.1% (topical retinoid) was selected as the baseline treatment, because good quality data from large trials were available, and for consistency purposes with the available baseline discontinuation data, as reported below. Adapalene 0.1% is the most commonly used topical retinoid for acne in England. Weighted RCT data on efficacy were derived from adapalene 0.1% trial arms with treatment duration of 12 to <24 weeks (which is the optimal treatment duration for adapalene), from studies conducted in Europe, North America or Australia that reported ITT data and were included in the guideline NMA. These countries were selected to reflect similar settings and epidemiological data to those in the UK. Following review of the available efficacy data, adapalene arm data from 2 RCTs were synthesised in order to estimate baseline efficacy for people with mild to moderate acne, using the data and approach shown in Table 14, and assuming a log-normal distribution for (100 + % CFB) based on review of % CFB data from a study reporting data from 4,081 people with moderate to severe facial acne that participated in 7 clinical trials of oral contraceptives or topical treatments conducted in Europe (Gerlinger 2008).

Table 14: Baseline efficacy (% change in total lesion count from baseline, CFB) for topical retinoids, estimated from data derived from adapalene 0.1% trial arms with treatment duration of 12 to <24 weeks, included in the NMA of efficacy of treatments for people with mild to moderate acne

Study ID	Country	Observations	% CFB
Gollnick 2009	North America/Europe	418	Median -52.30% (estimated SD 85.52)
Thiboutot 2006	North America	261	Median -48.20% (estimated SD 67.31)
Pooled % CFB*	**% CFB: mean -50.47%; ln (100 + % CFB): 3.90 SE of log-normal distribution of (100 + % CFB): 0.03**		

CFB: change from baseline; SD: standard deviation; SE; standard error of the mean

Study ID	Country	Observations	% CFB

SDs were not reported in the studies; they were imputed using the same methods used for the imputation of SDs in the NMA of efficacy (appendix M).
Available data were synthesised following the observation that (100 + % CFB) has a log-normal distribution, based on review of % CFB data from a study reporting data from 4,081 people with moderate to severe facial acne that participated in 7 clinical trials of oral contraceptives or topical treatments conducted in Europe (Gerlinger 2008).
The mean of $\ln(100+P)$ *can be obtained from the median of the percent change from baseline from:*

$$mean_{\ln(100+P),1} = \ln\left(100 + median_P\right)$$

where the subscript 1 denotes the baseline treatment.
Using properties of the log-Normal distribution, the standard error of $mean_{\ln(100+P),1}$ *is:*

$$se(mean_{\ln(100+P),1}) = \sqrt{\frac{1}{n}\ln\left(\frac{1}{2}\left(1+\sqrt{1+\left(\frac{2sd_P}{e^{mean_{(100+P)}}}\right)^2}\right)\right)}$$

The mean of $\ln(100+P)$ *was then pooled across the 2 RCTs using a fixed effect single arm meta-analysis.*

Subsequently, for each treatment k the mean of $\ln(100+P)$ is:

$$mean_{\ln(100+P),k} = \ln\left(\exp\left(mean_{\ln(100+P),1}\right) + d_k\right)$$

where d_k is the estimated mean change in the percentage change from baseline for treatment k relative to treatment 1 (topical retinoid), obtained from the NMA on the efficacy outcome.

Baseline risk of discontinuation

Baseline data on the absolute risk of discontinuation for any reason and due to intolerable side effects were derived from an observational study of 250 people with acne in Turkey, who were prescribed topical treatments (Dikicier 2019). This was the only identified observational study that provided data on people with acne discontinuing treatment for any reason and due to side effects. Of the 250 participants in the study, 75 were prescribed topical retinoids. Of them, 30 (40% of the sample) discontinued treatment for any reason, and 15 (20% of the sample) discontinued treatment due to intolerable side effects. The study sample had mild to moderate acne and therefore the data are directly applicable to the study population of the economic model.

Other clinical input parameters

Relationship between treatment efficacy (% CFB) and level of perceived acne symptom improvement and distribution of individuals' outcomes around the mean % CFB in the economic model

The relationship between a person's % CFB and their perceived acne symptom improvement was determined using an analysis of data from 4,081 people with moderate to severe facial acne that participated in 7 clinical trials of oral contraceptives or topical agents conducted in Europe (Gerlinger 2008) due to lack of alternative data specific to people with mild to moderate acne. The measure of efficacy in the trials was the % CFB of total acne lesion counts (objective, clinician-rated assessment). At the end of treatment, participants rated the change in the severity of their acne using the categories of "excellent improvement", "good improvement", "moderate improvement", "no improvement" as well as "aggravation" (subjective, participant-rated assessment). The authors then compared the % CFB of total acne lesion counts with participants' self-ratings, and applied nonparametric discriminant statistical analysis to determine the range of % CBF (upper and lower thresholds) that

corresponded to each level of improvement. They found that a 71.26% to 100% reduction in acne lesions corresponded to “excellent improvement”; a 53.14% to 71.26% reduction in acne lesions corresponded to “good improvement; a 28.20% to 53.14% reduction in acne lesions corresponded to “moderate improvement”; and a less than 28.20% reduction or any % increase in acne lesions corresponded to “no improvement / aggravation”.

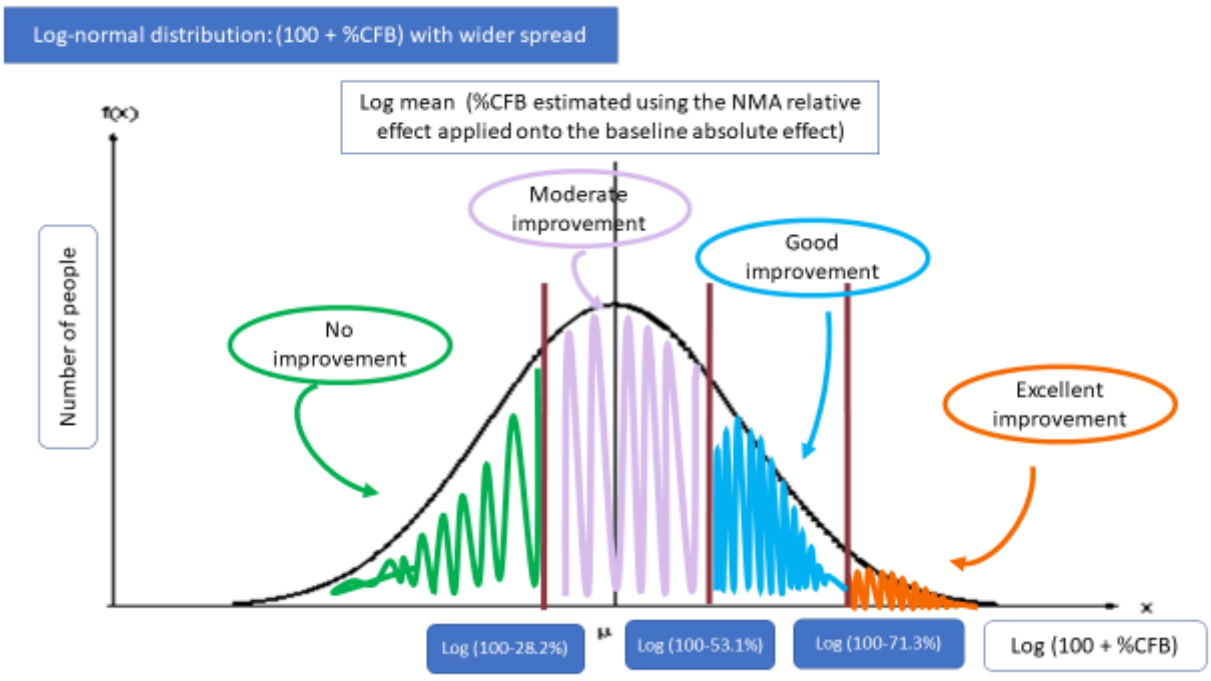
To estimate the proportion of people with excellent, good, moderate and no improvement in each cohort examined in the economic analysis, we needed to determine the distribution of people’s outcomes in each cohort around the mean % CFB at end of treatment, i.e. the spread of the distribution. The mean % CFB and the spread of the distribution determine the proportions of people with each level of improvement. A narrow spread means that people are distributed closer to the mean of the distribution. The impact of the spread of the distribution on allocating people in a cohort to different levels of perceived improvement is shown in Figure 11, which shows the allocation of people using a wider and a narrower spread around the same mean % CFB.

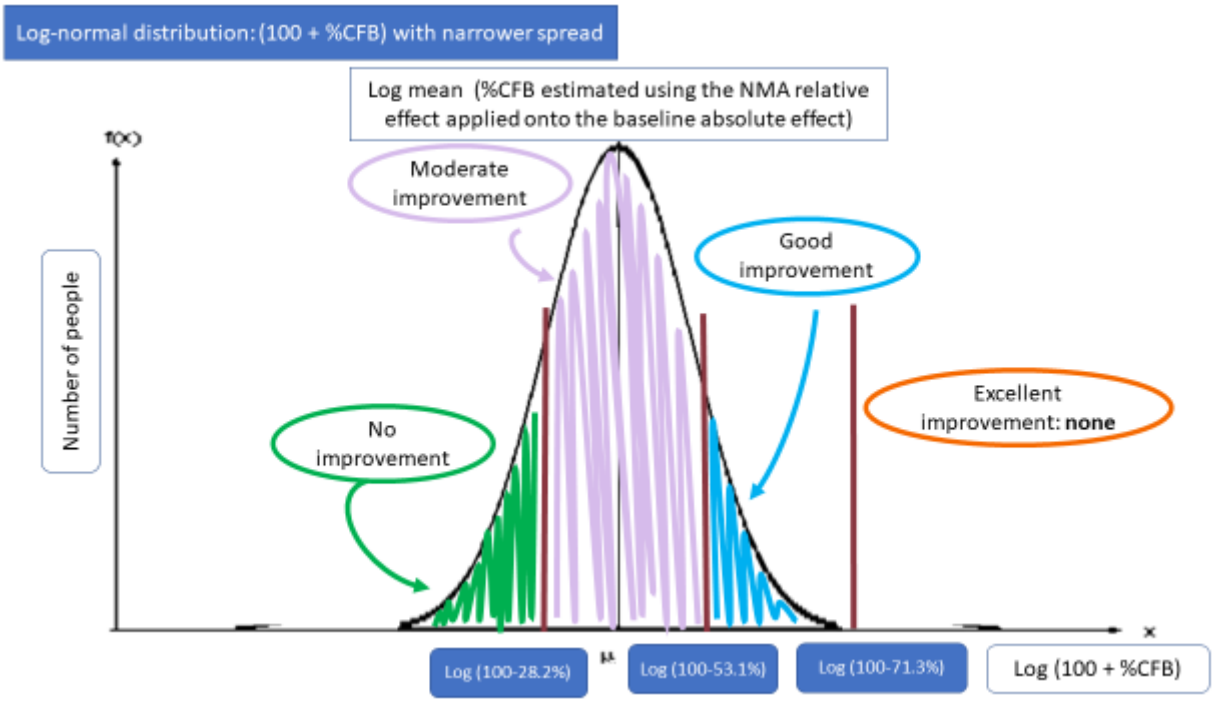
The spread around the mean % CFB was also determined using data from Gerlinger (2008), due to lack of more relevant data. According to this study, the median % CFB across cohorts was -62.3% with an interquartile range (IQR) of -79.49% to -40%; the (100 + % CFB) appeared to have a log-normal distribution. Using these data, the standard deviation (spread) around the mean was estimated as follows:

(100 + % CFB) had a median of 37.7 and IQR of 20.51 to 60. It’s log-normal distribution has therefore a mean of 3.02 and a standard error (SE) that equals (4.09-3.02)/(2*0.6745) = 0.80.

This spread (SE) around the log-normal mean of (100 + % CFB) was assumed to apply to all treatment cohorts at treatment endpoint and allowed estimation of the proportion of people with excellent, good, moderate and no improvement in every cohort, using the mean value of % CFB estimated for each treatment after applying its relative efficacy versus the baseline treatment (obtained from the NMA on efficacy) onto the absolute baseline effect.

Figure 11. Examples of the distribution of people in a cohort receiving treatment for acne, according to their level of perceived symptom severity, using the same mean % change from baseline (CFB) but different standard error (spread).





Risk of relapse according to the level of perceived acne symptom improvement

The risk of relapse following response to treatment was assumed to depend on the level of perceived acne symptom improvement. Based on the committee's expert opinion, the risk of relapse in people with mild to moderate acne one year after treatment initiation was 10%, 40% and 60% in people who experienced excellent, good and moderate improvement, respectively, following treatment. People who relapsed were assumed to return to the acne symptom status they had at treatment initiation, i.e. mild to moderate acne. People who experienced no improvement post-treatment were assumed to retain this acne symptom status until the end of modelling period.

Assumptions on the risk of relapse were made because relevant research is rather limited and characterised by high heterogeneity in study design, populations, types of acute and maintenance treatment received, and follow-up times. In reality, some people will experience only partial relapse (i.e. their symptoms will worsen but they will not return to their initial acne symptom status) and some others may further improve, for example from moderate to excellent improvement. However, to incorporate such events further assumptions would be required that would introduce additional uncertainty into the model. This simplification of events associated with relapse or with retaining post-treatment status until the end of the model is acknowledged as a limitation of the analysis.

Utility data and estimation of quality adjusted life years (QALYs)

In order to express outcomes in the form of QALYs, the health states of the economic model (initial level of acne, excellent improvement, good improvement, no improvement, relapse) need to be linked to appropriate utility scores. Utility scores represent the HRQoL associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on the HRQoL experienced in the health states under consideration.

The systematic review of utility data on acne-related heath states identified 3 studies that reported utility data corresponding to acne-related health states that met inclusion criteria (Chen 2008; Klassen 2000; Al Robaee 2009). There were 3 studies that were excluded after obtaining full text, and these are reported in appendix K, together with reasons for exclusion.

Chen (2008) reported utility scores derived from a convenience sample of 266 students (age range 14-18 years, 59% female, 65% of Asian origin) from public high schools in the US, who were graded with a score of ≥1 on the Investigator's Static Global Assessment (ISGA) scale for acne. The students provided valuations for hypothetical health states related to acne (100% clearance, 50% clearance, 100% clearance but with scarring), using the time trade-off technique (TTO). The utility value for each person's current acne health state was calculated using their valuation for a state of 'never having acne'; this utility value (for current state) subsequently served as an anchor state for the 3 hypothetical scenarios.

Klassen (2000) reported EQ-5D utility scores derived from 60 people aged ≥ 16 years with acne (mean 22 years, range 16-39; 38.7% females) identified through general practitioner referral letters to a tertiary dermatology centre in England. Participants in the study were prescribed either a course of oral isotretinoin (71%) or were given a variety of antibiotic, hormonal, physical, and topical treatments. The UK EQ-5D tariff, formed using the time trade-off (TTO) technique, was used (Dolan 1997). The authors reported utility scores before treatment, at 4 months post-treatment and at 12 months post-treatment. The mean Dermatology Life Quality Index (DLQI) score of the population was 9.2 before treatment, suggesting a moderate mean effect on people's quality of life, and fell at 3.5 at 4 months post-treatment and 2.2 at 12 months post-treatment, suggesting, at both time points, a small mean effect on people's quality of life.

Al Robaee (2009) reported mean SF-36 dimension scores from 454 people with acne (237 males, 217 females) visiting an outpatient clinic in Saudi Arabia. Participants were categorised by level of acne symptom severity into those having mild acne, moderate acne, severe acne and very severe acne; however, the method for determining the level of acne severity was not reported. EQ-5D scores were mapped from the SF-36 dimension scores for each level of acne symptom severity using the algorithm reported in Ara (2008).

An overview of the study characteristics, the methods used to define health states, and the health-state utility values reported by each of the three studies is provided in Table 15.

Table 15: Summary of available health-state utility data for people with acne

Study	Definition of health states	Utility measure, valuation method, population valuing	Health states, number of respondents & corresponding utility scores		
Chen 2008	Vignettes (hypothetical states) plus current state of acne from a convenience sample of 266 students (age range 14-18 years, 59% female, 65% of Asian origin) from public high schools in the US, who were graded with a score of ≥1 on the ISGA scale for acne. Note: utility value for current acne state was calculated using valuations for a state of 'never having acne' and served as an anchor state for the remaining 3 scenarios.	No measure used (vignettes and current state used) TTO students with acne in the US	Health state 100% clearance 50% clearance 100% clearance but with scarring Acne – current state	**N**	**Mean (SD)** **0.978 (0.073)** **0.967 (0.089)** **0.965 (0.091)** **0.961 (0.092)**
Klassen 2000	EQ-5D ratings from 60 people aged ≥ 16 years with acne (mean 22 years, range 16-39; 38.7% females) identified through general practitioner referral letters to a tertiary dermatology centre in England. Participants were prescribed either a course of oral isotretinoin (71%) or given a variety of antibiotic, hormonal, physical, and topical treatments. Mean (SD) DLQI score: before treatment 9.2 (5.8); 4 months post-treatment 3.5 (3.6); 12 months post-treatment 2.2 (3.3). DLQI SCORES – EFFECT ON RESPONDENTS' LIFE: 0 - 1 no effect at all; 2 - 5 small effect; 6 - 10 moderate effect; 11 - 20 very large effect; 21 - 30 extremely large effect	EQ-5D TTO UK adult general population	Health state Acne before treatment Acne 4 months post-treatment Acne 12 months post-treatment	**N** **56** **56** **54**	**Mean (SD)** **0.82 (0.16)** **0.89 (0.17)** **0.93 (0.15)**
Al Robaee 2009	SF-36 ratings obtained from 454 people with acne (237 males, 217 females) visiting an outpatient clinic in Saudi Arabia; method for determining level of acne severity not reported.	EQ-5D mapped from reported mean SF-36 dimension scores using the algorithm by Ara (2008) TTO UK adult general population	Health state Mild Moderate Severe Very severe	**N** **252** **153** **35** **14**	**Mean** **0.68** **0.69** **0.58** **0.75**

DLQI: dermatology life quality index; ***ISGA: investigator's static global assessment; N: number; SD: standard deviation; TTO: time trade-off***

According to NICE guidance on the selection of utility values for use in cost-utility analysis (NICE, 2013), the measurement of changes in HRQoL should be reported directly from people with the condition examined, or, if this is not possible, by their carers, and the valuation of health states should be based on public preferences elicited using a choice-based method, such as the time trade-off (TTO) or standard gamble (SG), in a representative sample of the UK population. NICE recommends the EQ-5D utility system (Dolan 1997) as the preferred measure of HRQoL in adults for use in cost-utility analysis of healthcare interventions.

The study by Chen (2008) was characterised by methodological limitations (as the current acne state, and not the death state, served as the lowest anchor state) and was not further considered. The committee noted that the population in Klassen (2000) had a mean DLQI baseline score of 9.2, corresponding to the upper level of 'moderate effects' in people's lives; nevertheless, they advised that this symptom level corresponds to mild to moderate acne. The study reported a utility value of 0.82 for pre-treatment acne, based on EQ-5D ratings. Thus, the committee expressed the opinion that the utility value of 0.82 characterised mild to moderate acne.

Al Robaee (2009) reported SF-36 ratings from people with acne in Saudi Arabia, converted to EQ-5D using a published mapping algorithm. The committee questioned the face validity of some of the estimated utility values (for example, the utility of severe acne was higher than all milder states) and highlighted that SF-36 ratings came from a population in Saudi Arabia with potentially different characteristics than those of people with acne in England. Therefore, this study was not further considered.

According to UK population norms for EQ-5D, the utility value in the general adult population aged <25 years in the UK is 0.94 (Kind 1999). The committee agreed that this age group was consistent with the mean age of the study population in the economic analysis and assumed that this utility value (0.94) corresponded to excellent improvement following acne treatment. For the estimation of utility values for good and moderate improvement, the utility values of 0.82 (corresponding to mild to moderate acne and also assumed to correspond to no improvement) and 0.94 (mean utility of general population assumed to correspond to excellent improvement) were used as the lowest and highest limit of acne-related utilities, respectively, and a linear relationship between utility and the level of perceived improvement was assumed. This resulted in estimated utility values of 0.86 and 0.90 corresponding to moderate and good improvement, respectively.

People who discontinued treatment due to side effects were assumed to experience deterioration in their HRQoL lasting while they were receiving their initiated treatment (i.e. during 25% of time of full course) plus 2 weeks after treatment discontinuation. A reduction in utility equal to the difference in utility between consecutive improvement levels was assumed over this period (i.e. 0.04).

Table 16 shows all utility values that were used in the economic analysis of treatments for people with mild to moderate acne.

Table 16. Relationship between efficacy (% CFB), perceived acne symptom improvement and utility values in people with mild to moderate acne

% CFB – related health state	Perceived improvement	Utility value
71.26% - 100% reduction in acne lesions	Excellent	0.94
53.14% - 71.26% reduction in acne lesions	Good	0.90
28.20% - 53.14% reduction in acne lesions	Moderate	0.86
<28.20% reduction or any % increase	None	0.82
Mild to moderate acne (baseline)	NA	0.82
Reduction in utility due to intolerable side effects	NA	-0.04

% CFB – related health state	Perceived improvement	Utility value
CFB: change from baseline; NA: non-applicable		

Changes in utility were assumed to occur linearly over the time period of the change. When running the probabilistic analysis, values were restricted so that utility values of milder states were not allowed to be lower than those of more severe health states.

Intervention resource use and costs

Intervention costs were estimated by combining resource use associated with each treatment, as described in relevant RCTs, modified to reflect optimal routine practice in the UK, with appropriate unit costs. Estimation of intervention costs took into account (as relevant for each treatment) the drug dosage & optimal duration of treatment, informed by optimal clinical practice and evidence from trials included in the guideline NMA; health professional time (GP and/or specialist care) considering the number of contacts over the course of treatment, including any follow-up care; any required laboratory testing; and operational procedures, including the number of sessions of physical treatments and any follow-up contacts. Unit costs were obtained from national sources (Curtis 2019; Department of Health and Social Care 2020; NHS Business Services Authority 2020; NHS Improvement 2020) and other published literature (Akhtar 2014).

People who discontinued treatment early were assumed to have incurred the following costs until discontinuation and before they moved on to average acne care:

- People discontinuing pharmacological treatments other than oral isotretinoin incurred the cost of 1 GP visit plus a month's drug supply.
- People discontinuing oral isotretinoin incurred the cost of 1 GP visit for referral, 1 specialist consultant-led dermatology first visit, 1 specialist dermatology follow-up visit (at the average cost of consultant-led and non-consultant led), a 2-month drug supply (in 2 separate prescriptions), 2 pregnancy urine tests (females only), 1 full blood count test, 1 urea & electrolytes test, 2 liver function tests and 2 serum lipid tests.
- People discontinuing therapy with chemical peels incurred the cost of 1 GP visit for referral, 1 specialist consultant-led dermatology first visit, 0.5 specialist dermatology follow-up visit (at the average cost of consultant-led and non-consultant led), and the amount of salicylic acid required for 1.5 peeling sessions (assuming that 50% of those discontinuing did so after the first peeling session and the other 50% discontinued after the second peeling session).
- People discontinuing other physical treatments (light therapies) incurred the cost of 1 GP visit for referral, 1 specialist consultant-led dermatology first visit, and 1 session of physical treatment.
- People discontinuing GP care incurred the cost of 1 GP visit.

In addition, people who discontinued treatment due to intolerable side effects incurred a further cost of a visit to a health professional: the cost of 1 GP visit was incurred by people who initiated GP care or pharmacological treatment other than oral isotretinoin; the cost of 1 specialist dermatologist visit was incurred by people who initiated oral isotretinoin or physical treatments (both light therapies and chemical peeling).

Details on the resource use and total costs of treatments for people with mild to moderate acne that were assessed in the economic analysis are provided in Table 17.

Table 17: Intervention costs of treatments for people with mild to moderate acne considered in the economic analysis (2019 prices)

Treatment class and modelled intervention	Resource use details[1]	Total intervention cost[2]
Topical retinoid: adapalene	Daily dosage: 1 g/day Acute treatment: 2 GP visits + 2 x 45g tubes Maintenance treatment: 1 GP visit + 2 x 45g tubes Resource use in discontinuers: 1 GP visit + 1 x 45g tube prescribed (0.67 needed)	Acute: £110.86 Maintenance: £71.86 Total: £182.72 Discontinuer: £55.43
Benzoyl peroxide (topical)	Daily dosage: 1 g/day Acute treatment: 2 GP visits + 2 x 50g tubes prescribed (1.8 needed) Maintenance treatment: 1 GP visit + 2 x 50g tubes prescribed (1.8 needed) Resource use in discontinuers: 1 GP visit + 1 x 50g tube prescribed (0.6 needed)	Acute: £86.26 Maintenance: £47.26 Total: £133.52 Discontinuer: £43.13
Azelaic acid (topical)	Daily dosage: 1 g/day Acute treatment: 2 GP visits + 3 x 30g tubes Maintenance treatment: 1 GP visit + 3 x 30g tubes Resource use in discontinuers: 1 GP visit + 1 x 30g tube	Acute: £91.47 Maintenance: £52.47 Total: £143.94 Discontinuer: £43.49
Topical lincosamides: topical clindamycin	Daily dosage: 1 g/day Acute treatment: 2 GP visits + 3 x 30g tubes Maintenance treatment: 1 GP visit + 3 x 30g tubes Resource use in discontinuers: 1 GP visit + 1 x 30g tube	Acute: £103.98 Maintenance: £64.98 Total: £168.96 Discontinuer: £47.66
Topical macrolides: topical erythromycin	Daily dosage: 1 ml/day Acute treatment: 2 GP visits + 3 x 30ml bottles Maintenance treatment: 1 GP visit + 3 x 30ml bottles Resource use in discontinuers: 1 GP visit + 1 x 30ml bottle	Acute: £105.75 Maintenance: £66.75 Total: £172.50 Discontinuer: £48.25
Topical acid: salicylic acid	Daily dosage: 1g/day Acute treatment: 2 GP visits + 1 x 450g tube (0.2 needed) Maintenance treatment: 1 GP visit + no tube prescribed (0.2 needed) Resource use in discontinuers: 1 GP visit + 1 x 450g tube	Acute: £90.50 Maintenance: £39.00 Total: £129.50 Discontinuer: £51.50
Benzoyl peroxide + topical retinoid (adapalene)	Daily dosage: 1 g/day Acute treatment: 2 GP visits + 2 x 45g tubes Maintenance treatment: 1 GP visit + 2 x 45g tubes Resource use in discontinuers: 1 GP visit + 1 x 45g tube prescribed (0.67 needed)	Acute: £117.06 Maintenance: £78.06 Total: £195.12 Discontinuer: £58.53

Treatment class and modelled intervention	Resource use details[1]	Total intervention cost[2]
Benzoyl peroxide + topical lincosamide (clindamycin)	Daily dosage: 1 g/day Acute treatment: 2 GP visits + 3 x 30g tubes Maintenance treatment: 1 GP visit + 3 x 30g tubes Resource use in discontinuers: 1 GP visit + 1 x 30g tube	Acute: £117.42 Maintenance: £78.42 Total: £195.84 Discontinuer: £52.14
Benzoyl peroxide + topical macrolide (erythromycin)	Daily dosage: benzoyl peroxide: 1 g/day; erythromycin: 1 ml/day Acute treatment: 2 GP visits + 2 x 50g tubes of benzoyl peroxide prescribed (1 needed) + 3 x 30ml bottles of erythromycin Maintenance treatment: 1 GP visit + 2 x 50g tubes of benzoyl peroxide prescribed (1 needed) + 3 x 30ml bottles of erythromycin Resource use in discontinuers: 1 GP visit + 1 x 50g tube of benzoyl peroxide prescribed (0.6 needed) + 1 x 30ml bottle of erythromycin	Acute: £114.01 Maintenance: £75.01 Total: £189.02 Discontinuer: £52.38
Azelaic acid + topical lincosamide (clindamycin)	Daily dosage: azelaic acid: 1 g/day; clindamycin: 1 g/day Acute treatment: 2 GP visits + 3 x 30g tubes of azelaic acid + 2 x 30g tubes of clindamycin Maintenance treatment: 1 GP visit + 1 x 30g tube of azelaic acid + 1 x 30g tube of clindamycin Resource use in discontinuers: 1 GP visit + 1 x 30g tube of azelaic acid + 1 x 30g tube of clindamycin	Acute: £117.45 Maintenance: £78.45 Total: £195.90 Discontinuer: £52.15
Azelaic acid + topical macrolide (erythromycin)	Daily dosage: azelaic acid: 1 g/day; erythromycin: 1 ml/day Acute treatment: 2 GP visits + 3 x 30g tubes of azelaic acid + 3 x 30ml bottles of erythromycin Maintenance treatment: 1 GP visit + 3 x 30g tubes of azelaic acid + 3 30ml bottles of erythromycin prescribed Resource use in discontinuers: 1 GP visit + 1 x 30g tube of azelaic acid + 1 x 30ml bottle of erythromycin	Acute: £119.22 Maintenance: £80.22 Total: £199.44 Discontinuer: £52.74
Topical retinoid + topical lincosamide: tretinoin + clindamycin	Daily dosage: 1 g/day Acute treatment: 2 GP visits + 3 x 30g tubes Maintenance treatment: 1 GP visit + 3 x 30g tubes Resource use in discontinuers: 1 GP visit + 1 x 30g tube	Acute: £113.82 Maintenance: £74.82 Total: £188.64 Discontinuer: £50.94
Topical retinoid (tretinoin) + topical macrolide (erythromycin)	Daily dosage: 1 g/day Acute treatment: 2 GP visits + 3 x 30g tubes	Acute: £100.41 Maintenance: £61.41

Treatment class and modelled intervention	Resource use details[1]	Total intervention cost[2]
	Maintenance treatment: 1 GP visit + 3 x 30g tubes Resource use in discontinuers: 1 GP visit + 1 x 30g tube	Total: £161.82 Discontinuer: £46.47
Topical macrolides (erythromycin) + topical anti-fungals (bifonazole)	Daily dosage: erythromycin: 1 ml/day; bifonazole: 1 g/day Acute treatment: 2 GP visits + 3 x 30ml bottles of erythromycin + 5 x 20g tubes of bifonazole prescribed (4.5 needed) Maintenance treatment: 1 GP visit + 3 x 30ml bottles of erythromycin + 4 x 20g tubes of bifonazole prescribed (4.5 needed) Resource use in discontinuers: 1 GP visit + 1 x 30ml bottle of erythromycin + 2 x 20g tubes of bifonazole prescribed (1.5 needed)	Acute: £121.90 Maintenance: £79.67 Total: £201.57 Discontinuer: £54.71
Oral isotretinoin - total cumulative dose < 120mg/kg (single course)	Daily dosage: 0.6 mg/kg/day; total cumulative dose over 6 months 109 mg/kg. Assuming mean weight of 70 kg, then daily dose is ≈ 40 mg/day Over 6 months: 12 packs of (30 x 20mg capsules) 1 GP visit for referral to specialist dermatology outpatient clinic Females: 7 dermatology outpatient visits (1 consultant-led first + 6 follow-up mixed consultant-/non-consultant-led) Males: 4 dermatology outpatient visits (1 consultant-led first + 3 follow-up mixed consultant-/non-consultant-led) Females only: Pregnancy urine test at initiation and every month (x 7 in total) Full blood count, urea & electrolytes: at initiation (2 tests in total) Liver function, serum lipids (cholesterol and triglycerides) at initiation; month 1; month 4; month 6 (2 tests x 4 times in total) Resource use in discontinuers: 1 GP visit for referral, 4 packs of (30 x 20mg) capsules, 1 specialist consultant-led dermatology first visit + 1 specialist dermatology mixed consultant-/non-consultant-led follow-up visit, 2 pregnancy urine tests (females only), 1 full blood count test, 1 urea & electrolytes test, 2 liver function tests, 2 serum lipid tests.	Total: £869.32 [females] £548.82 [males] Discontinuer: £298.94 [females] £296.94 [males]
Combined oral contraceptive: ethinylestradiol + norgestimate	Daily dosage: Ethinylestradiol 35 µg + Norgestimate 250 µg per day, for 21/28 days Acute treatment: 2 GP visits + 1 x 63 tablet box Maintenance treatment: 1 GP visit + 1 x 63 tablet box Resource use in discontinuers: 1 GP visit + 1 x 63 tablet box	Acute: £82.65 Maintenance: £43.65 Total: £126.30 Discontinuer: £43.65
Chemical peels: salicylic acid peel	1 GP visit for referral to specialist dermatology outpatient clinic 6 sessions: 6 x 10 ml peels	Total: £702.86 Discontinuer: £216.59

Treatment class and modelled intervention	Resource use details[1]	Total intervention cost[2]
	1 dermatology consultant-led outpatient first visit 7 dermatology outpatient follow-up visits (at an average cost of consultant/non-consultant-led follow-up visit) Resource in discontinuers: 1 GP visit + 1 specialist consultant-led dermatology first visit + 0.5 dermatology outpatient follow-up visit (at an average cost of consultant/non-consultant-led) + 1.5 x 10ml peel (assuming that 50% of those discontinuing will discontinue after the first peeling session and the other 50% will discontinue after the second peeling session)	
Photochemical therapy (blue light; or blue and red light)	1 GP visit for referral to specialist dermatology outpatient clinic 1 dermatology consultant-led outpatient first visit 3 photochemical therapy sessions 1 dermatology outpatient follow-up visit (at an average cost of consultant/non-consultant-led follow-up visit) Resource use in discontinuers: 1 GP visit + 1 specialist consultant-led dermatology first visit + 1 photochemical therapy session	Total: £546.14 Discontinuer: £253.21
Photochemical and photothermal therapy	1 GP visit for referral to specialist dermatology outpatient clinic 1 dermatology consultant-led outpatient first visit 3 photothermal therapy sessions 1 dermatology outpatient follow-up visit (at an average cost of consultant-/non-consultant-led follow-up visit) Resource use in discontinuers: 1 GP visit + 1 specialist consultant-led dermatology first visit + 1 photothermal therapy session Unit cost assumed to be equal to that of photodynamic therapy	Total: £850.82 Discontinuer: £354.77
GP care	Acute treatment: 2 GP visits Maintenance treatment: 1 GP visit Resource use in discontinuers: 1 GP visit	Acute: £78.00 Maintenance: £39.00 Total: £117.00 Discontinuer: £39

1 For all pharmacological treatment options other than oral isotretinoin the duration of 'acute' treatment is 3 months and the duration of maintenance treatment, received by those responding to acute treatment, is another 3 months. Duration of treatment with oral isotretinoin is 6 months; no maintenance treatment assumed.

2 Unit costs
Drug acquisition costs (NHS Business Services Authority 2020 except oral isotretinoin for which dispensation by a hospital pharmacy was assumed and acquisition cost was derived from Department of Health and Social Care, 2020)

Treatment class and modelled intervention	Resource use details[1]	Total intervention cost[2]
Adapalene 0.1% cream or gel, 45g: £16.43 *Adapalene 0.1% or 0.3% and benzoyl peroxide 2.5% gel, 45g: £19.53* *Azelaic acid 20% cream, 30 g: £4.49* *Benzoyl peroxide 4% cream, 50g: £4.13* *Benzoyl peroxide 3% or 5% and clindamycin 1% gel, 30g: £13.14* *Bifonazole 1% cream, 20g: £3.23* *Clindamycin 1% gel, 30g: £8.66* *Clindamycin 1% and tretinoin 0.025% gel, 30g: £11.94* *Erythromycin 40mg/ml and zinc acetate 12mg/ml lotion, 30ml: £9.25* *Ethinylestradiol 35µg + Norgestimate 250µg tablets x 63: £4.65* *Isotretinoin 10mg, 30 capsules: £5.48; 20mg, 30 capsules: £3.86* *Tretinoin 0.025% and erythromycin 2% gel, 30g: £7.47* *Salicylic acid 2% ointment, 450g: £12.50* *Salicylic acid 26% solution, 10 ml: £3.56 [for use in chemical peels]* *<u>Healthcare contact unit costs</u>* *GP: £39 per patient contact lasting 9.22 minutes, including direct care staff and qualification costs (Curtis 2019)* *Dermatology consultant-led outpatient first visit: £120 (NHS Improvement 2020; service code 330)* *Dermatology consultant-led outpatient follow-up visit: £112 (NHS Improvement 2020; service code 330)* *Dermatology non-consultant-led outpatient follow-up visit: £97 (NHS Improvement 2020; service code 330)* *<u>Procedure costs (NHS Improvement 2020)</u>* *Photodynamic therapy: £196 (weighted average national cost of day and outpatient cases; currency code JC46Z)* *Photochemical therapy: £94 (weighted average national cost of day and outpatient cases; currency code JC47Z)* *<u>Laboratory testing</u>* *Pregnancy urine test: £1 (assumption)* *All other testing: £2.90 (Akhtar 2014, uplifted to reflect 2019 price)*		

Cost of average acne care

People discontinuing one of the modelled treatments, people relapsing following improvement in acne symptoms, and people with no or moderate improvement following treatment were assumed to receive average acne care, comprising a mixture of care that is anticipated to be currently received by people with acne in the NHS. The mean cost of average acne care for people with acne was estimated based on an analysis of primary care consultations and prescription data of 318,515 people with acne, aged ≥ 8 years, over a 10-year period (2004-2013) in the UK (Francis 2017). The analysis included data obtained from people with a new ('index') acne consultation. A person was considered to have a new acne consultation if no primary care consultations and/or prescriptions for acne were recorded for this person in the year prior to their index consultation. Therefore, some people might have had previous consultations for acne more than 12 months before their index consultation. People with a new acne consultation were included in the analysis if follow-up data of at least one year following the new acne consultation were available. The study reported prescription data (types of drugs prescribed) at the index consultation, for the period during the subsequent 90 days after the index consultation, and during the year following the index consultation, including the first 90 days but excluding the index consultation.

The study found that, of people presenting with a new episode of acne, only one-third were seen in the subsequent 12 months. In total, 167,573 people were identified as having a new acne consultation with 12-month follow-up data being available. Of these, 44,809 (26.74%) did not receive a prescription for acne treatment during their index consultation, while 39,314 (23.46%) did not receive a prescription for acne treatment both at the index consultation and in the following 90 days. Most of the issued prescriptions amounted to 2-3 months' treatment.

In order to calculate an annual acne-related cost, estimates of the proportions of people receiving each type of treatment over one year and the duration of treatment were required; these were made using the following assumptions:

- People who were not prescribed an acne treatment at the index consultation and in the next 90 days were assumed to receive no prescription for acne treatment within the year after the index consultation. People not prescribed any acne-related medication over the first 90 days within index consultation were deemed to be non-representative of the economic model's study population, as they were assumed not to require prescribed treatment. Therefore, these people were excluded from the estimation of acne care costs.
- At the index consultation people were prescribed treatment lasting for 3 months. This is supported by the study finding that "most of the issued prescriptions amounted to 2-3 months' worth of treatment."
- Prescription data on the year after the index consultation were assumed to refer to a treatment duration of 6 months, as this is the optimal treatment duration (initial & maintenance treatment, where relevant) for most pharmacological treatments. Therefore, the cost of 6 months of treatment was attached to each type of prescription over this period. However, it is acknowledged that some people might have been treated for a longer and others for a shorter period than 6 months. Moreover, some people might have only been continuing medication from their index consultation over this follow-up period, and therefore their 'follow-up' medication might have lasted only for 3 months.

The final annual care cost comprised the sum of the weighted average cost of the index consultation and prescribing (assuming a 3-month treatment duration) and the weighted average cost of the consultations and prescribing over the year following the index consultation (assuming a 6-month treatment duration). This was estimated for the population of interest only, that is, after excluding people who did not receive a prescription for acne treatment both at the index consultation and in the following 90 days. Costs of all treatments included in average acne care were readily available from calculation of intervention costs for this analysis, or of the economic analysis of treatments for people with moderate to severe

acne; the only exception was co-cyprindiol, the cost of which was estimated specifically for this exercise.

The estimated cost from this exercise captures only primary acne care (with the exception of oral isotretinoin, which has been assumed to be prescribed in a dermatology specialist setting). However, some people with mild to moderate acne will receive specialist care. It was assumed that 5% of people receive specialist care and incur the cost of 2 specialist dermatology visits (1 consultant-led first visit and 1 follow-up visit at an average consultant/non-consultant-led cost) over one year. This cost was added to the estimated mean primary care cost of average acne care. The 5% figure was based on assumption after taking into account evidence that 8.5% of people with acne (which includes people with all levels of severity, from mild to severe) are referred to a dermatologist over 2 years (Purdy 2003). This percentage is likely to be lower in people with mild to moderate acne.

Based on the above, the mean annual average acne care cost for people with mild to moderate acne was estimated at £286 (price year 2019). Details on the GP consultation and prescription data and treatment costs that were synthesised in order to obtain this figure are provided in Table 18.

Because the estimated cost was based to a large degree on the committee's expert opinion and further assumptions, a sensitivity analysis was conducted, in which the estimated cost figure was varied by ±50% to explore its impact on the results of the economic analysis.

Table 18. Acne-related prescriptions and estimated average acne care annual cost incurred by people with mild to moderate acne

Prescribed ARM[1]	Index consultation			Following year			Index consultation		Following year	
	N	Population of interest		N	Population of interest		Cost	Weighted cost	Cost	Weighted cost
		n	%		n	%				
No AMR at index or next 90 days	*39,314*			*39,314*						
No ARM	44,809	*5,495**	4.28%	78,567	*39,253**	30.60%	£78.00	£3.34	£117.00	£35.81
Oral antibiotic alone	41,791	41,791	32.58%	32,750	32,750	25.53%	£108.64	£35.40	£170.62	£43.57
Topical antibiotic (+combined) alone	39,529	39,529	30.82%	16,806	16,806	13.10%	£108.91	£33.56	£178.82	£23.43
Topical non-antibiotic alone	20,875	20,875	16.28%	6,458	6,458	5.04%	£101.41	£16.51	£163.83	£8.25
Oral antibiotic + topical non-antibiotic	9,168	9,168	7.15%	12,009	12,009	9.36%	£134.91	£9.64	£223.15	£20.89
Oral antibiotic + topical antibiotic	4,671	4,671	3.64%	11,215	11,215	8.74%	£135.51	£4.93	£224.35	£19.62
Co-cyprindiol alone	4,014	4,014	3.13%	3,987	3,987	3.11%	£88.78	£2.78	£138.56	£4.31
Co-cyprindiol + any topical agent	793	793	0.62%	2,265	2,265	1.77%	£113.53	£0.70	£188.07	£3.32
Oral isotretinoin alone[2]	15	15	0.01%	47	47	0.04%	£370.98	£0.04	£741.95	£0.27
Oral isotretinoin + other ARM[2]	2	2	0.00%	98	98	0.08%	£394.06	£0.01	£788.13	£0.60
Other combination	1906	1,906	1.49%	3,371	3,371	2.63%	£127.98	£1.90	£211.86	£5.57
Total	167,573	128,259	100%	167,573	128,259	100%		**£108.82**		**£ 165.63**
Specialist care for people with mild to moderate acne[3]						5%			£224.50	**£11.23**
Total annual average acne care cost for people with mild to moderate acne[2]										**£285.68**

** calculated after subtracting 39,314 people without a ARM prescription at the index consultation and at next 90 days, from the 44,809 people who received no ARM prescription at index consultation and the 78,567 people who received no ARM prescription within the year following the index consultation, respectively. The latter might have been prescribed an ARM at the index consultation.*
1 prescription data on ARM from Francis (2017)
2 The reported cost of oral isotretinoin reflects resource use for females, including extra specialist visits and pregnancy urine tests. The total annual average acne care cost for males is slightly lower (£252.63)
3 5% figure based on assumption, after taking into account evidence that 8.5% of people with acne (which includes people with all levels of severity, from mild to severe) are referred to a dermatologist over 2 years (Purdy 2003); 2 specialist dermatology visits assumed (1 consultant-led first visit and 1 follow-up visit at an average consultant/non-consultant-led cost)
Costs of all treatments based on calculation of intervention costs (Table 17). For cost of co-cyprindiol, the following data and assumptions were used: Co-cyprindiol 63 tablets: £10.78 (NHS Business Services Authority); 2 GP visits and 21 tablets needed every 3 months; 3-month cost: £88.78; 6-month cost: £138.56
ARM: acne-related medication

Discounting

Discounting of costs and outcomes was not needed as the time horizon of the analysis was one year.

Handling uncertainty

Model input parameters were synthesised in a probabilistic analysis. This means that the input parameters were assigned probabilistic distributions (rather than being expressed as point estimates); this approach allowed more comprehensive consideration of the uncertainty characterising the input parameters and captured the non-linearity characterising the economic model structure. Subsequently, 10,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Results (mean costs and QALYs for each treatment) were calculated by averaging across the 10,000 iterations. This exercise provides more accurate estimates than those derived from a deterministic analysis (which utilises the mean value of each input parameter ignoring any uncertainty around the mean), by capturing the non-linearity characterising the economic model structure (Briggs 2006).

The distributions of the difference in efficacy (% CFB) as well as of the log-odds ratios of relative effects on discontinuation for any reason and due to side effects of all treatments versus topical retinoids were obtained from the respective NMAs, defined directly from values recorded in each of the 10,000 iterations used after thinning the 300,000 iterations performed in WinBUGS or OpenBUGS, as relevant.

Regarding baseline efficacy (% CFB), a log-normal distribution was assumed for (100 + % CFB), based on published literature.

The variability (spread) around the log (100 + % CFB) across all treatments and the thresholds were not assigned a distribution. Beta distribution was assigned to the baseline risk of discontinuation, the risk of relapse, utility values, the proportion of full course duration during which average acne care is received following treatment discontinuation, the proportion of people with moderate improvement after drug treatment other than oral isotretinoin who switch to average acne care between 3-6 months, and the proportion of people who receive average acne care following relapse or moderate or no improvement between 6-12 months. The average acne care cost was assigned a gamma distribution.

Uncertainty in intervention costs was taken into account by assigning probability distributions to the number of health professional contacts (GP visits and specialist outpatient contacts) and physical treatment sessions when estimating full course treatment costs. Number of contacts and physical treatment sessions were not assigned a distributions in people discontinuing treatment early, with the exception of the additional contacts attributed to discontinuation due intolerable side effects. Respective unit costs were assigned a normal distribution. Drug acquisition costs were not assigned a probability distribution, as these are not characterised by uncertainty.

Table 19 reports the mean values of all input parameters utilised in the economic model and provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

A number of deterministic one-way sensitivity analyses were also employed to explore the impact of alternative hypotheses on the results. The following scenarios were explored:

- The baseline % CFB for topical retinoids was varied by ± 50%.
- The baseline risk of discontinuation for any reason was varied by ± 50%.
- The spread (SE) around the log (100 +% CFB) was varied by ± 50%.
- The risk of relapse, following any improvement level, was varied by ± 50%.

- The average acne care cost was changed by ± 50%.
- The mean number of sessions of light therapies was increased to 4.
- People who improved after completion of any physical treatment did not receive average acne care between end of treatment and 6 months.
- The unit costs of photothermal therapy and of photochemical & photothermal therapy were assumed to equal the unit cost of photochemical therapy (rather than that of photodynamic therapy).

In addition, a probabilistic sensitivity analysis was run using efficacy data adjusted for bias due to small study size, derived from a respective bias-adjusted NMA on the efficacy outcome. The bias-adjusted efficacy data utilised in this analysis are provided in Table 19.

Table 19: Input parameters (deterministic values and probability distributions) that informed the economic model of treatments for people with mild to moderate acne

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
Difference in efficacy (% change of total lesion count from baseline) versus topical retinoids – base-case analysis			
		95% CrI	
GP care	-24.83	-31.81 to -17.87	Guideline NMA; distribution based on 10,000 iterations
BPO	-1.82	-10.81 to 7.09	
Azelaic acid	-3.60	-13.63 to 6.57	
Other topical acids	-6.55	-20.46 to 7.39	
Topical lincosamides	-12.28	-21.23 to -3.23	
Topical macrolides	-4.41	-14.63 to 5.91	
BPO + topical retinoid	6.99	-2.21 to 16.20	
BPO + topical lincosamide	0.39	-9.57 to 10.34	
BPO + topical macrolide	2.39	-17.13 to 22.13	
Topical retinoid + topical lincosamide	6.40	-7.85 to 20.63	
Topical retinoid + topical macrolide	-1.32	-22.19 to 19.35	
Azelaic acid + topical lincosamide	14.21	-6.68 to 34.67	
Azelaic acid + topical macrolide	11.09	-7.57 to 30.41	
Topical macrolide + topical anti-fungal	6.39	-17.33 to 29.81	
Oral isotretinoin - total cumul dose <120mg/kg	-0.22	-22.99 to 22.39	
Combined oral contraceptive	-9.98	-22.09 to 2.46	
Chemical peels	23.04	-5.10 to 51.25	
Photochemical therapy (blue light)	13.31	-2.49 to 29.21	
Photochemical therapy (blue and red light)	18.95	1.18 to 36.89	
Photochemical and photothermal therapy	10.82	-21.47 to 43.94	
Difference in efficacy (% change of total lesion count from baseline) versus topical retinoids – bias-adjusted analysis			
		95% CrI	
GP care	-18.50	-26.58 to -10.47	Guideline NMA; distribution based on 10,000 iterations
BPO	-2.66	-11.14 to 5.97	

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
Topical macrolides	-6.65	-16.69 to 3.70	
BPO + topical retinoid	7.86	-1.26 to 16.50	
BPO + topical lincosamide	-0.40	-9.71 to 8.98	
BPO + topical macrolide	1.63	-16.67 to 19.90	
Topical retinoid + topical lincosamide	5.91	-7.28 to 19.09	
Azelaic acid + topical lincosamide	11.88	-7.43 to 30.86	
Azelaic acid + topical macrolide	7.58	-10.36 to 24.97	
Topical macrolide + topical anti-fungal	4.29	-17.70 to 26.05	
Chemical peels	21.44	-4.93 to 47.82	
Photochemical therapy (blue light)	10.34	-5.07 to 26.20	
Photochemical therapy (blue and red light)	17.06	-0.03 to 34.53	
Log-odds ratios of discontinuation for any reason versus topical retinoids			
		95% CrI	Guideline NMA; distribution based on 10,000 iterations
GP care	0.00	-0.23 to 0.23	
BPO	-0.01	-0.31 to 0.28	
Azelaic acid	-0.16	-0.77 to 0.46	
Other topical acids	-0.04	-0.73 to 0.64	
Topical lincosamides	-0.25	-0.54 to 0.06	
Topical macrolides	-0.02	-0.49 to 0.46	
BPO + topical retinoid	-0.14	-0.46 to 0.16	
BPO + topical lincosamide	-0.16	-0.50 to 0.20	
BPO + topical macrolide	-0.12	-0.63 to 0.40	
Topical retinoid + topical lincosamide	-0.42	-0.99 to 0.15	
Topical retinoid + topical macrolide	-0.52	-1.19 to 0.13	
Azelaic acid + topical lincosamide	-0.23	-1.44 to 0.90	
Topical macrolide + topical anti-fungal	0.27	-0.54 to 1.06	
Oral isotretinoin - total cumul dose <120mg/kg	0.77	-1.03 to 2.70	
Combined oral contraceptive	-0.06	-0.43 to 0.31	
Chemical peels	-3.28	-9.30 to 0.31	

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
Photochemical therapy (blue light)	0.11	-0.77 to 0.98	
Photochemical therapy (blue and red light)	0.73	-0.21 to 1.68	
Photochemical and photothermal therapy	-0.44	-1.22 to 0.32	
Log-odds ratios of discontinuation due to side effects versus topical retinoid			
		95% CrI	
GP care	-1.16	-1.86 to -0.51	Guideline NMA; distribution based on 10,000 iterations
BPO	-0.06	-0.86 to 0.70	
Azelaic acid	-0.78	-1.98 to 0.41	
Other topical acids	-0.49	-2.25 to 1.23	
Topical lincosamides	-1.38	-2.24 to -0.52	
Topical macrolides	-1.29	-2.67 to 0.07	
BPO + topical retinoid	0.30	-0.35 to 0.95	
BPO + topical lincosamide	-0.53	-1.52 to 0.46	
BPO + topical macrolide	-0.45	-1.53 to 0.65	
Topical retinoid + topical lincosamide	-0.66	-1.78 to 0.38	
Topical retinoid + topical macrolide	-0.43	-1.74 to 0.88	
Topical macrolide + topical anti-fungal	0.65	-2.06 to 4.14	
Combined oral contraceptive	-0.47	-1.55 to 0.66	
Combined chemical peels	-0.43	-7.17 to 6.22	
Baseline parameters – topical retinoid			
% CFB (total lesion count)	-50.47	log-normal (100 + % CFB) mean: 3.90; SE: 0.03	Weighted data from 2 RCTs (Gollnick 2009, Thiboutot 2006)
Discontinuation for any reason	0.40	Beta: α=30; β=45	Dikicier 2019
Discontinuation due to side effects	0.20	Beta: α=15; β=15	
Variability (spread) of log (100 + % CFB) applied to all treatments	0.796	No distribution	Based on analysis of data obtained from 4,081 people with moderate to severe facial acne that participated in 7 clinical trials of oral contraceptives or topical agents conducted in Europe (Gerlinger 2008).

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
Perceived improvement thresholds (%CBF)			
Excellent / good	-71.26	No distribution	Gerlinger 2008
Good / moderate	-53.14	No distribution	
Moderate / no	-28.20	No distribution	
Amount of AAC received after discontinuation, relapse, moderate or no improvement		Beta distribution	
Proportion of full course duration during which AAC is received after discontinuation	0.75	α=75; β=25	Committee's expert opinion
Proportion of people with moderate improvement switching to AAC at 3-6 months	0.67	α=67; β=33	
Proportion of people with relapse, moderate or no improvement receiving AAC at 6-12 months	0.70	α=70; β=30	
Risk of relapse - end of year 1, following:		Beta distribution	Assumption based on committee's expert opinion
Excellent improvement	0.10	α=10; β=90	
Good improvement	0.40	α=40; β=60	
Moderate improvement	0.60	α=60; β=40	
Utility values		Beta distribution	Synthesis of available evidence (Al Robaee 2009 using a mapping algorithm from Ara 2008; Kind 1999; Klassen 2000) supplemented by committee's expert opinion and further assumptions and assuming a linear relationship between utility and level of perceived improvement.
Excellent improvement	0.94	α=94; β=6	
Good improvement	0.90	α=90; β=10	
Moderate improvement	0.86	α=86; β=14	
No improvement and mild to moderate acne	0.82	α=82; β=18	
Utility decrement - intolerable side effects	0.04	α=4; β=96	
Intervention costs – resource use			
<u>Number of GP contacts</u>			
0-3 months (acute treatment)	2	0.80: 2, 0.20: 1	Probabilities assigned to numbers of sessions; number of visits based on the committee's expert opinion; distribution based on assumption. Details on intervention costs are provided in Table 17.
3-6 months (maintenance treatment)	1	0.60: 1, 0.20: 2, 0.20: 0	
Management of intolerable side effects	1	0.80: 1, 0.20: 0	
	1	No distribution	

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
Referral to specialist care [oral isotretinoin & physical treatments]			
Number of dermatology specialist contacts	7	0.70: 7, 0.20: 6, 0.10: 5	
0-6 months, oral isotretinoin – women	4	0.70: 4, 0.30: 3	
0-6 months, oral isotretinoin - men	6	0.60: 8, 0.20: 6-7, 0.20: 5	
Chemical peeling	1	No distribution	
Initiation of other physical treatments	1	No distribution	
Follow-up of other physical treatments	1	0.90: 1, 0.20: 2	
Management of intolerable side effects			
Number of sessions (other physical treatments)	3	0.80: 3, 0.20: 2	
Number of laboratory tests (oral isotretinoin)	7	No distribution	
Pregnancy urine test (females only)	1	No distribution	
FBT, U&E	4	No distribution	British National Formulary, July 2020
LFT, serum lipids			
Intervention costs - unit costs			
GP	£39	Normal, SE=0.10 of mean	Curtis 2019; distribution based on assumption
Dermatology outpatient cons-led first visit	£120	Normal, SE=0.10 of mean	NHS Improvement 2020; service code 330
Dermatology outpatient cons-led FU visit	£112	Normal, SE=0.10 of mean	NHS Improvement 2020; service code 330
Dermatology outpatient non-cons-led FU visit	£97	Normal, SE=0.10 of mean	NHS Improvement 2020; service code 330
Photodynamic therapy	£196	Normal, SE=0.10 of mean	NHS Improvement 2020; weighted day/outpatient; JC46Z
Photochemical therapy	£94	Normal, SE=0.10 of mean	NHS Improvement 2020; weighted day/outpatient; JC47Z
Pregnancy urine test	£1	Normal, SE=0.10 of mean	Assumption
FBC, LFT, serum lipids, U&E - each	£3	Normal, SE=0.10 of mean	Akhtar 2014; uplifted to reflect 2019 price
Drug acquisition costs	See Table 17	No distribution	NHS Business Services Authority 2020; Department of Health and Social Care, 2020 All distributions based on assumptions

Input parameter	Mean deterministic value	Probability distribution	Source of data – comments
Annual average acne care cost (mild to moderate acne)	£286	Gamma: SE=0.30 of mean	Based on GP consultation and prescription data from people with acne (Francis 2017), combined with relevant intervention costs (Table 17).

AAC: average acne care; BPO: benzoyl peroxide; CFB: change from baseline; cons: consultant; CrI: credible intervals; cumul: cumulative; FBC: full blood count; FU: follow-up; LFT: liver function test; SE: standard error; U&E: urea and electrolytes

Presentation of the results

For each treatment option, the Net Monetary Benefit (NMB) was estimated for each iteration and averaged across the 10,000 iterations, determined by the formula

$$NMB = E \bullet \lambda - C$$

where E and C are the effects (QALYs) and total costs, respectively, of each treatment option, and λ represents the willingness-to-pay per unit of effectiveness, set at the NICE lower cost-effectiveness threshold of £20,000/QALY (NICE, 2014). The treatment with the highest NMB is the most cost-effective option (Fenwick 2001).

Incremental mean costs and effects (QALYs) of each treatment option versus GP care are also presented in the form of cost effectiveness planes.

The mean ranking by cost-effectiveness is reported for each treatment (out of 10,000 iterations), where a rank of 1 suggests that a treatment is the most cost-effective amongst all evaluated treatment options. The probability of the treatment with the highest NMB being the most cost-effective option is also provided, calculated as the proportion of the 10,000 iterations in which the treatment had the highest NMB amongst all treatment options considered in the analysis. The probability of cost-effectiveness has been estimated in a step-wise approach, according to which the most cost-effective treatment is omitted at each step, and the probability of cost-effectiveness of the next most cost-effective treatment amongst the remaining treatment options is re-calculated. The probabilities estimated following this approach reflect the uncertainty around the cost-effectiveness not only of the most cost-effective treatment, but also of the second, third, fourth, etc. most cost-effective treatment, after more cost-effective treatment options have been omitted from analysis. Finally, the cost-effectiveness acceptability frontier (CEAF) has been plotted, showing the treatment with the highest mean NMB over different cost-effectiveness thresholds (λ), and the probability that this treatment is the most cost-effective among those assessed (Fenwick 2001).

Validation of the economic model

The economic model (including the conceptual model and the identification and selection of input parameters) was developed by the health economist in collaboration with a health economics sub-group formed by members of the committee. As part of the model validation, all inputs and model formulae were systematically checked; the model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. The base-case results and results of sensitivity analyses were discussed with the committee to confirm their plausibility. In addition, the economic model (excel spreadsheet) and the model methods and results reporting in this appendix were checked for their validity and accuracy by a health economist that was external to the guideline development team.

Economic modelling results

The economic analysis included one treatment that is only suitable to females (combined oral contraceptive pill: ethinylestradiol + norgestimate). Moreover, the intervention cost of oral isotretinoin differs between sexes, due to the need for increased monitoring and pregnancy tests for females, and this may impact on its cost-effectiveness relative to other treatment options. Therefore, two analyses, for females and males, respectively, are presented.

Base-case economic analysis

The results of the base-case economic analysis for both sexes are provided in Table 20. The table provides the number of observations on each treatment class in the NMA of efficacy that informed the economic analysis, the mean QALYs and mean intervention and total costs

of each treatment option, the likelihood of a person having good or excellent improvement one year after initiation of each treatment, the mean NMB and ranking of each treatment, and its probability of being cost-effective in a step-wise approach at a threshold of £20,000/QALY. Treatments have been ordered from the most to the least cost-effective. Costs and NMB for oral isotretinoin, and also probabilities of cost-effectiveness and rankings of all treatment classes are provided separately for females and males.

The order of treatments from the most to the least cost-effective in the base-case analysis was azelaic acid + clindamycin (topical), azelaic acid + erythromycin (topical), photochemical therapy [blue & red], clindamycin + tretinoin (topical), erythromycin + bifonazole (topical), benzoyl peroxide + adapalene (topical), salicylic acid peel, benzoyl peroxide + erythromycin (topical), photochemical therapy [blue], tretinoin + erythromycin (topical), benzoyl peroxide + clindamycin (topical), adapalene (topical), benzoyl peroxide (topical), azelaic acid (topical), erythromycin (topical), salicylic acid (topical), ethinylestradiol + norgestimate (oral) (relevant only to females), clindamycin (topical), photochemical and photothermal therapy, GP care, oral Isotretinoin total dose <120mg/kg. The probability of azelaic acid + clindamycin (topical) being the most cost-effective treatment option was 0.30 for both females and males at the lower NICE cost-effectiveness threshold of £20,000/QALY.

Figure 12 provides the cost effectiveness plane of the base-case analysis. Each treatment class is placed on the plane according to its incremental total costs and QALYs compared with GP care, which has been placed at the origin. For oral isotretinoin two separate points are shown on the plane, for females and males, respectively.

The CEAF of the base-case analysis for females and males is shown in Figure 13 and Figure 14, respectively. In both sexes, benzoyl peroxide (topical) is the most cost-effective option at very low cost-effectiveness thresholds (up to £1000/QALY). Then, and up to a cost-effectiveness threshold of about £30,000/QALY, azelaic acid and clindamycin (topical) appears to be the most cost-effective option. For higher cost-effectiveness thresholds, photochemical therapy (blue and red) appears to be the most cost-effective treatment options for both sexes.

Table 20: Base-case results of economic modelling: treatments for people with mild to moderate acne

Treatment	N	NMB / person	Likelihood of excellent / good improvement at 1 year	Mean per person			Prob* best F	Mean rank F	Prob* best M	Mean rank M
				QALY	Intervention cost	Total cost	At a threshold of £20,000/QALY			
Azelaic acid + clindamycin (topical)	44	£17,328	0.52	0.878	£125	£228	0.30	3.97	0.30	3.95
Azelaic acid + erythromycin (topical)	40	£17,238	0.48	0.874	£125	£234	0.24	4.90	0.24	4.87
Photochemical therapy [blue & red]	69	£17,224	0.57	0.888	£370	£541	0.22	6.24	0.22	6.13
Clindamycin + tretinoin (topical)	276	£17,114	0.42	0.867	£120	£234	0.14	6.39	0.14	6.35
Erythromycin + bifonazole (topical)	74	£17,111	0.43	0.868	£113	£245	0.24	7.80	0.24	7.66
Benzoyl peroxide + adapalene (topical)	1057	£17,099	0.43	0.867	£121	£243	0.18	6.24	0.18	6.22
Salicylic acid peel	101	£17,070	0.62	0.890	£620	£734	0.32	9.99	0.32	9.71
Benzoyl peroxide + erythromycin (topical)	351	£17,029	0.39	0.863	£113	£238	0.23	9.04	0.23	8.89
Photochemical therapy [blue]	138	£17,014	0.50	0.880	£410	£584	0.27	10.30	0.27	10.05
Tretinoin + erythromycin (topical)	135	£16,970	0.36	0.860	£103	£225	0.28	10.57	0.28	10.35
Benzoyl peroxide + clindamycin (topical)	992	£16,966	0.36	0.861	£116	£244	0.22	10.15	0.22	10.05
Adapalene (topical)	1623	£16,950	0.36	0.860	£107	£242	0.19	10.49	0.20	10.40
Benzoyl peroxide (topical)	1109	£16,946	0.34	0.858	£79	£215	0.30	10.68	0.31	10.58
Azelaic acid (topical)	301	£16,918	0.33	0.857	£86	£219	0.30	11.70	0.33	11.55
Erythromycin (topical)	765	£16,892	0.33	0.856	£98	£234	0.33	12.76	0.38	12.55
Salicylic acid (topical)	106	£16,865	0.31	0.854	£82	£222	0.40	13.44	0.52	13.11
Ethinylestradiol + norgestimate (oral) [F]	2313	£16,810	0.29	0.851	£75	£218	0.44	15.12	Not relevant	
Clindamycin (topical)	3073	£16,760	0.27	0.850	£98	£237	0.55	16.88	0.52	16.26
Photochemical and photothermal therapy	107	£16,729	0.49	0.879	£670	£842	0.49	15.08	0.47	14.57
GP care	2005	£16,613	0.20	0.842	£66	£222	0.83	19.24	0.69	18.39
Oral Isotretinoin total dose <120mg/kg	54	£16,402 F £16,541 M	0.37	0.853	£524 F £391 M	£660 F £522 M	1.00	20.02	1.00	18.35

** estimated in a step-wise approach, according to which the most cost-effective intervention is omitted at each step, and the probability of cost-effectiveness of the next most cost-effective intervention amongst the remaining treatment options is re-calculated; F: females; M: males*

Figure 12. Base-case analysis: cost-effectiveness plane of treatments for people with mild to moderate acne

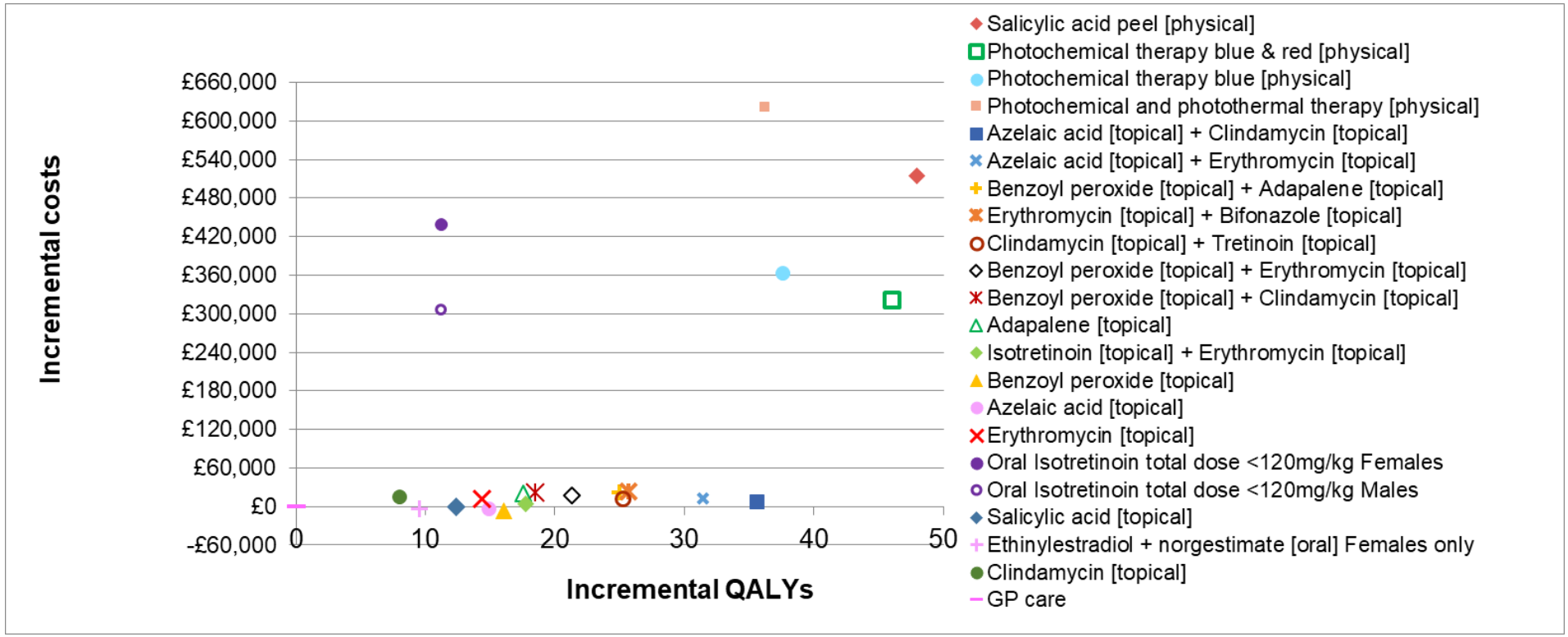


Figure 13. Base-case analysis: cost-effectiveness acceptability frontier of treatments for females with mild to moderate acne

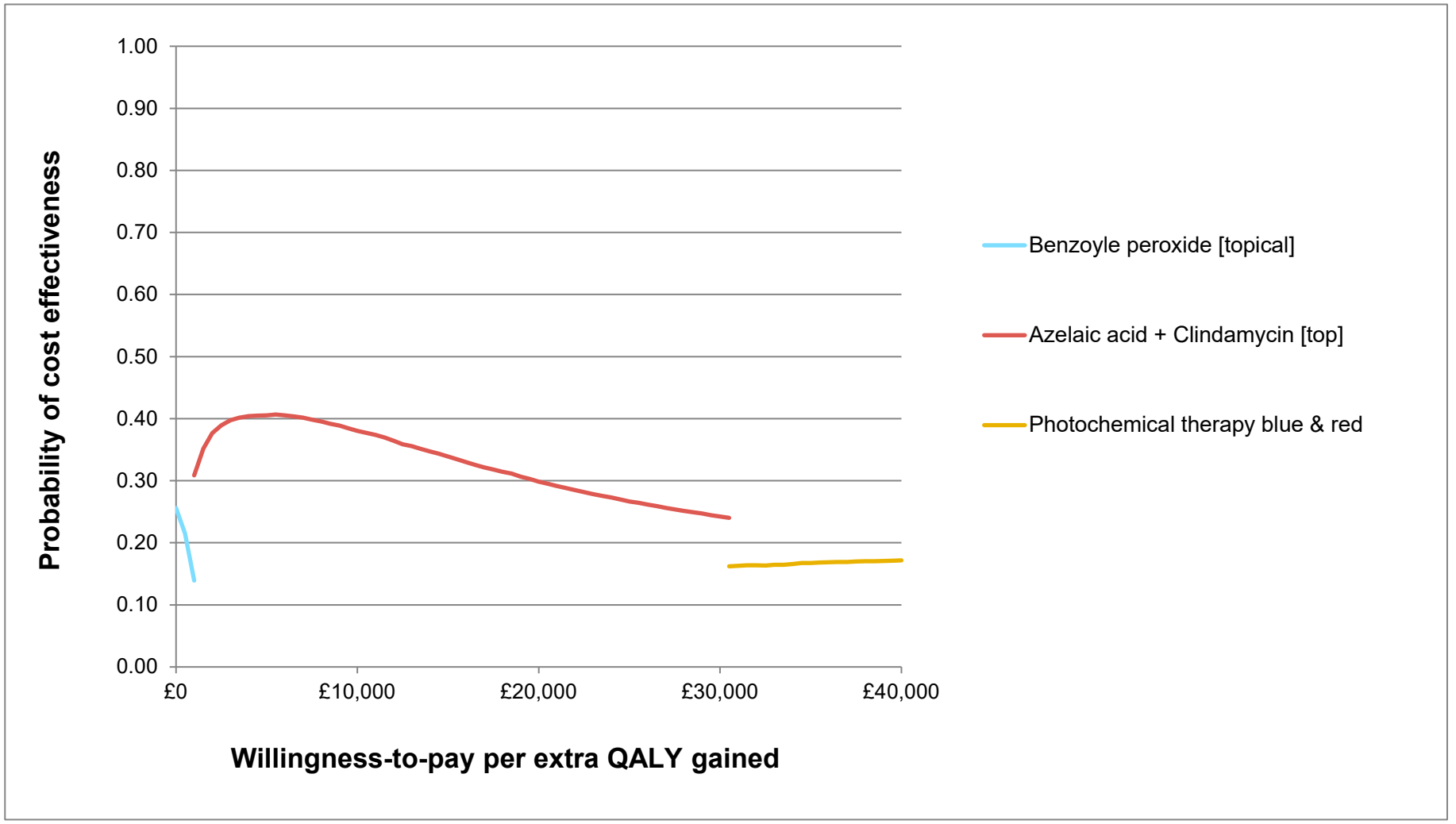
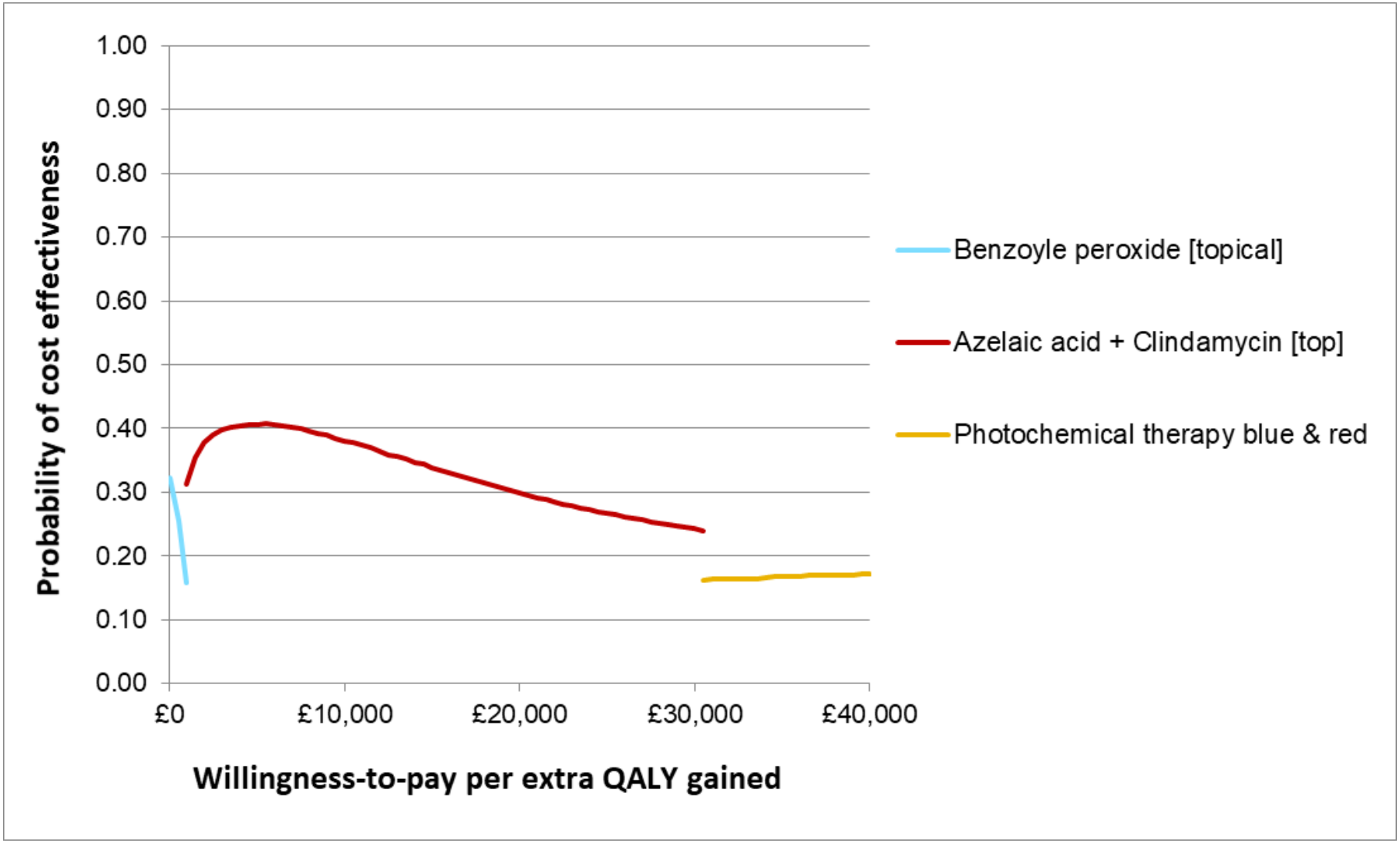


Figure 14. Base-case analysis: cost-effectiveness acceptability frontier of treatments for males with mild to moderate acne



Bias-adjusted economic analysis

Results of the bias-adjusted model are shown on Table 21. The bias-adjusted economic analysis included fewer treatments than the base-case analysis because fewer treatments showed evidence of effect versus placebo in the bias-adjusted NMA that informed the respective economic analysis. All treatments in the bias-adjusted economic analysis were suitable to both females and males, therefore the results of one analysis are provided for both sexes.

The order of treatments from the most to the least cost-effective in the bias-adjusted analysis was azelaic acid + clindamycin (topical), photochemical therapy [blue & red], azelaic acid + erythromycin (topical), benzoyl peroxide + adapalene (topical), clindamycin + tretinoin (topical), erythromycin + bifonazole (topical), salicylic acid peel, benzoyl peroxide + erythromycin (topical), adapalene (topical), benzoyl peroxide + clindamycin (topical), benzoyl peroxide (topical), photochemical therapy [blue], erythromycin (topical), GP care. The probability of azelaic acid + clindamycin (topical) being the most cost-effective treatment option was 0.31 at the lower NICE cost-effectiveness threshold of £20,000/QALY.

Figure 15 provides the cost effectiveness plane of the bias-adjusted analysis, whereas the CEAF of this analysis is shown in Figure 16. Like base-case analysis, in the bias-adjusted analysis benzoyl peroxide (topical) is the most cost-effective option at very low cost-effectiveness thresholds (up to £1000/QALY). Then, and up to a cost-effectiveness threshold of about £29,000/QALY, azelaic acid and clindamycin (topical) appears to be the most cost-effective option. For higher cost-effectiveness thresholds, photochemical therapy (blue and red) appears to be the most cost-effective treatment options for both sexes.

Results were overall robust to the scenarios explored through deterministic sensitivity analysis, with the exception of the relative cost-effectiveness of physical therapies (photochemical therapy and chemical peels) which was affected by most scenarios explored. It is noted that some of the scenarios involving changes in efficacy and the spread of the log (100 + % CFB) were affected by ceiling effects, when some treatments (or some people receiving treatment) reached 100% improvement and could not possibly improve further. Results of the bias-adjusted deterministic sensitivity analysis are shown in Table 22.

Table 21: Bias-adjusted results of economic modelling: treatments for people with mild to moderate acne

Treatment	N	NMB / person	Likelihood of excellent / good improvement at 1 year	Mean per person			Prob* best	Mean rank
				QALY	Intervention cost	Total cost	At a threshold of £20,000/QALY	
Azelaic acid + clindamycin (topical)	44	£17,264	0.49	0.875	£123	£231	0.31	3.59
Photochemical therapy [blue & red]	69	£17,163	0.55	0.885	£370	£545	0.19	5.58
Azelaic acid + erythromycin (topical)	40	£17,149	0.44	0.869	£123	£238	0.23	4.93
Benzoyl peroxide + adapalene (topical)	1057	£17,123	0.43	0.868	£121	£242	0.18	4.59
Clindamycin + tretinoin (topical)	276	£17,105	0.42	0.867	£120	£234	0.25	5.21
Erythromycin + bifonazole (topical)	74	£17,061	0.41	0.865	£112	£247	0.29	6.73
Salicylic acid peel	101	£17,029	0.61	0.888	£621	£736	0.36	7.98
Benzoyl peroxide + erythromycin (topical)	351	£17,017	0.38	0.863	£112	£239	0.40	7.30
Adapalene (topical)	1623	£16,957	0.36	0.860	£107	£242	0.24	8.29
Benzoyl peroxide + clindamycin (topical)	992	£16,956	0.36	0.860	£115	£245	0.37	8.48
Benzoyl peroxide (topical)	1109	£16,937	0.34	0.858	£79	£216	0.45	8.87
Photochemical therapy [blue]	138	£16,928	0.47	0.876	£410	£588	0.55	9.39
Erythromycin (topical)	765	£16,859	0.31	0.855	£97	£236	0.97	10.87
GP care	2005	£16,704	0.23	0.846	£67	£217	1.00	13.21

** estimated in a step-wise approach, according to which the most cost-effective intervention is omitted at each step, and the probability of cost-effectiveness of the next most cost-effective intervention amongst the remaining treatment options is re-calculated*

Figure 15. Bias-adjusted analysis: cost-effectiveness plane of treatments for people with mild to moderate acne

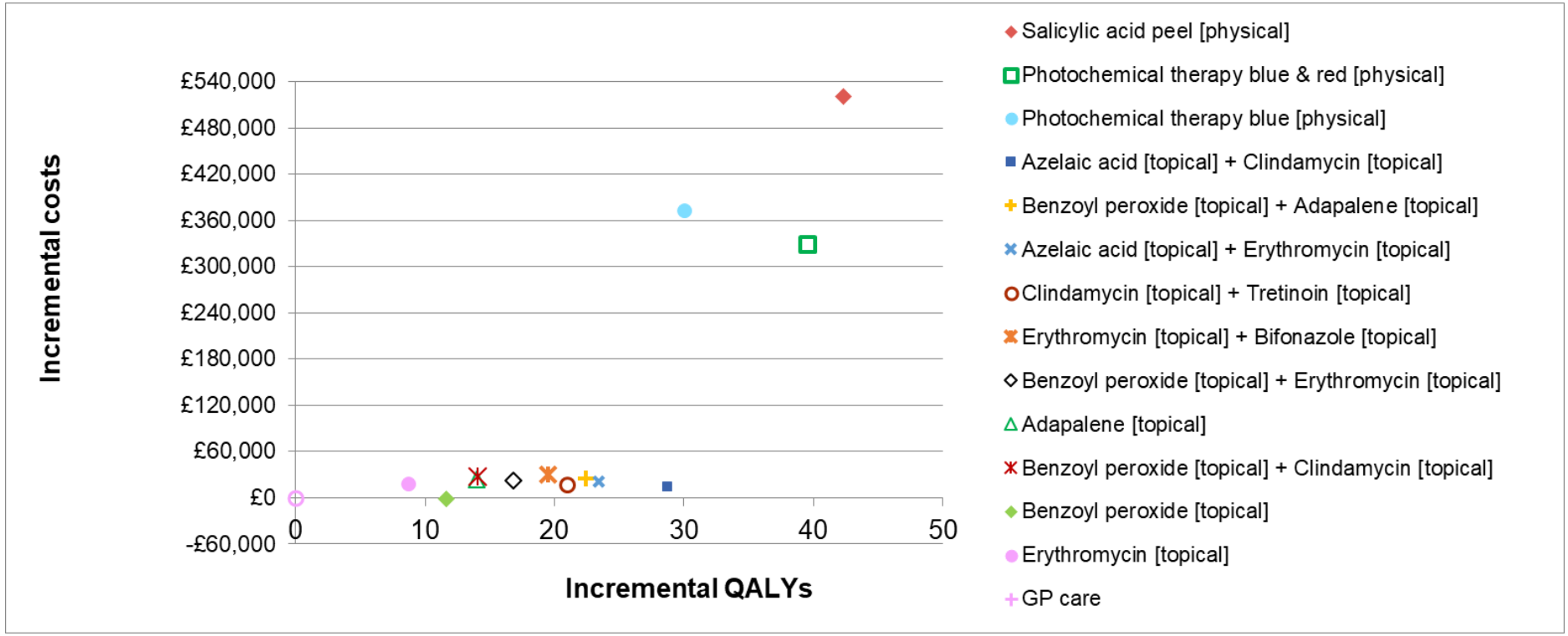


Figure 16. Bias-adjusted analysis: cost-effectiveness acceptability frontier of treatments for people with mild to moderate acne

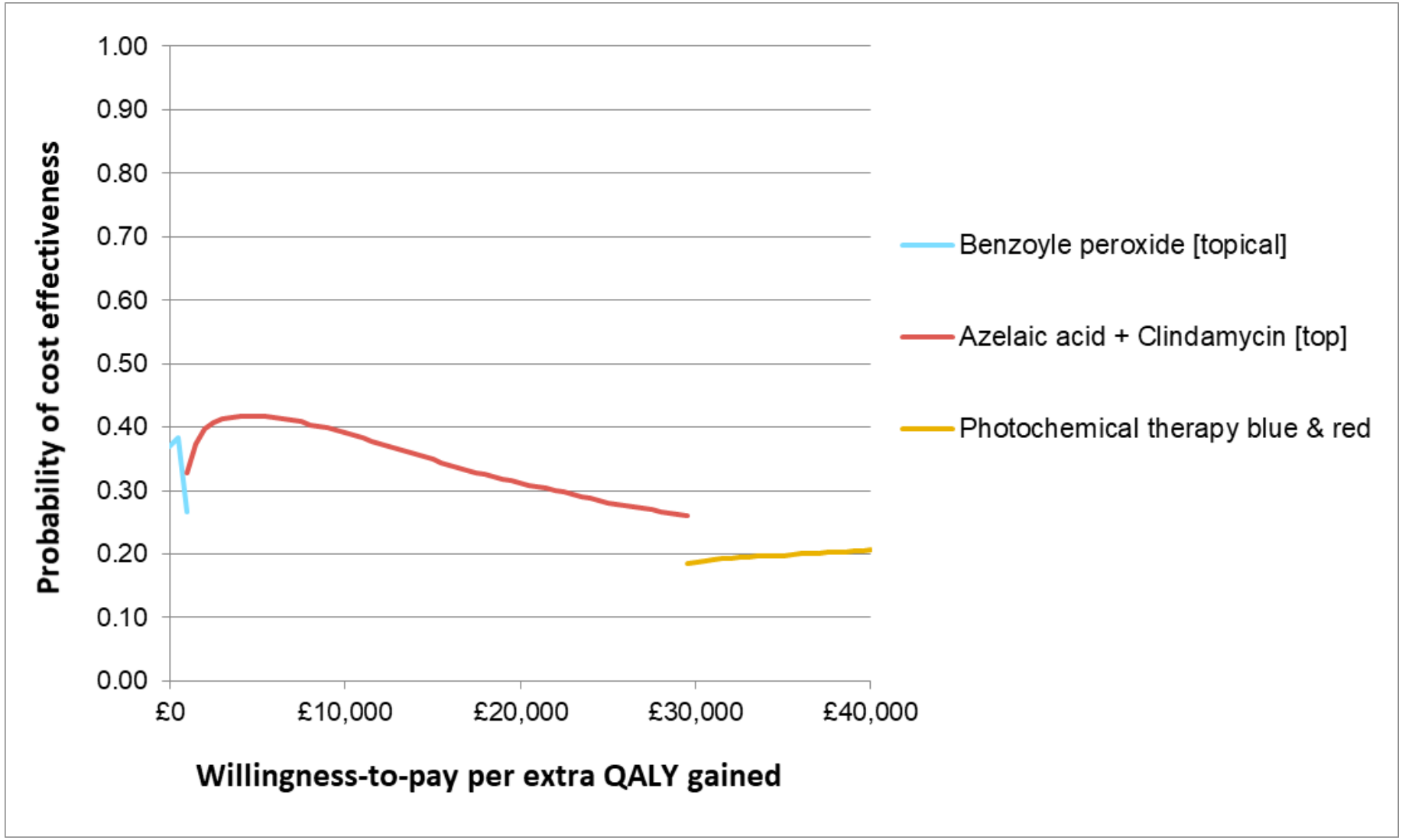


Table 22. Results of deterministic sensitivity analysis - bias-adjusted analysis

Base-case deterministic analysis		Topical retinoid baseline % CFB: 50% reduction		Topical retinoid baseline % CFB: 50% increase		Topical retinoid discontinuation risk for any reason: 50% reduction	
Treatment	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**
Azelaic acid + clindamycin (topical)	£17,308	Azelaic acid + clindamycin (topical)	£16,830	Azelaic acid + clindamycin (topical)	£18,072	Azelaic acid + clindamycin (topical)	£17,312
Azelaic acid + erythromycin (topical)	£17,203	Azelaic acid + erythromycin (topical)	£16,770	Photochemical therapy [blue & red]	£17,987	Azelaic acid + erythromycin (topical)	£17,206
Photochemical therapy [blue & red]	£17,202	BPO + adapalene (topical)	£16,756	Azelaic acid + erythromycin (topical)	£17,938	BPO + adapalene (topical)	£17,205
BPO + adapalene (topical)	£17,192	Clindamycin + tretinoin (topical)	£16,753	BPO + adapalene (topical)	£17,930	Clindamycin + tretinoin (topical)	£17,175
Clindamycin + tretinoin (topical)	£17,170	Erythromycin + bifonazole (topical)	£16,703	Clindamycin + tretinoin (topical)	£17,889	Photochemical therapy [blue & red]	£17,153
Erythromycin + bifonazole (topical)	£17,104	BPO + erythromycin (topical)	£16,700	Erythromycin + bifonazole (topical)	£17,805	Erythromycin + bifonazole (topical)	£17,117
BPO + erythromycin (topical)	£17,077	Adapalene (topical)	£16,676	Photochemical therapy [blue]	£17,774	BPO + erythromycin (topical)	£17,083
Adapalene (topical)	£17,039	BPO + clindamycin (topical)	£16,676	BPO + erythromycin (topical)	£17,746	Adapalene (topical)	£17,051
BPO + clindamycin (topical)	£17,035	BPO (topical)	£16,674	Adapalene (topical)	£17,689	BPO + clindamycin (topical)	£17,040
BPO (topical)	£17,018	Photochemical therapy [blue & red]	£16,633	BPO + clindamycin (topical)	£17,678	BPO (topical)	£17,034
Salicylic acid peel	£17,007	Erythromycin (topical)	£16,632	Salicylic acid peel	£17,665	Salicylic acid peel	£17,003
Photochemical therapy [blue]	£16,976	GP care	£16,559	BPO (topical)	£17,637	Erythromycin (topical)	£16,948
Erythromycin (topical)	£16,944	Photochemical therapy [blue]	£16,488	Erythromycin (topical)	£17,509	Photochemical therapy [blue]	£16,935
GP care	£16,800	Salicylic acid peel	£16,412	GP care	£17,234	GP care	£16,810
Topical retinoid discontinuation risk for any reason: 50% increase		**Spread (SE) around the log (100 +% CFB): 50% reduction**		**Spread (SE) around the log (100 + % CFB): 50% increase**		**Risk of relapse: 50% reduction**	
Treatment	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**
Azelaic acid + clindamycin (topical)	£17,304	Azelaic acid + clindamycin (topical)	£17,376	Azelaic acid + clindamycin (topical)	£17,268	Azelaic acid + clindamycin (topical)	£17,353
Photochemical therapy [blue & red]	£17,235	Photochemical therapy [blue & red]	£17,348	Azelaic acid + erythromycin (topical)	£17,192	Photochemical therapy [blue & red]	£17,248
Azelaic acid + erythromycin (topical)	£17,199	Azelaic acid + erythromycin (topical)	£17,217	BPO + adapalene (topical)	£17,180	Azelaic acid + erythromycin (topical)	£17,246
BPO + adapalene (topical)	£17,180	BPO + adapalene (topical)	£17,209	Clindamycin + tretinoin (topical)	£17,170	BPO + adapalene (topical)	£17,235
Clindamycin + tretinoin (topical)	£17,164	Salicylic acid peel	£17,199	Photochemical therapy [blue & red]	£17,117	Clindamycin + tretinoin (topical)	£17,212
Erythromycin + bifonazole (topical)	£17,092	Clindamycin + tretinoin (topical)	£17,164	Erythromycin + bifonazole (topical)	£17,115	Erythromycin + bifonazole (topical)	£17,146
BPO + erythromycin (topical)	£17,070	Erythromycin + bifonazole (topical)	£17,080	BPO + erythromycin (topical)	£17,104	BPO + erythromycin (topical)	£17,118
BPO + clindamycin (topical)	£17,029	Photochemical therapy [blue]	£17,029	Adapalene (topical)	£17,076	Adapalene (topical)	£17,080
Adapalene (topical)	£17,028	BPO + erythromycin (topical)	£17,025	BPO + clindamycin (topical)	£17,074	BPO + clindamycin (topical)	£17,075
Photochemical therapy [blue]	£17,015	Adapalene (topical)	£16,971	BPO (topical)	£17,069	BPO (topical)	£17,058
Salicylic acid peel	£17,014	BPO + clindamycin (topical)	£16,963	Erythromycin (topical)	£17,015	Salicylic acid peel	£17,053
BPO (topical)	£17,002	BPO (topical)	£16,926	Photochemical therapy [blue]	£16,944	Photochemical therapy [blue]	£17,021
Erythromycin (topical)	£16,940	Erythromycin (topical)	£16,819	GP care	£16,916	Erythromycin (topical)	£16,982

Base-case deterministic analysis	
Treatment	**NMB**
GP care	£16,789

Topical retinoid baseline % CFB: 50% reduction	
Treatment	**NMB**
GP care	£16,605

Topical retinoid baseline % CFB: 50% increase	
Treatment	**NMB**
Salicylic acid peel	£16,893

Topical retinoid discontinuation risk for any reason: 50% reduction	
Treatment	**NMB**
GP care	£16,833

Risk of relapse: 50% increase	
Treatment	**NMB**
Azelaic acid + clindamycin (topical)	£17,264
Azelaic acid + erythromycin (topical)	£17,159
Photochemical therapy [blue & red]	£17,157
BPO + adapalene (topical)	£17,148
Clindamycin + tretinoin (topical)	£17,127
Erythromycin + bifonazole (topical)	£17,061
BPO + erythromycin (topical)	£17,035
Adapalene (topical)	£16,999
BPO + clindamycin (topical)	£16,994
BPO (topical)	£16,978
Salicylic acid peel	£16,961
Photochemical therapy [blue]	£16,932
Erythromycin (topical)	£16,906
GP care	£16,766

Average acne care cost: 50% reduction	
Treatment	**NMB**
Azelaic acid + clindamycin (topical)	£17,360
Photochemical therapy [blue & red]	£17,281
Azelaic acid + erythromycin (topical)	£17,258
BPO + adapalene (topical)	£17,248
Clindamycin + tretinoin (topical)	£17,225
Erythromycin + bifonazole (topical)	£17,168
BPO + erythromycin (topical)	£17,139
Adapalene (topical)	£17,103
BPO + clindamycin (topical)	£17,097
BPO (topical)	£17,084
Salicylic acid peel	£17,060
Photochemical therapy [blue]	£17,057
Erythromycin (topical)	£17,012
GP care	£16,874

Average acne care cost: 50% increase	
Treatment	**NMB**
Azelaic acid + clindamycin (topical)	£17,256
Azelaic acid + erythromycin (topical)	£17,147
BPO + adapalene (topical)	£17,135
Photochemical therapy [blue & red]	£17,124
Clindamycin + tretinoin (topical)	£17,114
Erythromycin + bifonazole (topical)	£17,039
BPO + erythromycin (topical)	£17,015
Adapalene (topical)	£16,975
BPO + clindamycin (topical)	£16,972
BPO (topical)	£16,954
Salicylic acid peel	£16,952
Photochemical therapy [blue]	£16,896
Erythromycin (topical)	£16,876
GP care	£16,725

Mean number of physical therapy sessions increased to 4	
Treatment	**NMB**
Azelaic acid + clindamycin (topical)	£17,308
Azelaic acid + erythromycin (topical)	£17,203
BPO + adapalene (topical)	£17,192
Clindamycin + tretinoin (topical)	£17,170
Photochemical therapy [blue & red]	£17,163
Erythromycin + bifonazole (topical)	£17,104
BPO + erythromycin (topical)	£17,077
Adapalene (topical)	£17,039
BPO + clindamycin (topical)	£17,035
BPO (topical)	£17,018
Salicylic acid peel	£17,007
Erythromycin (topical)	£16,944
Photochemical therapy [blue]	£16,922
GP care	£16,800

No average acne care following completion of physical treatment	
Treatment	**NMB**
Azelaic acid + clindamycin (topical)	£17,308
Photochemical therapy [blue & red]	£17,237
Azelaic acid + erythromycin (topical)	£17,203
BPO + adapalene (topical)	£17,192
Clindamycin + tretinoin (topical)	£17,170
Erythromycin + bifonazole (topical)	£17,104
BPO + erythromycin (topical)	£17,077
Salicylic acid peel	£17,068
Adapalene (topical)	£17,039
BPO + clindamycin (topical)	£17,035

Base-case deterministic analysis		Topical retinoid baseline % CFB: 50% reduction		Topical retinoid baseline % CFB: 50% increase		Topical retinoid discontinuation risk for any reason: 50% reduction	
Treatment	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**	**Treatment**	**NMB**
Photochemical therapy [blue]	£17,020						
BPO (topical)	£17,018						
Erythromycin (topical)	£16,944						
GP care	£16,800						

BPO: benzoyl peroxide

Discussion – conclusions, strengths and limitations of economic analysis

The guideline economic analysis assessed the cost effectiveness of a range of topical, oral and physical treatments for people with mild to moderate acne. The interventions assessed were determined by the availability of efficacy data obtained from the NMAs that were conducted to inform this guideline.

In the base-case analysis, the order of treatments from the most to the least cost-effective was azelaic acid + clindamycin (topical), azelaic acid + erythromycin (topical), photochemical therapy [blue & red], clindamycin + tretinoin (topical), erythromycin + bifonazole (topical), benzoyl peroxide + adapalene (topical), salicylic acid peel, benzoyl peroxide + erythromycin (topical), photochemical therapy [blue], tretinoin + erythromycin (topical), benzoyl peroxide + clindamycin (topical), adapalene (topical), benzoyl peroxide (topical), azelaic acid (topical), erythromycin (topical), salicylic acid (topical), ethinylestradiol + norgestimate (oral) (relevant only to females), clindamycin (topical), photochemical and photothermal therapy, GP care, oral Isotretinoin total dose <120mg/kg. The probability of azelaic acid + clindamycin (topical) being the most cost-effective treatment option was 0.30 for both females and males at the lower NICE cost-effectiveness threshold of £20,000/QALY.

In the bias-adjusted analysis, which utilised efficacy data from a NMA that adjusted for small study bias, the order of treatments from the most to the least cost-effective was azelaic acid + clindamycin (topical), photochemical therapy [blue & red], azelaic acid + erythromycin (topical), benzoyl peroxide + adapalene (topical), clindamycin + tretinoin (topical), erythromycin + bifonazole (topical), salicylic acid peel, benzoyl peroxide + erythromycin (topical), adapalene (topical), benzoyl peroxide + clindamycin (topical), benzoyl peroxide (topical), photochemical therapy [blue], erythromycin (topical), GP care. The probability of azelaic acid + clindamycin (topical) being the most cost-effective treatment option was 0.31 at the lower NICE cost-effectiveness threshold of £20,000/QALY.

The probabilities of cost-effectiveness estimated in a step-wise approach for the top 15 treatments in ranking in the base-case analysis and the top 10 treatments in ranking in the bias-adjusted analysis did not exceed 0.40, although increasingly fewer treatment options were included in the step-wise analysis, indicating high uncertainty in the results.

Results of the economic analysis were overall robust to changes in input parameters tested in deterministic sensitivity analysis.

The analysis utilised clinical effectiveness parameters derived from NMAs on three outcomes: efficacy, discontinuation for any reason, and discontinuation due to side effects. This methodology enabled evidence synthesis from both direct and indirect comparisons between interventions, and allowed simultaneous inference on all treatments examined in pair-wise trial comparisons while respecting randomisation (Caldwell 2005; Lu 2004). The quality and limitations of RCTs considered in the NMAs have unavoidably impacted on the quality of the economic model clinical input parameters. For example, economic results may be have been affected by reporting and publication bias.

Effects for some interventions were informed by limited evidence; more specifically, azelaic acid + clindamycin (topical), azelaic acid + erythromycin (topical), photochemical therapy [blue & red], erythromycin + bifonazole (topical) and oral isotretinoin had fewer than 100 observations each, across the RCTs included in the NMA of efficacy.

Discontinuation data were not available for a number of treatments; in such cases, other treatments served as proxies, based on the committee's expert opinion. More specifically, the following proxies were used to inform discontinuation where relevant data were not available:

- azelaic acid was used as a proxy for combined azelaic acid and topical clindamycin as well as for combined azelaic acid and topical erythromycin (for discontinuation due to side effects only)
- combined azelaic acid and topical clindamycin was used as a proxy for combined azelaic acid and topical erythromycin (for discontinuation for any reason only)
- oral isotretinoin with total cumulative dose < 120mg/kg, photochemical therapy (blue), photochemical therapy (blue & red) and photochemical + photothermal therapy were assumed to have a risk of discontinuation due to side effects that was equal to the mean risk of discontinuation due to side effects of all other treatments considered in the economic analysis.

This lack of discontinuation data for some treatments and use of other treatements in the analysis as proxies for discontinuation is acknowledged as a limitation of the economic analysis. Nevertheless, it is noted that the impact of discontinuation data on the results of the economic model was relatively small as it affected only costs associated with discontinuation and not outcomes; this is because efficacy data used in the economic analysis were taken from intention-to-treat rather than completer analysis, where possible, and therefore they reflected effects on both those completing treatment and those discontinuing treatment early.

Global inconsistency checks and further inconsistency checks through node-splitting indicated that there was inconsistency between direct and indirect evidence considered in all three NMAs that informed the economic analysis. Moreover, heterogeneity across all NMAs was found to be high. It is also noted that the relative effects of most interventions versus placebo were large and characterised, in many cases, by considerably wide 95% credible intervals. These findings need to be taken into account when interpreting the results of the NMAs but also the cost effectiveness results.

The baseline risk of efficacy was derived from 2 large RCTs (N=679) of adapalene 0.1% in people with mild to moderate acne, as no relevant observational data were possible to identify. The baseline risk of discontinuation for any reason and due to intolerable side effects were derived from an observational study of 250 people with mild to moderate acne in Turkey, who were prescribed topical treatments, as this was the only identified observational study that provided such data. Baseline data were tested in deterministic sensitivity analysis.

The time horizon of the analysis was one year, which was considered adequate to capture longer terms and costs associated with a course of treatment for acne without significant extrapolation over the course of acne.

The relationship between a person's % change in total lesion count from baseline and their perceived acne symptom improvement was determined using data from people with moderate to severe facial acne due to lack of alternative data specific to people with mild to moderate acne.

Utility data used in the economic model were estimated based primarily on the committee's expert opinion, as a systematic review of studies reporting utility data for acne-related health states yielded a very small number of studies of overall low quality that either provided no data on acne-specific health states or lacked face validity. Nevertheless, the number of people with excellent or good improvement one year after treatment initiation was also estimated, to assist consideration of the relative cost-effectiveness of treatments beyond the QALY.

Intervention costs were estimated based on relevant information provided in the studies included in the NMA supplemented by the committee's expert opinion, in order to reflect routine NHS practice. Unit costs were taken from national sources.

Acne-related care costs were based on an analysis of primary care consultations and prescription data of 318,515 people with acne over a 10-year period in the UK, combined with the committee's expert opinion on resource use associated with prescribed treatments.

These data were not specific to people with mild to moderate acne and covered only primary care. Resource use and costs associated with specialist care received by people with mild to moderate acne were estimated by the committee and added onto the primary care cost estimate, in order to estimate the total annual healthcare cost incurred by people with mild to moderate acne.

All types of treatment for people with mild to moderate acne may lead to the development of side effects. Ideally, the economic model should incorporate costs and decrements in HRQoL associated with the risk of development of side effects. However, relevant data on side-effect rates for each treatment considered in the economic model, from large observational studies, were not readily available. Therefore, the impact of side effects on HRQoL and their associated management costs were not considered in the economic model. On the other hand, the analysis incorporated the impact of intolerable side effects on HRQoL and costs; however, the costs associated with management of intolerable side effects may have been underestimated, as they were limited to the cost of one healthcare professional contact. Antimicrobial resistance resulting from use of topical or oral antibiotics and associated costs were also not considered in the analysis. These omissions in the model structure are acknowledged as limitations of the analysis.

Overall conclusions from the guideline economic analysis

The guideline economic analysis suggests that all assessed topical, oral and physical treatments are more cost-effective for people with mild to moderate acne compared with GP care. According to the analysis that used efficacy data adjusted for small study bias, topical combinations such as azelaic acid combined with lincosamide or macrolide, benzoyl peroxide and adapalene, or clindamycin and tretinoin, as well as photochemical therapy [blue & red] are likely to comprise the most cost-effective treatment options for this population. Topical treatments such as benzoyl peroxide, macrolides and photochemical therapy [blue] appear to be less cost-effective, although more cost-effective than GP care alone. In-between, there is another group of treatments (topical macrolide + antifungal, topical benzoyl peroxide + macrolide or lincosamide, topical retinoids, and chemical peels) that occupied middle cost effectiveness rankings in the guideline economic analysis.

The guideline economic analysis was based on the best quality data derived from the guideline NMA. However, the NMAs were overall characterised by inconsistency between direct and indirect evidence, high between-study heterogeneity, as well as large effects and considerably wide 95% credible intervals for some treatments, and this should be taken into account when interpreting the results of the analysis.

References

Akhtar W, Chung Y (2014). Saving the NHS one blood test at a time. BMJ Qual Improv Rep 2(2), u204012.w1749.

Al Robaee AA (2009). Assessment of general health and quality of life in patients with acne using a validated generic questionnaire. Acta Dermatovenerol Alp Pannonica Adriat 18(4), 157-64.

Ara R, Brazier J (2008). Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value Health 11(7), 1131-1143.

Brazier J, Roberts J, Deverill M (2002) The estimation of a preference-based measure of health from the SF-36. Journal of Health Economics 21(2), 271-92

Briggs A, Sculpher M, Claxton K (2006) Decision Modelling for Health Economic Evaluation. New York, NY: Oxford University Press

British National Formulary (July 2020). Isotretinoin monitoring requirements. London: BMJ Group and the Royal Pharmaceutical Society of Great Britain. https://bnf.nice.org.uk/drug/isotretinoin.html#monitoringRequirements

Caldwell DM, Ades AE, Higgins JP (2005) Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 331(7521), 897-900

Chen CL, Kuppermann M, Caughey AB, Zane LT (2008). A community-based study of acne-related health preferences in adolescents. Arch Dermatol 144(8), 988-94.

Curtis L and Burns A (2019) Unit Costs of Health & Social Care 2019. Canterbury: PSSRU, University of Kent.

Department of Health and Social Care, Commercial Medicines Unit (2020). NHS Drugs and pharmaceutical electronic market information tool (eMIT). March 2020. https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

Dias S, Welton NJ, Sutton AJ, Ades AE (2011, last updated 2012). NICE DSU Technical Support Document 5: Evidence synthesis in the baseline natural history model. Available from http://www.nicedsu.org.uk

Dikicier BS (2019). Topical treatment of acne vulgaris: efficiency, side effects, and adherence rate. J Int Med Res 47(7), 2987-92.

Dolan P (1997) Modeling valuations for EuroQol health states. Medical Care 35(11), 1095-108.

Fenwick E, Claxton K, Sculpher M (2001) Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics 10(8), 779-87.

Francis NA, Entwistle K, Santer M, Layton AM, Eady EA, Butler CC (2017). 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 176(1), 107-115.

Gerlinger C, Städtler G, Götzelmann R, Graupe K, Endrika J (2008). A Non-inferiority Margin for Acne Lesion Counts. Drug Information Journal 42(6), 607-615.

Kind P, Hardman G, Macran S (1999). UK population norms for EQ-5D. Centre for Health Economics, University of York.

Klassen AF, Newton JN, Mallon E (2000). Measuring quality of life in people referred for specialist care of acne: comparing generic and disease-specific measures. J Am Acad Dermatol 2000 43(2 Pt 1), 229-33.

Lu G and Ades AE (2004) Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in Medicine 23(20), 3105-24

Lunn DJ, Thomas A, Best N, Spiegelhalter D (2000). WinBUGS-A Bayesian modelling framework: Concepts, structure, and extensibility. Statistics and Computing 10, 325-337

National Institute for Health and Care Excellence (2013) Guide to the Methods of Technology Appraisal 2013 (PMG 9). Available from: www.nice.org.uk/pmg9

National Institute for Health and Care Excellence (2014, last updated October 2018) Developing NICE guidelines: the manual (PMG 20). Available from: www.nice.org.uk/process/pmg20

NHS Business Services Authority, NHS Prescription Services (2020). NHS England and Wales. Electronic Drug Tariff. Issue: July 2020. Compiled on the behalf of the Department of

Health and Social Care. Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff

NHS Improvement (2020). National Schedule of NHS costs - Year 2018-19 - NHS trusts and NHS foundation trusts. Available from: https://improvement.nhs.uk/resources/national-cost-collection/

Spiegelhalter D, Thomas A, Best N, Lunn DJ (2003). WinBUGS user manual: Version 1.4. Cambridge: MRC Biostatistics Unit.

Appendix K – Excluded studies

Excluded studies for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Clinical studies

The excluded studies list below relates to all evidence reviews that used the same search output and these are studies that are excluded from all of the following reviews: mild-to-moderate NMA, moderate-to-severe NMA, mild-to-moderate pairwise and moderate-to-severe pairwise reports, as well as from refractory acne, maintenance of acne and polycystic ovary syndrome reports.

Table 23: Excluded clinical studies and reasons for their exclusion

Reference	Reason for exclusion
Abbasi, M. A. K., A., Aziz ur, Rehman, Saleem, H.,Jahangir, S. M.,Siddiqui, S. Z.,Ahmad, V. U.Preparation of new formulations of anti-acne creams and their efficacy. 2010. African Journal of Pharmacy and Pharmacology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Abdel Hay, R. H., R.,Abdel Hady, M.,Saleh, N.Clinical and dermoscopic evaluation of combined (salicylic acid 20% and azelaic acid 20%) versus trichloroacetic acid 25% chemical peel in acne: an RCT. 2019. Journal of Dermatological Treatment	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Abdel Meguid, A. M. A. E. A. A., D.,Omar, H.Trichloroacetic acid versus salicylic acid in the treatment of acne vulgaris in dark-skinned patients. 2015. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatmentsanalysis
Abdel-Naser, M. B. Z., C. C . Clindamycin phosphate/tretinoin gel formulation in the treatment of acne vulgaris. 2008. Expert Opinion on Pharmacotherapy	No relevant article type - expert opinion on pharmacotherapy
Abels, C. Glycolic acid: the effect is also now proven in acne. 2011a. Haut	Not in English language
Abramovits, W. G., A. Differin (adapalene) Gel, 0.3%. 2007. SKINmed	No relevant study design - not RCT
Abramovits, W. O., M., Gupta, A. K.Veltin gel (clindamycin phosphate 1.2% and tretinoin 0.025%). 2011. SKINmed	No relevant article type - non-systematic review
Adalatkhah, H. P., F., Sadeghi-Bazargani, H. Flutamide versus a cyproterone acetate-ethinyl estradiol combination in moderate acne: a pilot randomized clinical trial. 2011. Clinical, Cosmetic and Investigational Dermatology CCID	Moderate acne - no information on lesion counts at baseline and study is not relevant for

Reference	Reason for exclusion
	PCOS, maintenance or refractory treatments
Adams, J. T., P. Topical fusidic acid versus peroral doxycycline in the treatment of patients with acne vulgaris of the face. 1991. Current Therapeutic Research - Clinical and Experimental	No relevant intervention - suboptimal dose of doxycycline
Adams, R. M. B., K. H. An antiandrogen delta 1 chlormadinone acetate in acne: lack of effect topically. 1970a. Acta Dermato-Venereologica	Duplicate record
Adams, U. M. B., K. H. An antiandrogen delta 1 chlormadinone acetate in acne: lack of effect topically. 1970b. Acta Dermatologica	No relevant study population -insuficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Afzali, B. M. Y., E., Yaghoobi, R., Bagherani, N.,Dabbagh, M. A. Comparison of the efficacy of 5% topical spironolactone gel and placebo in the treatment of mild and moderate acne vulgaris: A randomized controlled trial. 2012. Journal of Dermatological Treatment	No relevant intervention - intervention & class not available in the UK
Agarwal, U. S. B., R. K., Bhola, K. Oral isotretinoin in different dose regimens for acne vulgaris: A randomized comparative trial. 2011. Indian Journal of Dermatology, Venereology and Leprology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Agren, U. M. A., M., Maenpaa-Liukko, K., Rantala, M. L.,Rautiainen, H.,Sommer, W. F.,Mommers, E.Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17beta-oestradiol compared with one containing levonorgestrel and ethinylestradiol on haemostasis, lipids and carbohydrate metabolism. 2011a. European Journal of Contraception and Reproductive Health Care	No relevant study population - participants did not have acne
Agren, U. M. A., M., Maenpaa-Liukko, K., Rantala, M. L.,Rautiainen, H.,Sommer, W. F.,Mommers, E.Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17beta-oestradiol in comparison to one containing levonorgestrel and ethinylestradiol on markers of endocrine function. 2011b. European Journal of Contraception and Reproductive Health Care	No relevant study population - participants did not have acne
Ahmad, H. M. Analysis of clinical efficacy, side effects, and laboratory changes among patients with acne vulgaris receiving single versus twice daily dose of oral isotretinoin. 2015. Dermatologic Therapy	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ahmadvand, A. Y., A., Yasrebifar, F., Mohammadi, Y.,Mahjub, R.,Mehrpooya, M.Evaluating the effects of oral and topical simvastatin in the treatment of acne vulgaris: A double-blind, randomized, placebo-controlled clinical trial. 2018. Current Clinical Pharmacology	Intervention not relevant I Simvastatin
Ahmed, I. S., M. Topical adapalene cream 0.1% v/s isotretinoin 0.05% in the treatment of acne vulgaris: A randomized open-label clinical trial. 2009. Journal of Pakistan Association of Dermatologists	No relevant outcomes reported
Ahn, G. R., Kim, J. M., Park, S. J., Li, K., Kim, B. J. Selective Sebaceous Gland Electrothermolysis Using a Single Microneedle	Reported outcomes relevant for the network meta-analysis but not in

Reference	Reason for exclusion
Radiofrequency Device for Acne Patients: A Prospective Randomized Controlled Study. 2019. Lasers in Surgery and Medicine.	enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Akamatsu, H. O., M., Nishijima, S., Asada, Y.,Takahashi, M.,Ushijima, T.,Niwa, Y.The inhibition of free radical generation by human neutrophils through the synergistic effects of metronidazole with palmitoleic acid: a possible mechanism of action of metronidazole in rosacea and acne. 1990. Archives of Dermatological Research	No relevant data reported - pharmokinetic study
Akaraphanth, R. K., W., Gritiyarangsan, P. Efficacy of ALA-PDT vs blue light in the treatment of acne. 2007. Photodermatology, Photoimmunology & Photomedicine	No relevant study design - not RCT
Akerlund, M.Clinical experience of a combined oral contraceptive with very low dose ethinyl estradiol. 1997. Acta Obstetricia et Gynecologica Scandinavica, Supplement	No relevant outcomes reported
Aksakal, A. B. K., M.,Onder, M.,Oztas, M. O.,Gurer, M. A.A comparative study of metronidazole 1% cream versus azelaic acid 20% cream in the treatment of acne. 1997. Gazi Medical Journal	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Albuquerque, R. G. d. R., M. A.,Hirotsu, C.,Hachul, H.,Bagatin, E.,Tufik, S.,Andersen, M. L.A randomized comparative trial of a combined oral contraceptive and azelaic acid to assess their effect on sleep quality in adult female acne patients. 2015. Archives of Dermatological Research	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Alexis, A. D. R., J. Q.,Desai, S. R.,Downie, J. B.,Draelos, Z. D.,Feser, C.,Forconi, R.,Fowler, J. F., Jr.,Gold, M.,Kaufman-Janette, J.,Lain, E.,Lee, M.,Ling, M.,Shamban, A. T.,Werschler, W. P.,Daniels, A.BPX-01 Minocycline Topical Gel Shows Promise for the Treatment of Moderate-to-severe Inflammatory Acne Vulgaris. 2018. The Journal of Clinical & Aesthetic Dermatology	No relevant intervention - intervention & class not available in the UK
Alexis, A. F. C.-B., F. E.,York, J. P.Adapalene/benzoyl peroxide gel 0.3%/2.5%: A safe and effective acne therapy in all skin phototypes. 2017. Journal of Drugs in Dermatology	No relevant data reported - post hock analysis according to Fitzpatrick skin type of Stein Gold 2016
Alexis, A. F. J., L. A.,Kerrouche, N.,Callender, V. D.A subgroup analysis to evaluate the efficacy and safety of adapalene-benzoyl peroxide topical gel in black subjects with moderate acne. 2014. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis of Thiboutot 2007, Gollnick 2009, Gold 2009
Alexis, A. F., Cook-Bolden, F., & Lin, T. Treatment of moderate-to-severe acne vulgaris in a hispanic population: a post-hoc analysis of the efficacy and tolerability of clindamycin 1.2%/benzoyl peroxide 3.75% gel. 2017. Journal of clinical and aesthetic dermatology	No relevant data reported - post hoc subgroup analysis for Hispanic population of Pariser 2014
Alirezai, M. M., J.,Jablonska, S.,Czernielewski, J.,Verschoore, M.Comparative study of the efficacy and tolerability of 0.1 and 0.03	Not in English language

Reference	Reason for exclusion
p.100 adapalene gel and 0.025 p.100 tretinoin gel in the treatment of acne. 1996. Annales de dermatologie ET de venereologie	
Alirezai, M. V., K.,Humbert, P.,Valensi, P.,Cambon, L.,Dupuy, P.A low-salt medical water reduces irritancy of retinoic acid in facial acne. 2000. European Journal of Dermatology	Intervention not targeted at acne but at treatment side effects
Allen, H.F., Mazzoni, C., Heptulla, R.A., Murray, M.A., Miller, N., Koenigs, L., Reiter, E.O. Randomized controlled trial evaluating response to metformin versus standard therapy in the treatment of adolescents with polycystic ovary syndrome. 2005. Journa of Pediatric Endocrinology and Metabolism	Not clear what proportion of participants had acne at baseline
Al-Mishari, M. A. Clinical and bacteriological evaluation of tetracycline and erythromycin in acne vulgaris. 1987. Clinical Therapeutics	Unclear if RCT
Amer, S. S., Nasr, M., Abdel-Aziz, R. T. A., Moftah, N. H., El Shaer, A., Polycarpou, E., Mamdouh, W., Sammour, O. Cosm-nutraceutical nanovesicles for acne treatment: Physicochemical characterization and exploratory clinical experimentation. 2020. International Journal of PharmaceuticsInt J Pharm	No relevant study design - not RCT
Amiri, M., Nahidi, F., Bidhendi-Yarandi, R., Khalili, D., Tohidi, M., Ramezani Tehrani, F.A comparison of the effects of oral contraceptives on the clinical and biochemical manifestations of polycystic ovary syndrome: A crossover randomized controlled trial. 2020. Human Reproduction	No relevant outcomes reported
An, W. X. Z., Z. H. Curative observation on herbal tea combined with ear acupoint in treating 120 middle school students with acne. 2016. Western journal of traditional chinese medicine[xi bu zhong yi yao]	Not in English language
Anadolu, R. Y. S., T.,Tarimci, N.,Birol, A.,Erdem, C.Improved efficacy and tolerability of retinoic acid in acne vulgaris: A new topical formulation with cyclodextrin complex PSI. 2004. Journal of the European Academy of Dermatology and Venereology	Insufficient information about severity of acne at baseline and study is not relevant for PCOS, maintenance or refractory treatments
Anonymous, Management of acne vulgaris. 1966. Drug & Therapeutics Bulletin	Duplicate record
Anonymous, Pharmacokinetic profile, safety, and tolerability of clascoterone topical cream 1% in subjects with moderate-to-severe acne vulgaris: an open-label phase IIa study. 2019. Journal of the American Academy of Dermatology	No relevant article type - conference abstract
Anonymous, Phase III Clinical Study of Clindamycin Phosphate Topical Gel (CLDM-T) in the Treatment of Acne Vulgaris: randomized Comparatie Study with Nadifloxacin Cream as a Control Drug. 1999b. Rinsho iyaku (journal of clinical therapeutics and medicines)	Not in English language
Anonymous, Retinoic acid in the treatment of acne. A report from the General Practitioner Research Group. 1974. Practitioner	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Anonymous, The Clinical Phase II Study of CLDM-T Gel in the Treatment of Acne Vulgaris: double-Blind Comparative Study, Evaluation of Efficacy, Safety and Optimal Concentration of CLDM-T Gel in the Treatment of Acne Vulgaris. 1999a. Rinsho iyaku (journal of clinical therapeutics and medicines)	Not in English language

Reference	Reason for exclusion
Anonymous, Treatment of moderate-to-severe facial acne vulgaris with the use of a solid-state fractional 589/1,319-nm laser. 2018. Journal of the American Academy of Dermatology	No relevant article type - conference abstract
Ansarin, H. S., S.,Behzadi, A. H.,Sadigh, N.,Hasanloo, J.Doxycycline plus levamisole: combination treatment for severe nodulocystic acne. 2008. Journal of drugs in dermatology : JDD	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Anstee, P. K., G. T.A prospective randomized study comparing the clinical effects of a norethisterone and a levonorgestrel containing low dose oestrogen oral contraceptive pills. 1993. Australian and New Zealand Journal of Obstetrics and Gynaecology	No relevant study population - participants did not have acne
Antoniou, C. D., C.,Sotiriadis, D.,Kalokasidis, K.,Kontochristopoulos, G.,Petridis, A.,Rigopoulos, D.,Vezina, D.,Nikolis, A.A multicenter, randomized, split-face clinical trial evaluating the efficacy and safety of chromophore gel-assisted blue light phototherapy for the treatment of acne. 2016. International Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Anyachukwu, C. C. O., O. K. K. Efficacy of adjunct (laser) therapy to topical agents among Southern Nigerian acne vulgaris patients. 2014. Acupuncture and Related Therapies	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ash, C. H., A.,Drew, S.,Whittall, R.A randomized controlled study for the treatment of acne vulgaris using high-intensity 414 nm solid state diode arrays. 2015. Journal of cosmetic and laser therapy	Unclear what treatment the control group received (over the counter products)
Aydin, F. C., T.,Senturk, N.,Yasar Turanli, A.Comparison of clinical efficacy of tretinoin 0.025% gel and adapalene 0.1% gel in the treatment of acne vulgaris. 2002. Ondokuz mayis universitesi tip dergisi	Not in English language
Aydinlik, S. L.-F., U.,Lehnert, J.Reduced estrogen ovulation inhibitor in acne therapy. Double-blind study comparing Diane-35 to Diane. 1986. Fortschritte der medizin	Not in English language
Aziz-Jalali, M. H. T., S. M.,Djavid, G. E.Comparison of red and infrared low-level laser therapy in the treatment of acne vulgaris. 2012. Indian Journal of Dermatology	No relevant study design as the study does not appear to be randomised - the same treatment was always applied to a give side of the face
Babaeinejad, S. K., E.,Fouladi, R. F.Comparison of therapeutic effects of oral doxycycline and azithromycin in patients with moderate acne vulgaris: What is the role of age?. 2011. Journal of Dermatological Treatment	No relevant study population - sample includes people with moderate acne but baseline severity not

Reference	Reason for exclusion
	reported according to lesion counts and study is not relevant for PCOS, maintenance or refractory treatments
Bae, B. G. P., C. O.,Shin, H.,Lee, S. H.,Lee, Y. S.,Lee, S. J.,Chung, K. Y.,Lee, K. H.,Lee, J. H.Salicylic acid peels versus Jessner's solution for acne vulgaris: a comparative study. 2013. Dermatologic surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Barak-Shinar, D. D., Z. D.A randomized controlled study of a novel botanical acne spot treatment. 2017. Journal of Drugs in Dermatology	No relevant intervention - study product was based on 10% herbal botanical ingredients with anti-inflammatory and anti-bacterial activity
Barranco, V. P.Effect of androgen-dominant and estrogen-dominant oral contraceptives on acne. 1974. Cutis; cutaneous medicine for the practitioner	No relevant study population - no information on the baseline severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Bassett, I. B. P., D. L.,Barnetson, R. S.A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. 1990. Medical Journal of Australia	No relevant intervention - tea-tree oil
Baugh, W. P. K., W. D.Nonablative phototherapy for acne vulgaris using the KTP 532 nm laser. 2005. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Baumann, L. S. O., C.,Yatskayer, M.,Dahl, A.,Figueras, K.Comparison of clindamycin 1% and benzoyl peroxide 5% gel to a novel composition containing salicylic acid, capryloyl salicylic acid, HEPES, glycolic acid, citric acid, and dioic acid in the treatment of acne vulgaris. 2013. Journal of drugs in dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Behrangi, E. A., E.,Tavakoli, T.,Mehran, G.,Atefi, N.,Esmaeeli, S.,Azizian, Z.Comparing efficacy of montelukast versus doxycycline in treatment of moderate acne. 2015. Journal of Research in Medical Sciences	No relevant intervention - montelukast
Behrangi, E., Sadeghi, S., Sadeghzadeh-Bazargan, A., Goodarzi, A., Ghassemi, M., Sepasgozar, S., Rohaninasab, M. The effect of metformin in the treatment of intractable and late onset acne: A	No relevant data reported - reports combined results for those with treatment-

Reference	Reason for exclusion
comparison with oral isotretinoin. 2019. Iranian Journal of Dermatology	resistant acne and those with severe acne with late onset acne; no subgroups reported and study is not relevant for PCOS, maintenance or refractory treatments
Belknap, B. S.Treatment of acne with 5% benzoyl peroxide gel or 0.05% retinoic acid cream. 1979. Cutis	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Belum, V. R. M., M. A.,Dusza, S. W.,Cercek, A.,Kemeny, N. E.,Lacouture, M. E.A prospective, randomized, double-blinded, split-face/chest study of prophylactic topical dapsone 5% gel versus moisturizer for the prevention of cetuximab-induced acneiform rash. 2017. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with metastatic colorectal cancer or head and neck squamous cell carcinoma
Bernstein, E. F.A pilot investigation comparing low-energy, double pass 1,450 nm laser treatment of acne to conventional single-pass, high-energy treatment. 2007. Lasers in Surgery and Medicine	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bernstein, J. E. S., A. R.Topically applied erythromycin in inflammatory acne vulgaris. 1980. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bershad, S. K. S., G.,Parente, J. E.,Tan, M. H.,Sherer, D. W.,Persaud, A. N.,Lebwohl, M.Successful treatment of acne vulgaris using a new method: results of a randomized vehicle-controlled trial of short-contact therapy with 0.1% tazarotene gel. 2002. Archives of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bettoli, V. B., A.,Zauli, S.,Toni, G.,Ricci, M.,Giari, S.,Virgili, A.Maintenance therapy for acne vulgaris: efficacy of a 12-month treatment with adapalene-benzoyl peroxide after oral isotretinoin and a review of the literature. 2013. Dermatology	Duplicate record
Bhatia, N. P., R.Randomized, observer-blind, split-face compatibility study with clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel and facial foundation makeup. 2015. Journal of Clinical and Aesthetic Dermatology	No relevant comparison - split face 6-hour RCT that examines cosmetic compatibility of make up with topical clindamycin and BPO gel
Bhavsar, B. C., B.,Sanmukhani, J.,Dogra, A.,Haq, R.,Mehta, S.,Mukherjee, S.,Subramanian, V.,Sheikh, S.,Mittal, R.Clindamycin 1% Nano-emulsion Gel Formulation for the Treatment of Acne Vulgaris: Results of a Randomized, Active Controlled, Multicentre,	No relevant study population - sample includes people with mild to severe acne and study

Reference	Reason for exclusion
Phase IV Clinical Trial. 2014. Journal of Clinical and Diagnostic Research JCDR	is not relevant for PCOS, maintenance or refractory treatments
Bissonnette, R. B., C., Seite, S.,Nigen, S.,Provost, N.,Maari, C.,Rougier, A.Randomized study comparing the efficacy and tolerance of a lipophillic hydroxy acid derivative of salicylic acid and 5% benzoyl peroxide in the treatment of facial acne vulgaris. 2009. Journal of Cosmetic Dermatology	No relevant intervention - intervention & class not available in the UK
Bissonnette, R. M., C., Nigen, S.,Provost, N.,Bolduc, C.Photodynamic therapy with methylaminolevulinate 80 mg/g without occlusion improves acne vulgaris. 2010. Journal of Drugs in Dermatology	No relevant comparison - photodynamic therapy with methylaminolevulinate with occlusion vs without occlusion
Bissonnette, R. P., Y., Drew, J.,Hofland, H.,Tan, J.Olumacostat glasaretil, a novel topical sebum inhibitor, in the treatment of acne vulgaris: A phase IIa, multicenter, randomized, vehicle-controlled study. 2017. Journal of the American Academy of Dermatology	No relevant intervention - intervention not licensed in the UK
Biswas, S. M., K. K., Dutta, R. N.,Sarkar, D. K.Comparative evaluation of the efficacy of four topical medications individually or in combination to treat grade I acne vulgaris. 2009. Journal of the Indian Medical Association	No relevant outcomes reported
Biyun, C.The clinical observation of treating acne vulgaris with "xiao cuo fang". 2004. Zhong yao cai = Zhongyaocai [Journal of Chinese medicinal materials]	Not in English language
Bladon, P. T. B., B. M., Cunliffe, W. J.Topical azelaic acid and the treatment of acne: A clinical and laboratory comparison with oral tetracycline. 1986. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Blaney, D. J. C., C. H. Topical use of tetracycline in the treatment of acne. A double blind study comparing topical and oral tetracycline therapy and placebo. 1976. Archives of Dermatology	No relevant intervention - intervention & class not available in the UK
Bleeker, J. H., L.,Vincent, J.Effect of systemic erythromycin stearate on the inflammatory lesions and skin surface fatty acids in acne vulgaris. 1981. Dermatologica	No relevant study population - sample includes people with mild to severe acne
Bodokh, I. J., Y., Lacour, J. Ph,Ortonne, J. P.Minocycline induces an increase in the number of excreting pilosebaceous follicles in acne vulgaris. A randomised study. 1997. Acta Dermato-Venereologica	No relevant data reported - pharmokinetic study
Bojar, R. A. E., E. A., Jones, C. E.,Cunliffe, W. J.,Holland, K. T.Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc. 1994. British Journal of Dermatology	Efficacy outcomes reported in figures only
Borglund, E. H., O., Nord, C. E.Impact of topical clindamycin and systemic tetracycline on the skin and colon microflora in patients with acne vulgaris. 1984. Scandinavian Journal of Infectious Diseases	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Borglund, E. K., B., Larsson-Stymne, B.,Strand, A.,Veien, N. K.,Jakobsen, H. B.Topical meclocycline sulfosalicylate, benzoyl peroxide, and a combination of the two in the treatment of acne vulgaris. 1991. Acta Dermato-Venereologica	No relevant study population - sample includes people with mild to severe acne and study

Reference	Reason for exclusion
	is not relevant for PCOS, maintenance or refractory treatments
Borhan, W. H. H., H. A.,Aboelnour, N. H.Efficacy of pulsed dye laser on acne vulgaris. 2014. Journal of american science	Insufficient information about treatment (unspecified topical antibiotic)
Botsali, A. K., P.,Uran, P.The effects of isotretinoin on affective and cognitive functions are disparate in adolescent acne vulgaris patients. 2019. Journal of Dermatological Treatment.	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bouloc, A. R., E.,Imko-Walczuk, B.,Moga, A.,Chadoutaud, B.,Dreno, B.A skincare combined with combination of adapalene and benzoyl peroxide provides a significant adjunctive efficacy and local tolerance benefit in adult women with mild acne. 2017. Journal of the European Academy of Dermatology and Venereology	No relevant intervention - compares emolients
Bourne, M. S.Comparison of two lotions for acne vulgaris. 1979. Practitioner	No relevant intervention - intervention & class not available in the UK
Bowman, S. G., M.,Nasir, A.,Vamvakias, G.Comparison of clindamycin/benzoyl peroxide, tretinoin plus clindamycin, and the combination of clindamycin/benzoyl peroxide and tretinoin plus clindamycin in the treatment of acne vulgaris: a randomized, blinded study. 2005. Journal of drugs in dermatology : JDD	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Bradford, L. G. M., L. F.Topical application of vitamin A acid in acne vulgaris. 1974. Southern Medical Journal	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Bran, E. L. R. A., A. Therapeutic effectiveness of clindamycin phosphate (1% solution) compared with tetracycline (solution) administered topically in the treatment of acne vulgaris. 1986. Medicina cutanea ibero-latino-americana	Not in English language
Brand, B. G., R.,Baker, M. D.,Poncet, M.,Greenspan, A.,Georgeian, K.,Soloff, A. M.Cumulative irritancy comparison of adapalene gel 0.1% versus other retinoid products when applied in combination with topical antimicrobial agents. 2003a. Journal of the American Academy of Dermatology	No relevant study population - participants did not have acne
Brand, B. G., R.,Baker, M. D.,Poncet, M.,Greenspan, A.,Georgeian, K.,Soto, P.,Arsonnaud, S.Cumulative Irritancy Potential of Adapalene Cream 0.1% Compared with Adapalene Gel 0.1% and Several Tretinoin Formulations. 2003b. Cutis	No relevant study population - participants did not have acne
Brand, E. L. R., A. Study of the therapeutic effectiveness of clindamycin phosphate (1% solution) versus tetracycline (solution)	Not in English language

Reference	Reason for exclusion
administered topically in the treatment of acne vulgaris. 1986. Medicina cutÃ¡nea ibero-latino-americana	
Brandt, H. A., P.,Ahokas, T.,Forstrom, L.,Jarvinen, T.,Keskitalo, R.,Lehtonen, L.,Plosila, M.,Rita, H.,Suramo, M. L.Erythromycin acistrate - An alternative oral treatment for acne. 1994. Journal of Dermatological Treatment	No relevant comparison - suboptimal dose
Breneman, D. L. A., M. C. Successful treatment of acne vulgaris in women with a new topical sodium sulfacetamide/sulfur lotion. 1993. International Journal of Dermatology	No relevant study design - not RCT
Breno, B. K., A.,Richard, A.,Rougier, A.Interest of a new salicylic acid derivative in the prevention of acne relapses. 2002. European journal of dermatology : EJD	No relevant article type - conference abstract
Brickman, S. S. L., W. D.,Gareau, J. Y.A double-blind evaluation of a topical antibiotic preparation in acne. 1980. Current Therapeutic Research - Clinical and Experimental	No relevant intervention - intervention & class not available in the UK
Brodell, R. T. S., B. J.,Rafal, E.,Toth, D.,Tyring, S.,Wertheimer, A.,Kerrouche, N.,Bucher, D.A fixed-dose combination of adapalene 0.1%BPO 2.5% allows an early and sustained improvement in quality of life and patient treatment satisfaction in severe acne. 2012. Journal of Dermatological Treatment	No relevant outcomes reported
Brogden, R. N. S., T. M.,Avery, G. S.Benzoyl peroxide acne lotions : an independent report. 1974. Drugs	No relevant article type - expert review
Brookes, D. B. M., R. M.,Sheil, L. P.,Flowers, I. M.,Poulter, G. A. Comparison of Tretinoin and a composite formulation in the treatment of acne. 1978. British Journal of Clinical Practice	No relevant study population - insufficient details reported to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Bubna, A. K.Metformin - For the dermatologist. 2016. Indian Journal of Pharmacology	Duplicate record
Bucknall, J. H. M., P. N. Comparison of tretinoin solution and benzoyl peroxide lotion in the treatment of acne vulgaris. 1977. Current Medical Research & Opinion	Not obtainable
Budden, M. G. Topical and oral tetracycline in the treatment of acne vulgaris. 1988. Practitioner	No relevant intervention - intervention & class not available in the UK
Burke, B. E., E. A.,Cunliffe, W. J.Benzoylperoxide versus topical erythromycin in the treatment of acne vulgaris. 1983. British Journal of Dermatology	No relevant study design - not RCT
Burkhart, C. G. B., C. N.Treatment of acne vulgaris without antibiotics: tertiary amine-benzoyl peroxide combination vs. benzoyl peroxide alone (Proactiv Solution). 2007. International Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Burton, J. E., G.A placebo-controlled study to evaluate the efficacy of topical tetracycline and oral tetracycline in the treatment of mild to moderate acne. 1990. Journal of International Medical Research	No relevant intervention - intervention & class not available in the UK
Burton, J. L. P., R. J.,Harris, J. I.Effect of 1% cyproterone acetate in Cetomacrogol cream BPC (formula A) on sebum excretion rate in patients with acne. 1976. British Journal of Dermatology	No relevant data reported - pharmokinetic study

Reference	Reason for exclusion
Callender, V. D.Fitzpatrick skin types and clindamycin phosphate 1.2%/benzoyl peroxide gel: Efficacy and tolerability of treatment in moderate to severe acne. 2012a. Journal of Drugs in Dermatology	No relevant data reported - post hoc analysis reporting results for people receiving clindamycin 2.1%/BPO 2.5% gel
Cambazard, F.Clinical efficacy of Velac, a new tretinoin and clindamycin phosphate gel in acne vulgaris. 1998. Journal of the European Academy of Dermatology & Venereology	No relevant study design - non-systematic review of tretinoin treatment
Cannizzaro, M. V. D., A.,Garofalo, V.,Del Duca, E.,Bianchi, L.Reducing the oral Isotretinoin skin side effects: Efficacy of 8% omega-ceramides, hydrophilic sugars, 5% niacinamide cream Compound in acne patients. 2018. Giornale Italiano di Dermatologia e Venereologia	Not in English language
Cao, J., Yang, G., Wang, Y., Liu, J. Acupoint Stimulation for Acne: A Systematic Review of Randomized Controlled Trials. 2013. Med Acupunct. 2013	No relevant intervention - systematic review about acupoint stimulation techniques used to treat acne
Cao, J., Yang, G., Wang, Y., Ping Liu, J., Smith, C.A., Luo, H., Liu. Y. Complementary therapies for acne vulgaris. 2015. Cochrane Database Syst Rev	Not relevant intervention - systematic review about complementary and alternative medicine for acne
Cao, T. T., E. S.,Chan, Y. H.,Yosipovitch, G.,Tey, H. L.Anti-pruritic efficacies of doxycycline and erythromycin in the treatment of acne vulgaris: a randomized single-blinded pilot study. 2018. Indian journal of dermatology, venereology and leprology	No relevant study design - not RCT
Carlborg, L. Cyproterone acetate versus Levonorgestrel combined with ethinyl estradiol in the treatment of acne. Results of a multicenter study. 1986. Acta Obstetricia et Gynecologica Scandinavica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Carlborg, L. Cyproterone acetate versus levonorgestrel combined with ethinylestradiol in the treatment of acne. Results of a multicenter study. 1987. Contraception fertilite sexualite	Duplicate record
Carmina, E. L., R. A.A comparison of the relative efficacy of antiandrogens for the treatment of acne in hyperandrogenic women. 2002. Clinical Endocrinology	Duplicate record
Caron, D. S., V.,Clucas, A.,Verschoore, M.Skin tolerance of adapalene 0.1% gel in combination with other topical antiacne treatments. 1997a. Journal of the American Academy of Dermatology	No relevant study population - participants did not have acne
Caron, D. S., V.,Kerrouche, N.,Clucas, A.Split-face comparison of adapalene 0. 1% gel and tretinoin 0.025% gel in acne patients. 1997b. Journal of the American Academy of Dermatology	No relevant outcomes reported
Cavicchini, S. C., R.Long-term treatment of acne with 20% azelaic acid cream. 1989. Acta Dermato-Venereologica, Supplement	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Cestone, E. M., A.,Zanoletti, V.,Zanardi, A.,Mantegazza, R.,Dossena, M.Acne RA-1,2, a novel UV-selective face cream for patients with	Efficacy outcomes reported in figures only

Reference	Reason for exclusion
acne: Efficacy and tolerability results of a randomized, placebo-controlled clinical study. 2017. Journal of Cosmetic Dermatology	
Chalker, D. K. S., A.,Smith, J. G., Jr.,Swann, R. W.A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. 1983. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Chan, H. C., G.,Santos, J.,Dee, K.,Co, J. K.A randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of lactoferrin with vitamin E and zinc as an oral therapy for mild to moderate acne vulgaris. 2017. International Journal of Dermatology	No relevant intervention - Lactoferrin + Vitamin E + Zinc
Chandrashekha, B. S. A., M.,Ruparelia, M.,Vaidya, P.,Aamir, R.,Shah, S.,Thilak, S.,Aurangabadkar, S.,Pal, S.,Saraswat, A.,et al.,Tretinoin nanogel 0.025% versus conventional gel 0.025% in patients with acne vulgaris: a randomized, active controlled, multicentre, parallel group, phase iv clinical trial. 2015. Journal of clinical and diagnostic research	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Chang, S. E. A., S. J.,Rhee, D. Y.,Choi, J. H.,Moon, K. C.,Suh, H. S.,Soyun, ChoTreatment of facial acne papules and pustules in Korean patients using an intense pulsed light device equipped with a 530- to 750-nm filter. 2007. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Chantalat, J., Liu, J. C. Six-week safety and efficacy evaluation of a synergistic microgel complex versus 10% benzoyl peroxide in the treatment of mild to moderate acne. Abstract P101. American Academy of Dermatology 64th Annual Meeting March 3-7, 2006. 2006. NA	No relevant article type - conference abstract
Charoenvisal, C. T., Y. Effects on acne of two oral contraceptives containing desogestrel and cyproterone acetate. 1996. International Journal of Fertility and Menopausal Studies	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Chi, C. I. Effects of Salvia miltiorrhiza extract on the improvement and prognosis of acne vulgaris. 2016.	No relevant intervention - Salvia miltiorrhiza extract
Chiou, W. L. Low intrinsic drug activity and dominant vehicle (placebo) effect in the topical treatment of acne vulgaris. 2012. International Journal of Clinical Pharmacology and Therapeutics	No relevant study design - not RCT
Chlebus, E., Serafin, M., Chlebus, M. Is maintenance treatment in adult acne important? Benefits from maintenance therapy with adapalene, and low doses of alpha and beta hydroxy acids. 2019. Journal of Dermatological Treatment	No relevant study design - the randomized comparison is of skin care regimen rather than maintenance treatment (adapalene in both groups)
Cho, S. B. L., J. H.,Choi, M. J.,Lee, K. Y.,Oh, S. H.Efficacy of the fractional photothermolysis system with dynamic operating mode on acne scars and enlarged facial pores. 2009. Dermatologic Surgery	Duplicate record

Reference	Reason for exclusion
Choudhury, S. C., S.,Sarkar, D. K.,Dutta, R. N.Efficacy and safety of topical nadifloxacin and benzoyl peroxide versus clindamycin and benzoyl peroxide in acne vulgaris: A randomized controlled trial. 2011. Indian Journal of Pharmacology	No relevant intervention - intervention & class not available in the UK
Christian, G. L. K., G. G. Clindamycin vs placebo as adjunctive therapy in moderately severe acne. 1975. Archives of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Christiansen, J. H., P.,Reymann, F.The retinoic acid derivative Ro 11 1430 in Acne vulgaris. A controlled multicenter trial against retinoic acid. 1977. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Christiansen, J. H., P.,Reymann, F.Treatment of acne vulgaris with the retinoic acid derivative Ro 11-1430. A controlled clinical trial against retinoic acid. 1976. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Christiansen, J. V. G., E.,Ludvigsen, K.,Konstman Meier, C. H.,Norholm, A.,Osmundsen, P. E.,Pedersen, D.,Rasmussen, K. A.,Reiter, H.,Reymann, F.,et al.,Topical vitamin A acid (Airol) and systemic oxytetracycline in the treatment of acne vulgaris. A controlled clinical trial. 1974a. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Christiansen, J. V. G., E.,Ludvigsen, K.,Meier, C. H.,Norholm, A.,Pedersen, D.,Rasmussen, K. A.,Reiter, H.,Reymann, F.,Sylvest, B.,et al.,Topical tretinoin, vitamin A acid (Airol) in acne vulgaris. A controlled clinical trial. 1974b. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Chu, A. H., F. J.,Plott, R. T.The comparative efficacy of benzoyl peroxide 5%/erythromycin 3% gel and erythromycin 4%/zinc 1.2% solution in the treatment of acne vulgaris. 1997. British Journal of Dermatology	No relevant study population - sample includes people with too narrow range of acne severity criteria and study is not relevant for PCOS, maintenance or refractory treatments
Chularojanamontri, L. T., P.,Kulthanan, K.,Varothai, S.,Winayanuwattikun, W.A double-blinded, randomized, vehicle-controlled study to access skin tolerability and efficacy of an anti-inflammatory moisturizer in treatment of acne with 0.1% adapalene gel. 2016. Journal of Dermatological Treatment	No relevant intervention - Adaplene with or without Eucerin mositurizer
Clucas, A. V., M.,Sorba, V.,Poncet, M.,Baker, M.,Czernielewski, J.Adapalene 0.1% gel is better tolerated than tretinoin 0.025% gel in acne patients. 1997. Journal of the American Academy of Dermatology	Duplicate publication from Cunliffe 1997 trial

Reference	Reason for exclusion
Cochran, R. J. T., S. B.,Flannigan, S. A.Topical zinc therapy for acne vulgaris. 1985. International Journal of Dermatology	No relevant study design - not RCT
Colver, G. B. M., P. S.,Dawber, R. P.Cyproterone acetate and two doses of oestrogen in female acne; a double-blind comparison. 1988. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Coman, G. C. H., A. C.,Mazloom, S. E.,Chavan, R. N.,Kolodney, M. S.A randomized, split-face, controlled, double-blind, single-centre clinical study: transient addition of a topical corticosteroid to a topical retinoid in patients with acne to reduce initial irritation. 2017. British Journal of Dermatology	No relevant article type - letter to editor
Cook-Bolden, F. E. Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and benzoyl peroxide (3.75%) aqueous gel in moderate or severe adolescent acne vulgaris. 2015. Journal of Clinical and Aesthetic Dermatology	No relevant data reported - post hoc age analysis of Pariser 2014
Cook-Bolden, F. E. Treatment of moderate to severe acne vulgaris in a Hispanic population: A post-hoc analysis of efficacy and tolerability of clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel. 2012. Journal of Drugs in Dermatology	No relevant data reported - post hoc subgroup analysis by ethnicity of Thiboutot 2008
Cook-Bolden, F. E. W., S. H.,Guenin, E.,Bhatt, V.Novel Tretinoin 0.05% Lotion for Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris in a Hispanic Population. 2019. Journal of drugs in dermatology : JDD	No relevant data reported - post hoc subgroup analysis of Hispanic participants in Tyring 2018
Cook-Bolden, F. E., Gold, M. H., Guenin, E. Tazarotene 0.045% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris in Adult Males. 2020. Journal of drugs in dermatology : JDD	Not obtainable
Corlin, R. M., B.,Mack, H. A. Oral administration of low doses of 13-cis-retinoic acid in acne papulopustulosa. Results of a multicenter study. 1984. Der hautarzt; zeitschrift fur dermatologie, venerologie, und verwandte gebiete	Not in English language
Cotterill, J. A.Benzoyl peroxide. 1980. Acta Dermato-Venereologica. Supplementum	Duplicate record
Coughlin, C. C. S., S. M.,Horwinski, J.,Sfyroera, G.,Bugayev, J.,Grice, E. A.,Yan, A. C.The preadolescent acne microbiome: A prospective, randomized, pilot study investigating characterization and effects of acne therapy. 2017. Pediatric Dermatology	No relevant data reported - microbiome study
Cremoncini, C. V., E.,Libroia, A. Treatment of hirsutism and acne in women with two combinations of cyproterone acetate and ethinylestradiol. 1976. Acta Europaea Fertilitatis	No relevant study design - not RCT
Cullberg, G. H., L.,Mattsson, L. A.,Mobacken, H.,Samsioe, G. Effects of a low-dose desogestrel-ethinylestradiol combination on hirsutism, androgens and sex hormone binding globulin in women with a polycystic ovary syndrome. 1985. Acta Obstetricia et Gynecologica Scandinavica	No relevant study population – study focuses on women with PCOS and hirsuitism rather than acne and study is not relevant for other evidence reviews
Cunliffe, W. J. B., B.,Dodman, B.,Gould, D. J.A double-blind trial of a zinc sulphate/citrate complex and tetracycline in the treatment of acne vulgaris. 1979. British Journal of Dermatology	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Cunliffe, W. J. C., J. A. Clindamycin as an alternative to tetracycline in severe acne vulgaris. 1973. Practitioner	No relevant study design - not RCT
Cunliffe, W. J. C., J. A.,Williamson, B. The effect of a medicated wash on acne, sebum excretion rate and skin surface lipid composition. 1972. British Journal of Dermatology	No relevant article type - letter to editor
Cunliffe, W. J. C., R.,Dreno, B.,Forstrom, L.,Heenen, M.,Orfanos, C. E.,Privat, Y.,Aguilar, A. R.,Meynadier, J.,Alirezai, M.,Jablonska, S.,Shalita, A.,Weiss, J. S.,Chalker, D. K.,Ellis, C. N.,Greenspan, A.,Katz, H. I.,Kantor, I.,Millikan, L. E.,Swinehart, J. M.,Swinyer, L.,Whitmore, C.,Czernielewski, J.,Verschoore, M.Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and U.S. multicenter trials. 1997a. Journal of the American Academy of Dermatology	No relevant study design - combined publication of Cunliffe 1997 & US trial
Cunliffe, W. J. C., R.,Dreno, B.,Forstrom, L.,Heenen, M.,Orfanos, C. E.,Privat, Y.,Robledo Aguilar, A.,Poncet, M.,Verschoore, M.Efficacy and safety comparison of adapalene (CD271) gel and tretinoin gel in the topical treatment of acne vulgaris. A European multicentre trial. 1997b. Journal of Dermatological Treatment	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Cunliffe, W. J. D., F. W.,Dunlap, F.,Gold, M. H.,Gratton, D.,Greenspan, A.Randomised, controlled trial of the efficacy and safety of adapalene gel 0.1% and tretinoin cream 0.05% in patients with acne vulgaris. 2002. European Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Cunliffe, W. J. F., R. A.,Greenwood, N. D.,Hetherington, C.,Holland, K. T.,Holmes, R. L.,Khan, S.,Roberts, C. D.,Williams, M.,Williamson, B.Tetracycline and acne vulgaris: a clinical and laboratory investigation. 1973. British Medical Journal	No relevant study population - insufficient details about acne severity reported and study is not relevant for PCOS, maintenance or refractory treatments
Cunliffe, W. J. G., D.,Goode, K.,Stables, G. I.,Boorman, G. C.A double-blind investigation of the potential systemic absorption of isotretinoin, when combined with chemical sunscreens, following topical application to patients with widespread acne of the face and trunk. 2001. Acta Dermato-Venereologica	No relevant data reported - pharmokinetic study
Cunliffe, W. J. G., E.,Belaich, S.,Meynadier, J.,Alirezai, M.,Thomas, L.A comparison of the efficacy and safety of lymecycline and minocycline in patients with moderately severe acne vulgaris. 1998. European Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments

Reference	Reason for exclusion
Cunliffe, W. J. H., K. T.Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. 1989. Acta Dermato-Venereologica, Supplement	No relevant study design - not RCT
Cunliffe, W. J. S., C.,Forster, R. A. Topical benzoyl peroxide increases the sebum excretion rate in patients with acne. 1983. British Journal of Dermatology	No relevant data reported - pharmokinetic study
Cunliffe, W. J.A new topical retinoid--why a new topical acne therapy?. 1998. British Journal of Dermatology	No relevant article type - commentary
Dainichi, T. K., A.,Ueda, S.,Tajiri, R.,Fumimori, T.,Kakuma, T.,Hashimoto, T.Skin tightening effect using fractional laser treatment: I. A randomized half-side pilot study on faces of patients with acne. 2010. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Damkerngsuntorn, W., Rerknimitr, P., Panchaprateep, R., Tangkijngamvong, N., Kumtornrut, C., Kerr, S. J., Asawanonda, P., Tantisira, M. H., Khemawoot, P. The Effects of a Standardized Extract of Centella asiatica on Postlaser Resurfacing Wound Healing on the Face: A Split-Face, Double-Blind, Randomized, Placebo-Controlled Trial. 2020. Journal of Alternative & Complementary MedicineJ Altern Complement Med	No relevant intervention - laser with extract of Centella asiatica
Danto, J. L. M., W. S.,Stewart, W. D.,Nelson, A. J.A controlled trial of benzoyl peroxide and precipitated sulfur cream in acne vulgaris. 1966. Applied Therapeutics	No relevantstudy population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Darley, C. R. M., J. W.,Besser, G. M.,Munro, D. D.,Kirby, J. D.Low dose prednisolone or oestrogen in the treatment of women with late onset or persistent acne vulgaris. 1983. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Darne, S. H., E. L.,Seukeran, D. C.Evaluation of the clinical efficacy of the 1450 nm laser in acne vulgaris: A randomized split-face, investigator-blinded clinical trial. 2011. British Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Darne, S. H., E.,Seukeran, D. C.Treatment of inflammatory acne with a 1450-nm smoothbeam diode laser: A split-face randomized single-blinded controlled trial. 2009. British Journal of Dermatology	No relevant article type - conference abstract
Dayal, S., Kalra, K. D., Sahu, P. Comparative study of efficacy and safety of 45% mandelic acid versus 30% salicylic acid peels in mild-to-moderate acne vulgaris. 2019. Journal of Cosmetic DermatologyJ	Duplicate of Dayal 2020 first published online 2019
de Arruda, L. H. K., V.,Bastos Filho, A.,Mazzaro, C. B.A prospective, randomized, open and comparative study to evaluate the safety and efficacy of blue light treatment versus a topical benzoyl peroxide 5% formulation in patients with acne grade II and III. 2009. Anais brasileiros de dermatologia	Not in English language

Reference	Reason for exclusion
De Leeuw, J. V. D. B., N.,Bjerring, P.,Martino Neumann, H. A. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid 0.5% liposomal spray and intense pulsed light in combination with topical keratolytic agents. 2010. Journal of the European Academy of Dermatology and Venereology	No relevant data reported - article reports that study is RCT but does not report comparative data
Degreef, H. V. B., G. Double-blind evaluation of a miconazole - benzoyl peroxide combination for the topical treatment of acne vulgaris. 1982a. Dermatologica	Duplicate record
Del Rosso JQ, Kircik L, Gallagher CJ.Comparative efficacy and tolerability of dapsone 5% gel in adult versus adolescent females with acne vulgaris.	Posthoc analysis of Draelos 2007
Del Rosso, J. Q. Clindamycin phosphate 1.2%/tretinoin 0.025% gel for the treatment of acne vulgaris: Which patients are most likely to benefit the most?. 2015. Journal of Clinical and Aesthetic Dermatology	Duplicate record
Del Rosso, J. Q. K., L.,Gallagher, C. J.Comparative efficacy and tolerability of dapsone 5% gel in adult versus adolescent females with acne vulgaris. 2015. Journal of Clinical and Aesthetic Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Del Rosso, J. Q. Study results of benzoyl peroxide 5%/clindamycin 1% topical gel, adapalene 0.1% gel, and use in combination for acne vulgaris. 2007. Journal of drugs in dermatology : JDD	No relevant study population - no details of inclusion criteria reported and study is not relevant for PCOS, maintenance or refractory treatments
Del Rosso, J. Q. The use of topical azelaic acid for common skin disorders other than inflammatory rosacea. 2006. Cutis	Duplicate record
Deshmukh, S. N. B., V. A.,Mahajan, M. M.,Sujata Dudhgaonkar, D.,Mishra, D.Comparison of efficacy and safety of topical 1% nadifloxacin and tretinoin 0.025% combination therapy with 1% clindamycin and tretinoin 0.025% combination therapy in patients of mild-to-moderate acne. 2018. Perspectives in Clinical Research	No relevant intervention - intervention & class not available in the UK
DeVillez, R. L.Clinical comparison of the safety and efficacy of Brevoxyl gel and Benzamycin gel. 1992. Drug Investigation	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Dhawan, S. S. Comparison of 2 clindamycin 1%-benzoyl peroxide 5% topical gels used once daily in the management of acne vulgaris. 2009. Cutis; cutaneous medicine for the practitioner	No relevant comparison - clindamycin/BPO topical gel with the hydrating excipients dimethicone and glycerin vs without hydrating excipients
Dieben Th, O. M. V., L.,Theeuwes, A.,Coelingh Bennink, H. J. T.The effects of CTR-24, a biphasic oral contraceptive combination, compared to Diane-35 in women with acne. 1994. Contraception	No relevant study population - insufficient details about types of lesions to determine severity of participants

Reference	Reason for exclusion
Divers, L. S.A new preparation for the topical treatment of acne vulgaris. Report of a year's study. 1966. Journal of the College of General Practitioners	No relevant study design - not RCT
Do Nascimento, L. V. G., A. C. M.,Magalhaes, G. M.,De Faria, F. A.,Guerra, R. M.,Almeida, F. D. C.Single-blind and comparative clinical study of the efficacy and safety of benzoyl peroxide 4% gel (BID) and adapalene 0.1% Gel (QD) in the treatment of acne vulgaris for 11 weeks. 2003. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne
Dogra, A. S., V. K.,Minocha, Y. C.Comparative evaluation of retinoic acid, benzoyl peroxide and erythromycin lotion in acne vulgaris. 1993. Indian journal of dermatology, venerology and leprology	No relevant study population - sample includes people with mild to severe acne
Dominguez, J. H., M. T.,Celayo, J. L.,Dominguez-Soto, L.,Teixeira, F.Topical isotretinoin vs. topical retinoic acid in the treatment of acne vulgaris. 1998. International Journal of Dermatology	No relevant data - insufficient data reported
Donadini, A.Is topical antibiotic therapy associated with the same oral treatment useful in patients with acne?. 1989. Ann ital dermatol clin sper	Not in English language and also no relevant study design - not RCT
Dosik, J. E., H.,Stuart, I.Topical minocycline foam 4%: Results of four phase 1 studies evaluating the potential for phototoxicity, photoallergy, sensitization, and cumulative irritation. 2019. Journal of immunotoxicology	No relevant study population - participants did not have acne
Dosik, J. S. G., R. D.,Arsonnaud, S.Cumulative irritancy comparison of topical retinoid and antimicrobial combination therapies. 2006. Skinmed	No relevant study population - participants did not have acne
Dosik, J. S. H., K.,Arsonnaud, S.Cumulative irritation potential of adapalene 0.1% cream and gel compared with tazarotene cream 0.05% and 0.1%. 2005b. Cutis	No relevant study population - participants did not have acne
Dosik, J. S. H., K.,Arsonnaud, S.Cumulative irritation potential of adapalene 0.1% cream and gel compared with tretinoin microsphere 0.04% and 0.1%. 2005a. Cutis	No relevant study population - participants did not have acne
Draelos, Z. D. Assessing the value of botanical anti-inflammatory agents in an OTC acne treatment regimen. 2015. Journal of Drugs in Dermatology	No relevant comparison/intervention - compares over-the-counter skin care regimens with/without added botanicals
Draelos, Z. D. C., E.,Maloney, J. M.,Elewski, B.,Poulin, Y.,Lynde, C.,Garrett, S.Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. 2007. Journal of the American Academy of Dermatology	No relevant data reported - reports pooled results from 2 trials combined
Draelos, Z. D. C., V.,Young, C.,Dhawan, S. S.The effect of vehicle formulation on acne medication tolerability. 2008. Cutis	No relevant outcomes reported
Draelos, Z. D. E., K.,Rom, D.Five-day study to judge the short-term effect of a benzoyl peroxide 3% gel on acne lesions. 2016. Journal of cosmetic dermatology	No relevant outcomes reported
Draelos, Z. D. M., A.,Smiles, K.The effect of 2% niacinamide on facial sebum production. 2006. Journal of Cosmetic and Laser Therapy	No relevant study population - participants did not have acne
Draelos, Z. D. P., A.,Alio Saenz, A. B.Randomized tolerability analysis of clindamycin phosphate 1.2%-tretinoin 0.025% gel used with benzoyl peroxide wash 4% for acne vulgaris. 2010. Cutis	No relevant intervention - queous-based gel (clindamycin phosphate 1.2%-tretinoin 0.025%) when used in conjunction with a BPO wash 4%

Reference	Reason for exclusion
Draelos, Z. D. R., D. A.,Kempers, S. E.,Bruce, S.,Peredo, M. I.,Downie, J.,Chang-Lin, J. E.,Berk, D. R.,Ruan, S.,Kaoukhov, A.Treatment response with once-daily topical dapsone gel, 7.5% for acne vulgaris: Subgroup analysis of pooled data from two randomized, double-blind stu. 2017. Journal of Drugs in Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Draelos, Z. D. S., A. R.,Thiboutot, D.,Oresajo, C.,Yatskayer, M.,Raab, S.A multicenter, double-blind study to evaluate the efficacy and safety of 2 treatments in participants with mild to moderate acne vulgaris. 2012. Cutis; cutaneous medicine for the practitioner	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Drake, L. Comparative efficacy and tolerance of Cleocin T topical gel (clindamycin phosphate topical gel) versus oral minocycline in the treatment of acne vulgaris. 1990. Data on file (technical report from pharmacia and upjohn ltd)	No relevant article type - not published in peer reviewed journal
Dreno, B. B., V.,Ochsendorf, F.,Layton, A. M.,Perez, M.,Dakovic, R.,Gollnick, H.Efficacy and safety of clindamycin phosphate 1.2%/tretinoin 0.025% formulation for the treatment of acne vulgaris: Pooled analysis of data from three randomised, double-blind, parallel-group, phase III studies. 2014. European Journal of Dermatology	No relevant data reported - pooled analysis of 3 studies combined, 2 of which include people with mild to severe acne. Data for third study reported in Schleslinger 2009
Dreno, B. M., D.,Alirezai, M.,Amblard, P.,Auffret, N.,Beylot, C.,Bodokh, I.,Chivot, M.,Daniel, F.,Humbert, P.,Meynadier, J.,Poli, F.Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris. 2001. Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Dreno, B. T., J.,Rivier, M.,Martel, P.,Bissonnette, R.Adapalene 0.1%/benzoyl peroxide 2.5% gel reduces the risk of atrophic scar formation in moderate inflammatory acne: a split-face randomized controlled trial. 2016. Journal of the european academy of dermatology and venereology : JEADV	Duplicate record
Dreno, B. T., J.,Rivier, M.,Martel, P.,Bissonnette, R.Adapalene 0.1%/benzoyl peroxide 2.5% gel reduces the risk of atrophic scar formation in moderate inflammatory acne: a split-face randomized controlled trial. 2017. Journal of the European Academy of Dermatology and Venereology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Dudhia, S. S., R. B.,Agrawal, P.,Shah, A.,Date, S.Efficacy and safety of clindamycin gel plus either benzoyl peroxide gel or adapalene gel in the treatment of acne: a randomized open-label study. 2015. Drugs and Therapy Perspectives	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for

Reference	Reason for exclusion
	pairwise comparisons - including PCOS, maintenance and refractory treatments
Dunlap, F. E. B., M. D.,Plott, R. T.,Verschoore, M.Adapalene 0.1% gel has low skin irritation potential even when applied immediately after washing. 1998a. British Journal of Dermatology, Supplement	No relevant comparison - compares adapalene 0.1% gel application immediately after washing to a delayed application
Dunlop, K. J. B., R. S.A comparative study of isolutrol versus benzoyl peroxide in the treatment of acne. 1995. The Australasian journal of dermatology	No relevant intervention - Isolutrol
Eady, E. A. B., B. M.,Pulling, K.,Cunliffe, W. J.The benefit of 2% salicylic acid lotion in acne - A placebo-controlled study. 1996a. Journal of dermatological treatment	No relevant data reported - for example, not possible to extract the number of participants in each treatment group
Eady, E. A. B., R. A.,Jones, C. E.,Cove, J. H.,Holland, K. T.,Cunliffe, W. J.The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. 1996b. British Journal of Dermatology	No relevant outcomes reported
Eady, E. A. B., R. A.,Jones, C. E.,Cove, K. T.,Cunliffe, W. J.The effects of acne therapy with a combination of benzoyl peroxide and erythromycin on carriage of eryhtromycin resistant cutaneous propionobacteria. 1994. British journal of dermatology	No relevant article type - conference abstract
Ede, M.A double blind, comparative study of benzoyl peroxide, benzoyl peroxide chlorhydroxyquinoline, benzoyl peroxide chlorhydroxyquinoline hydrocortisone, and placebo lotions in acne. 1973. Current Therapeutic Research - Clinical and Experimental	No relevant intervention
Egan, N. L., M. C.,Baker, M. M.Randomized, controlled, bilateral (split-face) comparison trial of the tolerability and patient preference of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. 2001. Cutis; cutaneous medicine for the practitioner	No relevant study population - sample includes people with mild, moderate and severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Eichenfield, L. E. J., J. L.,Dirschka, T.,Taub, A. F.,Lynde, C.,Graeber, M.,Kerrouche, N.Treatment of 2,453 acne vulgaris patients aged 12-17 years with the fixed-dose adapalene-benzoyl peroxide combination topical gel: efficacy and safety. 2010a. Journal of Drugs in Dermatology: JDD	Subgroup analysis of Stein Gold 2016
Eichenfield, L. F. A. S., A. B.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. 2011. Journal of Drugs in Dermatology: JDD	No relevant study population - sample includes people with mild to severe acne acne and study is not relevant for PCOS, maintenance or refractory treatments
Eichenfield, L. F. D., Z.,Lucky, A. W.,Herbert, A. A.,Sugarman, J.,Gold, S.,Rudisill, D.Treatment of acne in children 9-11 with a fixed dose combination. 2013b. Pediatric Dermatology	No relevant article type - conference abstract
Eichenfield, L. F. H., A. A.,Schachner, L.,Paller, A. S.,Rossi, A. B.,Lucky, A. W.Tretinoin microsphere gel 0.04% pump for treating acne vulgaris in preadolescents: A randomized, controlled study. 2012a. Pediatric Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS,

Reference	Reason for exclusion
	maintenance or refractory treatments
Eichenfield, L. F. K., A. C.Moderate to severe acne in adolescents with skin of color: Benefits of a fixed combination clindamycin phosphate 1.2% and benzoyl peroxide 2.5% aqueous gel. 2012b. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis of Thiboutot 2008
Eichenfield, L. F. S., J. L.,Guenin, E.,Harris, S.,Bhatt, V.Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris in a preadolescent population. 2019. Pediatric Dermatology	No relevant data reported - post hock analysis of Tyring 2018
Eichenfield, L. F. T., D.,Shalita, A.,Swinyert, L.,Tanghetti, E.,Tschen, E.,Parr, L.A three-step acne system containing solubilized benzoyl peroxide versus benzoyl peroxide/clindamycin in pediatric patients with acne. 2009a. Journal of clinical and aesthetic dermatology	No relevant data reported - subgroup analysis of Thiboutout 2009
Eichenfield, L. F. W., M.A novel gel formulation of 0.25% tretinoin and 1.2% clindamycin phosphate: Efficacy in acne vulgaris patients aged 12 to 18 years. 2009b. Pediatric Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Eichenfield, L. F., Sugarman, J. L., Guenin, E., Bhatt, V. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris in a preadolescent population. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant article type - conference abstract
El Aziz Ragab, M. A. O., S. S.,Collier, A.,El-Wafa, Raha,Gomaa, N.The effect of continuous high versus low dose oral isotretinoin regimens on dermcidin expression in patients with moderate to severe acne vulgaris. 2018. Dermatologic Therapy	No relevant article type - letter to editor
Elbaum, D. J.Comparison of the stability of topical isotretinoin and topical tretinoin and their efficacy in acne. 1988. Journal of the American Academy of Dermatology	No relevant study population - insuficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
El-Fakahany, H. M., W.,Abdallah, F.,Abdel-Raouf, H.,Abdelhakeem, M.Fractional microneedling: A novel method for enhancement of topical anesthesia before skin aesthetic procedures. 2016. Dermatologic Surgery	No relevant intervention - skin microneedling for treatment of atrophic scars
El-Latif, A. A. H., F. A.,Elshahed, A. R.,Mohamed, A. G.,Elsaie, M. L.Intense pulsed light versus benzoyl peroxide 5% gel in treatment of acne vulgaris. 2014. Lasers in Medical Science	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ellis, C. N. G., W. R.,Stone, D. Z.,Heezen-Wehner, J. L.A comparison of cleocin T solution cleocin T gel, and placebo in the treatment of acne vulgaris. 1988. Cutis	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ellis, C. N. L., J.,Katz, H. I.,Goldfarb, M. T.,Hickman, J.,Jones, T. M.,Tschen, E.Therapeutic studies with a new combination benzoyl peroxide/clindamycin topical gel in acne vulgaris. 2001b. Cutis	No relevant data - reports 3 trials but full article is not available; no information about number

Reference	Reason for exclusion
	of participants assigned to each group in trials reported
Ellis, C. N. L., J.,Katz, H. I.,Goldfarb, M. T.,Hickman, J.,Jones, T. M.Therapeutic studies with a new combination benzoyl peroxide/clindamycin topical gel in acne vulgaris.(erratum appears in Cutis 2001 Mar;67(3): 257). 2001a. Cutis; cutaneous medicine for the practitioner	Duplicate record
Ellis, C. N. M., L. E.,Smith, E. B.,Chalker, D. M.,Swinyer, L. J.,Katz, I. H.,Berger, R. S.,Mills, O. H.,Baker, M.,Verschoore, M.,et al.,Comparison of adapalene 0.1% solution and tretinoin 0.025% gel in the topical treatment of acne vulgaris. 1998. British journal of dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Elman, M. S., M.,Harth, Y.The effective treatment of acne vulgaris by a high-intensity, narrow band 405-420 nm light source. 2003. Journal of Cosmetic and Laser Therapy	No relevant data - reoprts data from 3 trials. No relevant population - sample includes people with mild to severe acne in first 2 trials, and insufficient details about types of lesions to determine severity of participants in one trial and study is not relevant for PCOS, maintenance or refractory treatments
ElRefaei, A. M. A. S., H. A.,Sorour, N. E.Salicylic-mandelic acid versus glycolic acid peels in Egyptian patients with acne vulgaris. 2015. Journal of the egyptian women's dermatologic society	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Enshaieh,The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: a randomized, double-blind placebo-controlled study. 2007. NA	No relevant intervention - tea tree oil gel
Ereaux, L. P.A new lotion for the treatment of acne vulgaris. 1965. Canadian Medical Association journal	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ergin, S. E., C.,Baysal, V.,Yayli, G.An acne study focused on erythromycin: Benzoyl peroxide alone or with topical erythromycin against Propionibacterium acnes in acne vulgaris. 2001. Gazi Medical Journal	Outcomes reported in figures only
Erkkola, R. H., E.,Luikku, J.,Lumme, R.,Mannikko, H.,Aydinlik, S.Ovulation inhibitors containing cyproterone acetate or desogestrel in the treatment of hyperandrogenic symptoms. 1990. Acta Obstetricia et Gynecologica Scandinavica	No relevant study population - participants did not have acne
Ernst, E., Huntley, A. Tea tree oil: a systematic review of randomized clinical trials. 2000. Forsch Komplementarmed Klass Naturheilkd	No relevtan intervention - systematic review about

Reference	Reason for exclusion
	tea tree oil for various dermatological conditions
Ersoy, L. K., A.,Kilic, I.,Koc, K.,Sen, S.Topical spironolactone in acne vulgaris. 1996. Nouvelles dermatologiques	Not in English language
Euctr, C. Z. Assessment of efficacy and safety of a new gel with 10 mg/g clindamycin and 30 mg/g benzoyl peroxide in comparison with the approved preparation DUACÃ‚Â® 10 mg/g + 30 mg/g Gel and the underlying vehicle in patients with mild to moderate acne. 2018.	No relevant study design - not RCT
Euctr, F. R. Randomized double-blind study on the benefit of spironolactone for treating acne of adult woman. 2017.	No relevant study design - not RCT
Exner, J. H. C., H.,Dahod, S.,Pochi, P. E.Topical erythromycin/zinc effect on acne and sebum secretion. 1983. Current Therapeutic Research - Clinical and Experimental	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Fabbrocini, G. I., R.,Faggiano, A.,Del Prete, M.,Donnarumma, M.,Marasca, C.,Marciello, F.,Savastano, R.,Monfrecola, G.,Colao, A.Low glycaemic diet and metformin therapy: A new approach in male subjects with acne resistant to common treatments. 2016. Clinical and Experimental Dermatology	No relevant intervention - metformin plus a hypocaloric diet
Fabbrocini, G. R., A. B.,Thouvenin, M. D.,Peraud, C.,Mengeaud, V.,Bacquey, A.,Saint Aroman, M.Fragility of epidermis: acne and post-procedure lesional skin. 2017. Journal of the European Academy of Dermatology and Venereology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Faghihi, G. J., K.,Tajmirriahi, N.,Abtahi-Naeini, B.,Nilforoshzadeh, M.,Radan, M.,Hosseini, S. M.The efficacy of oral isotretinoin versus cyproterone compound in female patients with acne and the triad of cutaneous hyperandrogenism: A randomized clinical trial. 2014. Advanced Biomedical Research	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Faghihi, G. K.-I., A.,Hosseini, S. M.,Radan, M. R.,Nilforoushzadeh, M. A. Efficacy of intense pulsed light combined with topical erythromycin solution 2% versus topical erythromycin solution 2% alone in the treatment of persistent facial erythematous acne macules. 2015. Journal of isfahan medical school	No relevant study design - not RCT
Faghihi, G. R., M.,Abtahi-Naeini, B.,Nilforoushzadeh, M. A.The efficacy of 5% dapsone gel plus oral isotretinoin versus oral isotretinoin alone in acne vulgaris: A randomized double-blind study. 2014. Advanced Biomedical Research	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments

Reference	Reason for exclusion
Faghihi, G. V., A.,Asilian, A.,Radan, M. R.,Esteki, H.,Elahidoost, M.Comparative efficacy of filtered blue light (emitted from sunlight) and topical erythromycin solution in acne treatment: A randomized controlled clinical trial. 2011. Journal of Pakistan Association of Dermatologists	No relevant study design - not RCT (split face study but same treatments always applied to left & right)
Faloia, E. F., S.,Mancini, V.,Morosini, P.,De Pirro, R.Treatment with a gonadotropin-releasing hormone agonist in acne or idiopathic hirsutism. 1993. Journal of Endocrinological Investigation	No relevant study design - not RCT
Falsetti, L. Acne treatment with a new estroprogestinic biphasic combination containing desogestrel. 1991. Acta Europaea Fertilitatis	Not obtainable
Fan, L. H., Xu, C. R.A randomised controlled trial of Bimaisen (Compound Erythromycin and Benzoyl Peroxide) versus metronidazole in the treatment of acne (Chinese). 1998. Journal of clinical dermatology	Not in English language
Fanta, D. S., N.Miconazole-benzoyl peroxide: a new combination for extending the topical therapy of acne. 1984. Zeitschrift fur hautkrankheiten	Not in English language
Farina, M. C., L.,Palumbo, M.,De Leo, V.,Morgante, G.,Cianci, A.Effectiveness of an oral contraceptive containing ethinyl-estradiol combined with drospirenone in the treatment of symptomatic hyperandrogenism. 2006. Italian journal of gynaecology and obstetrics	No relevant study popualtion - article reports 2 trials, both of which are in people with hyperandrogenism and study is not relevant for PCOS, maintenance or refractory treatments
Farrell, L. N. S., J. S.,Stranieri, A. M.The treatment of severe cystic acne with 13-cis-retinoic acid. Evaluation of sebum production and the clinical response in a multiple-dose trial. 1980. Journal of the American Academy of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Fatemi, F. N., J.,Nasab, S. S.,Nilforoushzadeh, M. A. Treatment of acne vulgaris using the combination of topical erythromycin and Miconazole. 2014. Journal of Skin and Stem Cell	Insufficent detail in reporting - unclear how many participants received each treatment
Fatum, B. H., H. H. V.,Mortensen, E.Topical treatment of acne vulgaris with the vitamin A acid derivate motretinide (Tasmaderm), tretinoin (Airol) and a placebo cream. 1980. Ugeskrift for laeger	Not in English language
Feldman, S. R. T., J.,Poulin, Y.,Dirschka, T.,Kerrouche, N.,Manna, V.The efficacy of adapalene-benzoyl peroxide combination increases with number of acne lesions. 2011. Journal of the American Academy of Dermatology	No relevant data reported - meta-analysis of Thiboutot 2007, Gollnick 2009, and Stein Gold 2009
Fenske, N. A. M., J. L. Cutaneous pigmentation due to minocycline hydrochloride. 1980. Journal of the American Academy of Dermatology	No relevant study design - not RCT
Ferahbas, A. U., S.,Aykol, D.,Borlu, M.,Uksal, U.Clinical Evaluation of Roxithromycin: A Double-Blind, Placebo-Controlled and Crossover Trial in Patients with Acne Vulgaris. 2004. Journal of Dermatology	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Fernandez, J. R. R., K.,Voronkov, M.,Feng, X.,Stock, J. B.,Stock, M.,Gordon, J. S.,Shroot, B.,Christensen, M. S.,Perez, E.SIG1273: a new cosmetic functional ingredient to reduce blemishes and Propionibacterium acnes in acne prone skin. 2012. Journal of Cosmetic Dermatology	No relevant intervention - Disodium Tetramethylhexadecenyl succinyl Cysteine
Feucht, C. L. A., B. S.,Chalker, D. K.,Smith, J. G., Jr.Topical erythromycin with zinc in acne. A double-blind controlled study. 1980. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Fisher, A. A.Erythromycin "free base" -a nonsensitizing topical antibiotic for infected dermatoses and acne vulgaris. 1977. Cutis	No relevant article type - non-systematic review
Fisk, W.A., Lev-Tov, H.A., Sivamani, R.K. Botanical and phytochemical therapy of acne: a systematic review. 2014. Phytother Res	No relevant intervention - systematic review about the use of botanical agents in the treatment of acne
Fleischer, A. B. S., A.,Eichenfield, L. F.,Abramovits, W.,Lucky, A.,Garrett, S.Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4% or moisturizer for the treatment of acne vulgaris: a 12-week, randomized, double-blind study. 2010. Journal of drugs in dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Fluhr, J. W. B., B.,Gloor, M.,Hoffler, U.In-vitro and in-vivo efficacy of zinc acetate against Propionibacteria alone and in combination with erythromycin. 1999. Zentralblatt fur Bakteriologie	No relevant study population - sample includes people with mild to severe acne
Fonseca, E. F., C.,Camarasa, J. G.,Olmos, L.,Del Pinos, J.,Rodriguez, T.,San Martin, J. C.,Roman, P.,Asin, M.,Sambricio, F.,et al.,Erythromycin lauryl sulphate in combination with tretinoin in the topical treatment of acne vulgaris. A multicentre double-blind clinical trial. 1995b. Journal of dermatological treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Fonseca, E. F., C.,Camarasa, J. G.Erythromycin lauryl sulphate in combination with tretinoin in the topical treatment of acne vulgaris. A multicentrie double-blind clinical trial. 1995a. Indian journal of dermatology, venerology and leprology	Duplicate record
Forbat, E. A.-N., F.Nonvascular uses of pulsed dye laser in clinical dermatology. 2019. Journal of Cosmetic Dermatology.	Duplicate record
Francomano, M. G., G.,Bertoni, L.,Seidenari, S.Instrumental and clinical assessment of the efficacy and tolerability of a topical product with benzoyl peroxide combined with a detergent for acneic skin. 2000. Giornale italiano di dermatologia e venereologia	Not in English language
Frank, S. B. Topical treatment of acne with a tetracycline preparations: results of a multi-group study. 1976. Cutis	No relevant study design - not RCT
Franz, E. R., B.,Weidner-Strahl, S.The effectiveness of topical antibacterials in acne: a double-blind clinical study. 1978. Journal of International Medical Research	Not obtainable
Fraser, N. B. M., R. A.,Stewart, T. W.,Thornton, E. J.Treatment of acne vulgaris comparing two similar lotion formulations, one with ('Actinac') and one without chloramphenicol. 1980. Current Medical Research & Opinion	No relevant comparison - Actinac with/without chloramphenicol

Reference	Reason for exclusion
Fried, R. N., M.Acne quality of life and patient satisfaction following treatment with tretinoin pump. 2009. Journal of Drugs in Dermatology: JDD	No relevant study design - not RCT
Fu, W. W., Fang, L., Gu, J., Shun, J. F. Clinical efficacy and safety of 5% benzoyl peroxide gel combined with 0.1% adapalene gel in the treatment of acne vulgaris: a multicenter, randomized study. 2003. Chinese journal of dermatology	Not in English language
Fulton, J. E., Jr.,Pablo, G.Topical antibacterial therapy for acne. Study of the family of erythromycins. 1974. Archives of Dermatology	No relevant data reported
Fyrand, O. J., H. B. Water-based versus alcohol-based benzoyl peroxide preparations in the treatment of acne vulgaris. 1986. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Galvin, S. A. G., R.,Baker, M.,Guibal, F.,Tuley, M. R.Comparative tolerance of adapalene 0.1% gel and six different tretinoin formulations. 1998. British Journal of Dermatology, Supplement	No relevant study population - participants did not have acne
Gammon, W. R. M., C.,Lantis, S.Comparative efficacy of oral erythromycin versus oral tetracycline in the treatment of acne vulgaris. A double-blind study. 1986. Journal of the American Academy of Dermatology	Dosage of erythromycin lower than BNF value
Gandola, M. A., G.,Barba, C.,Bassi, R.,Binazzi, M.,Landi, G.,Levi, L.,Randazzo, D.,Serri, F.,Villano, A. P.Topical vitamin A acid in the treatment of acne vulgaris (a controlled multicenter trial). 1976. Archives for dermatological research = archiv fur dermatologische forschung	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Gans, E. H. K., A. M. Comparative efficacy of clindamycin and benzoyl peroxide for in vivo suppression of Propionibacterium acnes. 2002. Journal of Dermatological Treatment	No relevant data reported - pharmokinetic study
Garg, V. K. S., S.,Sarkar, R.Glycolic acid peels versus salicylic-mandelic acid peels in active acne vulgaris and post-acne scarring and hyperpigmentation: a comparative study. 2009. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Geiger, J. M. H., L.,Harms, M.,Saurat, J. H.Oral 13-cis retinoic acid is superior to 9-cis retinoic acid in sebosuppression in human beings. 1996. Journal of the American Academy of Dermatology	No relevant study population - participants did not have acne
Genina, E. A. B., A. N.,Simonenko, G. V.,Odoevskaya, O. D.,Tuchin, V. V.,Altshuler, G. B.Low-intensity indocyanine-green laser phototherapy of acne vulgaris: pilot study. 2004. Journal of biomedical optics	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ghovvati, M., Kord Afshari, G., Ahmad Nasrollahi, S., Firooz, A., Samadi, A., Karimi, M., Talebi, Z., Kolahdooz, S., Vazirian, M. Efficacy of topical cinnamon gel for the treatment of facial acne vulgaris: A preliminary study. 2019. Biomedical Research and Therapy	No relevant study design - not RCT

Reference	Reason for exclusion
Gibson, J. R. D., C. R.,Harvey, S. G.,Barth, J.Oral trimethoprim versus oxytetracycline in the treatment of inflammatory acne vulgaris. 1982. British Journal of Dermatology	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Gibson, J. R.Azelaic acid 20% cream (AZELEX) and the medical management of acne vulgaris. 1997. Dermatology Nursing	No relevant article type - expert review
Gloor, M. H., A.,Friederich, H. C.Trial of benzoyl peroxide treatment of acne vulgaris. EXPERIMENTELLE UNTERSUCHUNGEN ZUR BENZOYLPEROXYDTHERAPIE DER ACNE VULGARIS. 1975. ZHAUTKR	Not in English language
Goforoushan, F. A., H.,Goldust, M.Efficacy of vitamin E to prevent dermal complications of isotretinoin. 2013. Pakistan Journal of Biological Sciences	No relevant comparison - compares efficacy of treatment to alleviate isotretinoin dermal complications
Goh, C. L. T., M. B.,Briantais, P.,Kaoukhov, A.,Soto, P.Adapalene gel 0.1% is better tolerated than tretinoin gel 0.025% among healthy volunteers of various ethnic origins. 2009. Journal of Dermatological Treatment	No relevant study population - participants did not have acne
Gold, L. S. B., H.,Rueda, M. J.,Kerrouche, N.,Dreno, B.Adapalene-benzoyl peroxide gel is efficacious and safe in adult female acne, with a profile comparable to that seen in teen-aged females. 2016. Journal of Clinical and Aesthetic Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Gold, L. S., Dhawan, S., Weiss, J., Draelos, Z. D., Ellman, H., Stuart, I.Open-label extension study evaluating long-term safety and efficacy of FMX101 4% minocycline foam for moderate-to-severe acne vulgaris. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant data reported - reported reports results on open-label part of trial only
Gold, M. H. B., V. L.,Boring, M. M.,Bridges, T. M.,Biron, J. A.,Carter, L. N.The use of a novel intense pulsed light and heat source and ALA-PDT in the treatment of moderate to severe inflammatory acne vulgaris. 2004. Journal of Drugs in Dermatology: JDD	No relevant study design - not RCT
Gold, M. H. R., J.,Goldman, M. P.,Bridges, T. M.,Bradshaw, V. L.,Boring, M. M.,Guider, A. N.A multicenter clinical evaluation of the treatment of mild to moderate inflammatory acne vulgaris of the face with visible blue light in comparison to topical 1% clindamycin antibiotic solution. 2005. Journal of drugs in dermatology : JDD	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Gold, M. H. S., N. S.,Bradshaw, V. L.,Boring, M. M.A randomized, controlled, double-blind study of localized low-heat treatment of acne lesions. 2007. Cosmetic Dermatology	No relevant data reported - response study
Gold, M. H. S., W.,Biron, J. A.Clinical efficacy of home-use blue-light therapy for mild-to moderate acne. 2011. Journal of Cosmetic and Laser Therapy	No relevant intervention - only 2 individual lesions treated per patient
Gold, M. H., Korotkor., A.Sub-group analyses from a trial of a fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide	No relevant article type - non-systematic review

Reference	Reason for exclusion
3.75% gel for the treatment of moderate-to-severe acne vulgaris. 2015. Journal of Clinical and Aesthetic Dermatology	
Gold, M. R. M., A. P.A randomised, double-blind, multicentre, multinational comparison of 2% fusidic acid lotion and 1% clindamycin lotion in patients with acne vulgaris on the face. 1996. European journal of clinical research	Not obtainable
Goldman, M. P. B., S. M.A single-center study of aminolevulinic acid and 417 NM photodynamic therapy in the treatment of moderate to severe acne vulgaris. 2003. Journal of Drugs in Dermatology: JDD	No relevant study design - not RCT
Goldstein, J. A. S.-S., A.,Thomsen, R. J.,Pochi, P. E.,Shalita, A. R.,Strauss, J. S.Comparative effect of isotretinoin and etretinate on acne and sebaceous gland secretion. 1982. Journal of the American Academy of Dermatology	No relevant comparison - isotretinoin vs etretinate
Gollnick, H. G., K.Azelaic acid for the treatment of acne: Comparative trials. 1989. Journal of Dermatological Treatment	No relevant article type - expert review
Gollnick, H. P. G., K.,Zaumseil, R. P.Azelaic acid 15% gel in the treatment of acne vulgaris. Combined results of two double-blind clinical comparative studies. 2004. Journal der Deutschen Dermatologischen Gesellschaft [Journal of the German Society of Dermatology]	Not in English language
Gollnick, H. P. M. V., K.,Hermann, J.,Blume, U.,Hahn, H.,Haustein, U. F.,Orfanos, C. E.Topical quinolone OPC-7251: A clinical and microbiological study in acne. 1994. European Journal of Dermatology	No information on the baseline severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Goltz, R. W. C., G. M.,Schnieders, J. R.,Neidert, G. L.A comparison of Cleocin T 1 percent solution and Cleocin T 1 percent lotion in the treatment of acne vulgaris. 1985. Cutis	No relevant data - insufficient data reported
Goltz, R. W. K., S.Oral tetracycline treatment on bacterial flora in acne vulgaris. 1966. Archives of Dermatology	No relevant data reported - bacterial flora study
Gonzalez, P. V., R.,Cirigliano, M.The tolerability profile of clindamycin 1%/benzoyl peroxide 5% gel vs. adapalene 0.1%/benzoyl peroxide 2.5% gel for facial acne: Results of a randomized, single-blind, split-face study. 2012. Journal of Cosmetic Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Goodfellow, A. A.-Z., J.,Carter, G.Oral spironolactone improves acne vulgaris and reduces sebum excretion. 1984. British Journal of Dermatology	No relevant outcomes reported
Goreshi, R. S., A.,Ehst, B. D.A double-blind, randomized, bilateral comparison of skin irritancy following application of the combination acne products clindamycin/tretinoin and benzoyl peroxide/adapalene. 2012. Journal of Drugs in Dermatology	No relevant outcomes reported
Goswami, B. C. B., B.,Barua, A. B.,Olson, J. A. Topical retinoyl beta-glucuronide is an effective treatment of mild to moderate acne vulgaris in Asian-Indian patients. 1999. Skin Pharmacology & Applied Skin Physiology	No relevant intervention - retinoyl beta-glucuronide
Goujon, C. G., P.,Violin, L.,Larnier, C.Biometric and clinical comparative assay of Roaccutane gel (0.05% isotretinoin) versus Retacnyl cream (0.05% tretinoin) in the treatment of moderate retentional acne on the face. 1995. Nouvelles Dermatologiques	Not in English language
Gould, D. J. E., R.,Cunliffe, W. J.Oral tetracycline and retinoic acid gel in acne. 1978. Practitioner	No relevant study design - unclear if RCT

Reference	Reason for exclusion
Graupe, K. C., W. J.,Gollnick, H. P.,Zaumseil, R. P.Efficacy and safety of topical azelaic acid (20 percent cream): an overview of results from European clinical trials and experimental reports. 1996. Cutis	No relevant study design - not RCT
Green, L. C., M.,Gwazdauskas, J. A.,Gonzalez, P.The tolerability profile of clindamycin 1%/benzoyl peroxide 5% gel vs. adapalene 0.1%/benzoyl peroxide 2.5% gel for facial acne: Results of two randomized, single-blind, split-face studies. 2012. Journal of Clinical and Aesthetic Dermatology	No relevant data reported - reports pooled results from 2 trials combined
Green, L. J. D. R., J. Q.Efficacy and Tolerability of a Three-Step Acne System Containing a Solubilized Benzoyl Peroxide Lotion versus a Benzoyl Peroxide/Clindamycin Combination Product: An Investigator-Blind, Randomized, Parallel-Group Study. 2008. The Journal of Clinical & Aesthetic Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Green, L. K., L. H.,Gwazdauskas, J.Randomized, controlled, evaluator-blinded studies conducted to compare the efficacy and tolerability of 3 over-the-counter acne regimens in subjects with mild or moderate acne. 2013. Journal of drugs in dermatology	No relevant comparison - compares over-the-counter 3-part skin care regimens inclunding BPO, SAL etc which have been discontinued (MaxClarity, Proactiv, Murad)
Greenwood, R. B., B.,Cunliffe, W. J.Evaluation of a therapeutic strategy for the treatment of acne vulgaris with conventional therapy. 1986. British Journal of Dermatology	No relevant study design - not RCT
Gregory, A. N. T., C. R.,Leibowitz, K. R.,Lane, M.A study on the use of a novel light and heat energy system to treat acne vulgaris. 2004. Cosmetic Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Griffiths, C. E. E., J. T.,Bernard, B. A.,Rossio, P.,Cromie, M. A.,Finkel, L. J.,Shroot, B.,Voorhees, J. J.Comparison of CD271 (adapalene) and all-trans retinoic acid in human skin: dissociation of epidermal effects and CRABP-II mRNA expression. 1993. Journal of Investigative Dermatology	No relevant study population - participants did not have acne
Grimes, P. C., V.Tazarotene cream for postinflammatory hyperpigmentation and acne vulgaris in darker skin: A double-blind, randomized, vehicle-controlled study. 2006. Cutis	No relevant study population - sample includes people with post-inflammatory hyperpigmentation and acne and study is not relevant for PCOS, maintenance or refractory treatments
Grosshans, E. F., A.,Guibaud, B.Clinical evaluation of a topical ethyl lactate treatment of acne vulgaris (author's transl). 1978. Annales de dermatologie ET de venereologie	Not English language
Grosshans, E. M., R.,Mascaro, J. M.,Torras, H.,Meynadier, J.,Alirezai, M.,Finlay, A. Y.,Soto, P.,Poncet, M.,Verschoore, M.,Clucas, A.Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes

Reference	Reason for exclusion
particular reference to the onset of action and impact on quality of life. 1998. British Journal of Dermatology, Supplement	were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Grove, G. Z., C.,Gwazdauskas, J.Tolerability and irritation potential of four topical acne regimens in healthy subjects. 2013. Journal of Drugs in Dermatology	No relevant study population - participants did not have acne
Gruber, F. G.-G., H.,Kastelan, M.,Brajac, I.,Lenkovic, M.,Zamolo, G.Azithromycin compared with minocycline in the treatment of acne comedonica and papulo-pustulosa. 1998b. Journal of Chemotherapy	No relevant study design - not RCT
Gu, W. Z., X. Q.,Wu, J. D.Cuochuang Heji and acupuncture and cupping treatment on acne vulgaris. 2016b. Liaoning journal of traditional chinese medicine [liaoning zhong yi za zhi]	No relevant intervention - Cuochuang Heji and acupuncture
Gu,Cuochuang Heji and acupuncture and cupping treatment on acne vulgaris. 2016a. NA	Duplicate record
Guerrier, C. J. W. T., E. J.Double-blind comparison of two similar lotion formulations, one without and the other with hydrocortisone acetate ('Actinac') in the treatment of acne vulgaris. 1980. Current Medical Research and Opinion	No relevant comparison - Actinac with/without chloramphenicol
Guin, J. D.Topical clindamycin: A double-blind study comparing clindamycin phosphate with clindamycin hydrochloride. 1979. International Journal of Dermatology	No relevant study population - insufficient information to determine acne severity
Guin, J. D.Treatment of acne vulgaris with topical clindamycin phosphate: a double-blind study. 1981. International Journal of Dermatology	No relevant study population - insufficient information to determine acne severity
Gunning, D. B. B., A. B.,Lloyd, R. A.,Olson, J. A.Retinoyl beta-glucuronide: A nontoxic retinoid for the topical treatment of acne. 1994. Journal of Dermatological Treatment	No relevant intervention - retinoyl beta-glucuronide
Gupta, A. K. G., M. D.,Abramovits, W.Ziana (clindamycin phosphate 1.2% and tretinoin 0.025%)gel. 2007. SKINmed	No relevant study design - not RCT
Gwiezdzinski, Z. U., S.,Szelemej, R.2.5% Solution of flutamide (a nonsteroidal antiandrogen) in the topical treatment of acne vulgaris. A double-blind randomized study. 1997. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Habbema, L. K., B.,Menke, H. E.,Doornweerd, S.,De Boulle, K.A 4% erythromycin and zinc combination (Zineryt) versus 2% erythromycin (Eryderm) in acne vulgaris: A randomized, double-blind comparative study. 1989a. British Journal of Dermatology	No relevant data reported - study does not report number of participants randomised or who completed in each group
Habbema, L. K., B.,Menke, H. E.,Doornweerd, S.,De, B. K.A 4% erythromycin and zinc combination (Zineryt (R)) versus 2% erythromycin (Eryderm (R)) in acne vulgaris: a randomized, double-blind comparative study. 1989b. British journal of dermatology	Duplicate record
Haedersdal, M. T.-B., K.,Wiegell, S. R.,Wulf, H. C.Long-pulsed dye laser versus long-pulsed dye laser-assisted photodynamic therapy for acne vulgaris: A randomized controlled trial. 2008. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Hajheydari, Z. S., M.,Morteza-Semnani, K.,Soltani, A.Effect of Aloe vera topical gel combined with tretinoin in treatment of mild and moderate acne vulgaris: A randomized, double-blind, prospective trial. 2014. Journal of Dermatological Treatment	No relevant intervention - aloe vera
Halbe, H. W. d. M., N. R.,Bahamondes, L.,Petracco, A.,Lemgruber, M.,de Andrade, R. P.,da Cunha, D. C.,Guazelli, C. A.,Baracat, E. C.Efficacy and acceptability of two monophasic oral contraceptives containing ethinylestradiol and either desogestrel or gestodene. 1998. The European journal of contraception & reproductive health care : the official journal of the European Society of Contraception	No relevant study population - participants did not have acne
Hammerstein, J. M., J.,Leo-Rossberg, I.,Moltz, L.,Zielske, F.Use of cyproterone acetate (CPA) in the treatment of acne, hirsutism and virilism. 1975. Journal of Steroid Biochemistry	No relevant study design - not RCT
Han, G., Armstrong, A. W., Desai, S. R., Guenin, E.Novel Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris in an Asian Population. 2019. Journal of drugs in dermatology : JDD	Not obtainable
Handojo, I.Retinoic acid cream (Airol cream) and benzoyl-peroxide in the treatment of acne vulgaris. 1979b. Southeast Asian Journal of Tropical Medicine & Public Health	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Handojo, I.The combined use of topical benzoyl peroxide and tretinoin in the treatment of acne vulgaris. 1979a. International Journal of Dermatology	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Harcup, J. W. C., J.The treatment of acne vulgaris in general practice. A double-blind assessment of co-trimoxazole and tetracycline. 1980. Practitioner	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Hare, P. J.Benzoyl peroxide gel compared with retinoic acid in acne vulgaris. 1975. British Journal of Clinical Practice	No relevant study design - not RCT
Harms, M. P., I.,Ceyrac, D.,Saurat, J. H.Isotretinoin ineffective topically. 1985. Lancet (london, england)	No relevant study design - not RCT
Harper, J. C. R., W. E.,Zeichner, J. A.,Guenin, E.,Bhatt, V.,Pillai, R.Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. 2019. Journal of Dermatological Treatment.	No relevant data reported - post hoc subgroup analyis by ethncity and sex of Tyring 2019
Harper, J. C., Baldwin, H., Stein Gold, L., Guenin, E.Efficacy and Tolerability of a Novel Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate or Severe Acne Vulgaris in Adult Females. 2019. Journal of drugs in dermatology : JDD	Not obtainable
Harper, J. C., Roberts, W. E., Zeichner, J. A., Guenin, E., Bhatt, V., Pillai, R.Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. 2020. Journal of Dermatological Treatment	No relevan data reported - reports post hoc analysis of Tyring 2018
Harper, J. C.Gender as a clinically relevant outcome variable in acne: benefits of a fixed combination clindamycin phosphate (1.2%) and	No relevant data reported - post hoc subgroup

Reference	Reason for exclusion
benzoyl peroxide (2.5%) aqueous gel. 2012. Journal of Drugs in Dermatology: JDD	analysis presenting data for male and female groups straitified by age
Harper, J. C.The efficacy and tolerability of a fixed combination clindamycin (1.2%) and benzoyl peroxide (3.75%) aqueous gel in patients with facial acne vulgaris: Gender as a clinically relevant outcome variable. 2015. Journal of Drugs in Dermatology	No relevant data reported - post hoc subgroup analysis by gender of Pariser 2014
Hashimoto, Y. S., Y.,Mizuno, Y.,Hasegawa, T.,Matsuba, S.,Ikeda, S.,Monma, T.,Ueda, S.Salicylic acid peels in polyethylene glycol vehicle for the treatment of comedogenic acne in Japanese patients. 2008. Dermatologic Surgery	No relevant study design - not RCT
Hatwal, A. B., R. P.,Agrawal, J. K.,Singh, G.,Bajpai, H. S.Spironolactone and cimetidine in treatment of acne. 1988. Acta Dermato-Venereologica	No relevant intervention - h2-receptor antagonist - cimetidine
Hayashi, N. K., E.,Nogita, T.,Fujiyama, M.,Kawashima, M.A randomized placebo-controlled investigator-blinded face split study of 20% azelaic acid cream to evaluate the efficacy and safety in Japanese patients with acne vulgaris. 2012. Journal of Dermatology	No relevant article type - conference abstract
Hayashi, N. K., I.,Siakpere, O.,Endo, A.,Hatanaka, T.,Yamada, M.,Kawashima, M.Clindamycin phosphate 1.2%/benzoyl peroxide 3% fixed-dose combination gel versus topical combination therapy of adapalene 0.1% gel and clindamycin phosphate 1.2% gel in the treatment of acne vulgaris in Japanese patients: A multicenter, randomized, investigator-blind, parallel-group study. 2018. Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Hayashi, N. K., M. Multicenter randomized controlled trial on combination therapy with 0.1% adapalene gel and oral antibiotics for acne vulgaris: Comparison of the efficacy of adapalene gel alone and in combination with oral faropenem. 2012. Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Hayashi, N. K., M. Study of the usefulness of moisturizers on adherence of acne patients treated with adapalene. 2014. Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Hayashi, N. K., M.Efficacy of oral antibiotics on acne vulgaris and their effects on quality of life: a multicenter randomized controlled trial using minocycline, roxithromycin and faropenem. 2011. Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Hebert, A., Thiboutot, D., Stein Gold, L., Cartwright, M., Gerloni, M., Fragasso, E., Mazzetti, A. Efficacy and Safety of Topical Clascoterone Cream, 1%, for Treatment in Patients with Facial Acne: Two Phase 3 Randomized Clinical Trials. 2020. JAMA Dermatology.	No relevant intervention - scoterone cream in the UK
Hellgren, L. V., J. Changes of skin surface lipids in acne vulgaris after treatment with trimethoprim-sulphamethoxazole. 1976. Dermatologische Monatsschrift	Not in English language
Hellgren, L. V., J.Topical erythromycin for acne vulgaris. 1980. Dermatologica	No relevant data reported - participants received intervention for between 4 and 8 weeks
Herndon, J. H., Jr.,Stephens, T. J.,Trookman, N. S.,Rizer, R. L.,Preston, N.,Caveney, S.,Gottschalk, R. W.A comparison of the tolerability of adapalene 0.1% cream and adapalene 0.1% lotion in healthy individuals. 2012. SKINmed	No relevant study population - participants did not have acne

Reference	Reason for exclusion
Hersle, K. G., H.Minocycline in acne vulgaris: a double blind study. 1976. Current Therapeutic Research - Clinical and Experimental	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Heymann, W. R.Hyperandrogenism and the skin. 2004. Journal of the American Academy of Dermatology	No relevant study design - not RCT
Hjorth, N. G., K.Azelaic acid for the treatment of acne. A clinical comparison with oral tetracycline. 1989. Acta Dermato-Venereologica. Supplementum	No relevant data - insufficient data reported
Hjorth, N. S., D.,Dela, K.Topical anhydrous aluminum chloride formulation in the treatment of acne vulgaris: A double-blind study. 1985. Cutis	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Hjorth, N. S., H.,Thomsen, K.,Dela, K.Meclosorb(), a new topical antibiotic agent in the treatment of acne vulgaris: A double-blind clinical study. 1984. Acta Dermato-Venereologica	No relevant study population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Ho, S. G. Y., C. K.,Chan, N. P.,Shek, S. Y.,Kono, T.,Chan, H. H.A retrospective analysis of the management of acne post-inflammatory hyperpigmentation using topical treatment, laser treatment, or combination topical and laser treatments in oriental patients. 2011. Lasers in Surgery & Medicine	Duplicate record
Hong, S. B. L., M. H.Topical aminolevulinic acid-photodynamic therapy for the treatment of acne vulgaris. 2005. Photodermatology, Photoimmunology & Photomedicine	No relevant study design - not RCT
Hongcharu, W. T., C. R.,Chang, Y.,Aghassi, D.,Suthamjariya, K.,Anderson, R. R.Topical ALA-photodynamic therapy for the treatment of acne vulgaris. 2000. Journal of Investigative Dermatology	Efficacy outcomes reported in figures only
Honorato, J. A., J. R.,Sandoval, C. A.,Quintanilla, E.Double-blind, randomized and controlled clinical trial on the efficacy of topical clindamycin in the treatment of acne. 1988. Revista de farmacologia clinica y experimental	Not in English language
Horfelt, C. S., B.,Larko, O.,Faergemann, J.,Wennberg, A. M.Photodynamic therapy for acne vulgaris: a pilot study of the dose-response and mechanism of action. 2007. Acta Dermato-Venereologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Hubbell, C. G. H., E. R.,Rist, T.,White Jr, J. W.Efficacy of minocycline compared with tetracycline in treatment of acne vulgaris. 1982. Archives of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Hughes, B. R.A double blind evaluation of topical isotretinoin, benzoyl peroxide and placebo in patients with acne. Abstract. 1989. British journal of dermatology	No relevant article type - conference abstract
Hurwitz, S.The combined effect of vitamin A acid and benzoyl peroxide in the treatment of acne. 1976. Cutis	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ianosi, S. N., D.,Branisteanu, D. E.,Popescu, M.,Calina, D.,Zlatian, O.,Docea, A. O.,Marinas, M. C.,Iordache, A. M.,MitruÈ›, P.,et al.,Comparative efficacy of oral contraceptive versus local treatment versus intense pulsed light combined with vacuum in endocrine acne in women. 2018. Journal of biological regulators and homeostatic agents	No relevant outcomes reported
Ibbotson, S. H.Topical 5-aminolaevulinic acid photodynamic therapy for the treatment of skin conditions other than non-melanoma skin cancer. 2002. British Journal of Dermatology	Duplicate record
Iglesias, L.Everyday doxycycline (oral) for 16 weeks vs everyday doxycycline (oral) for the first 4 weeks and on alternate days for the next 12 weeks in the treatment of acne vulgaris. (Spanish). 1992. Actas dermo-sifiliograficas	Not in English language
Ikeno, H. O., K.Open study comparing sodium L-ascorbyl-2-phosphate 5% lotion versus adapalene 0.1% gel for acne vulgaris. 2007. Cosmetic Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ilknur, T. D., M.,Bicak, M. U.,Ozkan, S.Glycolic acid peels versus amino fruit acid peels for acne. 2010. Journal of Cosmetic and Laser Therapy	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
In Jae, J. D. J., H.,Dong Hyun, K.,Yoon, M. S.,Lee, H. J.Comparative study of buffered 50% glycolic acid (pH 3.0) + 0.5% salicylic acid solution vs Jessner's solution in patients with acne vulgaris. 2018. Journal of cosmetic dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Inman, P. G., B.,McNay, R. A.Acne and the pill. 1971. Newcjiedj	Not obtainable
Iraji, F. M., A.,Naji, S. M.,Siadat, A. H.The efficacy of topical cyproterone acetate alcohol lotion versus placebo in the treatment of the mild to moderate acne vulgaris: A double blind study. 2006. Dermatology Online Journal	No relevant intervention - topical cyproterone acetate alcohol lotion
Ito, K. M., S.,Hamada, M.,Tokunaga, T.,Kokuba, H.,Tashiro, K.,Yano, I.,Yasumoto, S.,Imafuku, S.Efficacy and Safety of the Traditional	No relevant study population - sample

Reference	Reason for exclusion
Japanese Medicine Keigairengyoto in the Treatment of Acne Vulgaris. 2018b. Dermatology Research and Practice	includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Ito,Efficacy and Safety of the Traditional Japanese Medicine Keigairengyoto in the Treatment of Acne Vulgaris. 2018a. NA	Duplicate record
Jaffary, F. F., G.,Saraeian, S.,Hosseini, S. M.Comparison the effectiveness of pyruvic acid 50% and salicylic acid 30% in the treatment of acne. 2016. Journal of research in medical sciences	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Jaffary, F. N., M. A.,Koupaiee, H. S.,Faghihi, G.,Hosseini, S. M.,Sokhanvari, F.,Ansari, N.,Sadeghian, G.Omeprazole versus doxycycline combination therapy with topical erythromycin the treatment of acne vulgaris: a randomized clinical trial. 2017. Tehran university medical journal	Not in English language
Jaffe, G. V. G., J. J.,Constad, D.Benzoyl peroxide in the treatment of acne vulgaris: a double-blind, multi-centre comparative study of 'Quinoderm' cream and 'Quinoderm' cream with hydrocortisone versus their base vehicle alone and a benzoyl peroxide only gel preparation. 1989. Current Medical Research and Opinion	No relevant study design - not RCT
Jang, M. S. D., K. S.,Kang, J. S.,Jeon, Y. S.,Suh, K. S.,Kim, S. T.A comparative split-face study of photodynamic therapy with indocyanine green and indole-3-acetic acid for the treatment of acne vulgaris. 2011. British Journal of Dermatology	No relevant study design - not RCT
Jarratt, M. T. B., T.Efficacy and safety of clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: A randomized, double-blind, vehicle-controlled study. 2012. Journal of Drugs in Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Jarratt, M. T. J., T. M.,Chang-Lin, J. E.,Tong, W.,Berk, D. R.,Lin, V.,Kaoukhov, A.Safety and pharmacokinetics of once-daily dapsone gel, 7.5% in patients with moderate acne vulgaris. 2016. Journal of Drugs in Dermatology	No relevant study population - sample includes mild to severe acne. Participants had 20 to 50 inflammatory lesions (papules and pustules)
Jarratt, M. W., C. P.,Alio Saenz, A. B.Tazarotene foam versus tazarotene gel: A randomized relative bioavailability study in acne vulgaris. 2013. Clinical Drug Investigation	No relevant data reported - bioavailability study
Jawade, S. A. S., V. A.,Kondalkar, A. R.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. 2016. Iranian Journal of Dermatology	No relevant study population - sample includes people mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Jelinek, J. J. Hydrocuorothiazide and the control of premenstrual exacerbation of acne. 1972. Arcilderii	No relevant study population -insuficient information to determine

Reference	Reason for exclusion
	severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Ji, S. Z. T., P.,Li, G. Q.,Liu, L. L.,Chen, X. X.,Zhu, X. J.A comparison of 10% benzoyl peroxide cream and 5% benzoyl peroxide gel in the treatment of acne vulgaris. 2000. The chinese journal of clinical pharmacology	Not in English language
Jih, M. H. F., P. M.,Goldberg, L. H.,Robles, M.,Glaich, A. S.,Kimyai-Asadi, A.The 1450-nm diode laser for facial inflammatory acne vulgaris: Dose-response and 12-month follow-up study. 2006. Journal of the American Academy of Dermatology	No relevant intervention - compares 2 fluences of 1450-nm laser
Jin, X. Y. D., W.,Hu, X.,Wang, J.,Zou, D. J.Changes of sex hormone levels in male acne patients with normal serum testosterone and effect of antiandrogen therapy. 2009. Academic journal of second military medical university	Not in English language
Johnson, K. H.Are oral contraceptives (OCPs) with antiandrogenic progestins preferred over other OCPs in patients with acne?. 2002. Journal of Family Practice	No relevant study design - not RCT
Jones, D. H. K., K.,Miller, A. J.,Cunliffe, W. J.A dose-response study of 13-cis-retinoic acid in acne vulgaris. 1983. British Journal of Dermatology	Not possible to extract relevant data
Jones, T. M. J., S.,Alio Saenz, A. B.Bioavailability of clindamycin from a new clindamycin phosphate 1.2%-benzoyl peroxide 3% combination gel. 2013. Clinical Pharmacology in Drug Development	No relevant data reported - pharmokinetic study
Jorizzo, J. G., R.,Nighland, M.Tretinoin microsphere gel in younger acne patients. 2008. Journal of drugs in dermatology : JDD	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Juhlin, L. M., G.,Ohman, S.Topical triamcinolone acetonide and chlorhydroxyquinoline in acne. 1968. Acta Derm	No relevant study population - insufficient information to determine acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Jung, J. Y. H., J. S.,Ahn, C. H.,Yoon, J. Y.,Kwon, H. H.,Suh, D. H.Prospective randomized controlled clinical and histopathological study of acne vulgaris treated with dual mode of quasi-long pulse and Q-switched 1064-nm Nd:YAG laser assisted with a topically applied carbon suspension. 2012. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Jung, J. Y. K., H. H.,Yeom, K. B.,Yoon, M. Y.,Suh, D. H.Clinical and histological evaluation of 1% nadifloxacin cream in the treatment of acne vulgaris in Korean patients. 2011. International Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Jung, J. Y. L., J. H.,Ryu, D. J.,Lee, S. J.,Bang, D.,Cho, S. B.Lower-fluence, higher-density versus higher-fluence, lower-density treatment with a 10,600-nm carbon dioxide fractional laser system: A split-face, evaluator-blinded study. 2010a. Dermatologic Surgery	Duplicate record

Reference	Reason for exclusion
Jung, J. Y. Y., M. Y.,Hong, J. S.,Suh, D. H.Treatment of acne vulgaris with a low fluence 1064-nm Nd: YAG laser after applying carbon suspension. 2010b. Journal of Dermatology. Conference: 1st Eastern Asia Dermatology Congress, EADC2010. Fukuoka Japan. Conference Publication:	No relevant article type - conference abstract
Jurairattanaporn, N. C., T.,Ophaswongse, S.,Udompataikul, M.Comparative trial of silver nanoparticle gel and 1% clindamycin gel when use in combination with 2.5% benzoyl peroxide in patients with moderate acne vulgaris. 2017. Journal of the Medical Association of Thailand	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Jurzyk, R. S. S., R. L.,Rose, L. I.Antiandrogens in the treatment of acne and hirsutism. 1992. American Family Physician	No relevant studyd design - not RCT
Kabir, M. S., S.,Raza, A.,Kanwal, S.,Tanvir, T.Comparison of efficacy of adapalene (0.1% gel) monotherapy ve adapalene (0.1%) plus benzyl peroxide (2.5%) combination therapy for treatment of mild to moderate acne vulgaris. 2018. Pakistan Journal of Medical and Health Sciences	No relevant data reported
Kainz, J. T. B., G.,Auer-Grumbach, P.,Lackner, V.,Perl-Convalexius, S.,Popa, R.,Wolfesberger, B.Azelaic acid 20 % cream: effects on quality of life and disease severity in adult female acne patients. 2016. Journal der Deutschen Dermatologischen Gesellschaft	Duplicate record
Kakita, L. Tazarotene versus tretinoin or adapalene in the treatment of acne vulgaris. 2000. Journal of the American Academy of Dermatology	No relevant article type - commentary article
Kaminaka, C. U., M.,Matsunaka, H.,Furukawa, F.,Yamomoto, Y.Clinical evaluation of glycolic acid chemical peeling in patients with acne vulgaris: a randomized, double-blind, placebo-controlled, split-face comparative study. 2014. Dermatologic surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kang, A. L., A.,Herrmann, J.,Moy, R.Treatment of moderate-to-severe facial acne vulgaris with solid-state fractional 589/1,319-nm laser. 2019. Journal of Clinical and Aesthetic Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kantikosum, K. C., Y.,Chottawornsak, N.,Asawanonda, P.The efficacy of glycolic acid, salicylic acid, gluconolactone, and licochalcone a combined with 0.1% adapalene vs adapalene monotherapy in mild-to-moderate acne vulgaris: A double-blinded within-person comparative study. 2019. Clinical, Cosmetic and Investigational Dermatology	No relevant study design - not RCT
Kantner, V. S., E. Topical effects of oxytetracycline in acne vulgaris. 1970. Ceskoslovenska dermatologie	Not in English language

Reference	Reason for exclusion
Kar, B. R. T., S.,Panda, M.Comparative study of oral isotretinoin versus oral isotretinoin + 20% salicylic Acid peel in the treatment of active acne. 2013. Journal of Cutaneous & Aestheic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Karoglan, A., Paetzold, B., Pereira de Lima, J., Bruggemann, H., Tuting, T., Schanze, D., Guell, M., Gollnick, H. Safety and Efficacy of Topically Applied Selected Cutibacterium acnes Strains over Five Weeks in Patients with Acne Vulgaris: An Open-label, Pilot Study. 2019. Acta Dermato-Venereologica	No relevant study desgin - the first phase was not randomised and the interventions are not relevant in the second phase
Karsai, S. S., L.,Raulin, C.The pulsed-dye laser as an adjuvant treatment modality in acne vulgaris: A randomized controlled single-blinded trial. 2010. British Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Katsambas, A. T., A. A.,Stratigos, J.Topical clindamycin phosphate compared with oral tetracycline in the treatment of acne vulgaris. 1987. British Journal of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Katz, H. I. K., S.,Akin, M. D.,Dunlap, F.,Whiting, D.,Norbart, T. C.Effect of a desogestrel-containing oral contraceptive on the skin. 2000. European Journal of Contraception & Reproductive Health Care	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. H., H.,Alio Saenz, A. B.,Ono, M.,Yamada, M.Clindamycin phosphate 1.2%-benzoyl peroxide 3.0% fixed-dose combination gel has an effective and acceptable safety and tolerability profile for the treatment of acne vulgaris in Japanese patients: A phase III, multicentre, randomised, single-blinded, active-controlled, parallel-group study. 2015. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. H., H.,Alio Saenz, A. B.,Ono, M.,Yamada, M.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. 2014. Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. H., S.,Czernielewski, J.,Miyachi, Y.Adapalene gel 0.1% - Topical retinoid-like molecule - For the treatment of Japanese	No relevant population - sample includes people

Reference	Reason for exclusion
patients with acne vulgaris: A multicenter, randomized, investigator-blinded, dose-ranging study. 2007. Skin Research	with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. H., S.,Loesche, C.,Miyachi, Y.Adapalene gel 0.1% is effective and safe for Japanese patients with acne vulgaris: A randomized, multicenter, investigator-blinded, controlled study. 2008. Journal of Dermatological Science	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. N., T.,Katsuramaki, T.Open-label, randomized, multicenter, phase III study to evaluate the safety and efficacy of benzoyl peroxide gel in long-term use in patients with acne vulgaris: A secondary publication. 2017a. Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. S., S.,Furukawa, F.,Matsunaga, K.,Akamatsu, H.,Igarashi, A.,Tsunemi, Y.,Hayashi, N.,Yamamoto, Y.,Nagare, T.,et al.,Twelve-week, multicenter, placebo-controlled, randomized, double-blind, parallel-group, comparative phase II/III study of benzoyl peroxide gel in patients with acne vulgaris: a secondary publication. 2017b. Journal of dermatology	No relevant study population - includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kawashima, M. Y., M.,Parish, C.Clindamycin 1%/benzoyl peroxide 3% gel, a new topical combination product, is effective in Japanese patients with acne vulgaris. 2013. Journal of Investigative Dermatology	No relevant article type - conference abstract
Kayhan, S. S., I.,Saracoglu, Z. N.,Aksu, A. E. K.,Tozun, M.Comparison of safety and efficacy of oral azithromycin-topical adapalene versus oral doxycycline-topical adapalene in the treatment of acne vulgaris and determination of the effects of these treatments on patients' quality of life. 2012. Turkderm deri hastaliklari ve frengi arsivi	Not in English language
Kaymak, Y. T., E.,Taner, Y.Comparison of depression, anxiety and life quality in acne vulgaris patients who were treated with either isotretinoin or topical agents. 2009. International Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kelidari, H. R. S., M.,Hajheydari, Z.,Akbari, J.,Morteza-Semnani, K.,Akhtari, J.,Valizadeh, H.,Asare-Addo, K.,Nokhodchi, A.Spironolactone loaded nanostructured lipid carrier gel for effective treatment of mild and moderate acne vulgaris: A randomized, double-blind, prospective trial. 2016. Colloids and Surfaces B: Biointerfaces	No relevant intervention - intervention & class not available in the UK
Kelly, S. D., E.,Fearns, S.,McKinnon, C.,Carter, R.,Gerlinger, C.,Smithers, A.Effects of oral contraceptives containing ethinylestradiol with either drospirenone or levonorgestrel on various parameters associated with well-being in healthy women: a randomized, single-blind, parallel-group, multicentre study. 2010. Clinical drug investigation	No relevant study population - participants did not have acne
Kerscher, M. R., T.,Bayrhammer, J.,Schramm, G.Effects of an oral contraceptive containing chlormadinone and ethinylestradiol on acne-prone skin of women of different age groups: an open-label, single-centre, phase IV study. 2008. Clinical Drug Investigation	No relevant study deisgn - not RCT

Reference	Reason for exclusion
Kessler, E. F., K.,Chia, C.,Rogers, C.,Anna Glaser, D.Comparison of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne vulgaris. 2008. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Khaki, I., Valiani, M., Mohammadbeigi, A.Evaluation the effect of auriculotherapy on the clinical signs of single girls with polycystic ovary syndrome: A single-blinded clinical trial. 2019. Clinical Cancer Investigation Journal	No relevant intervention - acupuncture
Khan, M. K., N. U.,Anwar, M. I.,Noor, S. M.A comparison of the efficacy of topical adapalene gel 0.1% with tretinoin gel 0.025% in mild acne vulgaris. 2017. Journal of Pakistan Association of Dermatologists	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kharfi, M. T., N. B.,Zeglaoui, F.,Ezzine, N.,Mokhtar, I.,Kamoun, F.,Kamoun, M. R.Evaluate the efficacy and safety of topical glycolic acid (Glyco A 12%) and retinoin acid (Kefrane 0'05%) on facial acne lesions. 2001a. Tunisie medicale	Not in English language
Kharfi, M. T., N.,Zeglaoui, F.,Ezzine, N.,Mokhtar, I.,Kamoun, F.,Kamoun, M. R.Comparative study of the efficacy and tolerance of 12% glycolic acid cream and 0.05% retinoic acid cream for polymorphic acne. 2001b. Tunisie medicale	Not in English language
Khodaeiani, E. F., R. F.,Amirnia, M.,Saeidi, M.,Karimi, E. R.Topical 4% nicotinamide vs. 1% clindamycin in moderate inflammatory acne vulgaris. 2013. International Journal of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Khodaeinai, E. B., S.,Amirnia, M.,Shokry, J.,Karimi, L. R.,Fouladi, D. F.,Sedaghat, K.Efficacy of 10% azelaic acid gel with hydro-alcoholic or alcohol-free bases in mild to moderate acne vulgaris; the first clinical trial. 2014. Journal of Medical Sciences (Faisalabad)	Outcomes reported in figures only
Kim, B. J. L., H. G.,Woo, S. M.,Youn, J. I.,Suh, D. H.Pilot study on photodynamic therapy for acne using indocyanine green and diode laser. 2009. Journal of Dermatology	Data reported in figures only
Kim, B. K., H.,Kim, J. E.,Lee, S. H.Retinyl retinoate, a retinoid derivative improves acne vulgaris in double-blind, vehicle-controlled clinical Study. 2013. Tissue engineering and regenerative medicine	No relevant study design - not RCT
Kim, S. J. B., J. H.,Koh, J. S.,Bae, M. I.,Lee, S. J.,Shin, M. K.The effect of physically applied alpha hydroxyl acids on the skin pore and comedone. 2015. International journal of cosmetic science	No relevant study population - sample includes people with acne-prone skin, no further details reported and study is not relevant for PCOS,

Reference	Reason for exclusion
	maintenance or refractory treatments
Kim, S. W. M., S. E.,Kim, J. A.,Eun, H. C.Glycolic acid versus Jessner's solution: which is better for facial acne patients? A randomized prospective clinical trial of split-face model therapy. 1999. Dermatologic surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kim, W. J. P., J. M.,Ko, H. C.,Kim, B. S.,Kim, M. B.,Song, M.A split-faced, observer-blinded comparison study of topical adapalene/benzoyl peroxide and adapalene in the treatment of Asian acne patients. 2013. Journal of Drugs in Dermatology: JDD	No relevant article type - letter to editor
King, K. J., D. H.,Daltrey, D. C.,Cunliffe, W. J.A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate and microbial population. 1982. British Journal of Dermatology	No relevant data reported - sebum excretion study
Kircik, L. H. B., V.,Martin, G.,Pillai, R.Randomized, double-blind, split-face study to compare the irritation potential of two topical acne formulations over a 21-day treatment period. 2016. Journal of Drugs in Dermatology	No relevant study population - participants did not have acne
Kircik, L. H.Comparative efficacy and safety results of two topical combination acne regimens. 2009b. Journal of Drugs in Dermatology	No relevant data reported - study recruited participants for 4 (n=23) or 12 wk (n=42) trial of BPO/CLIND gel vs solubilized BPO gel but reports data for all participants
Kircik, L. H.Fixed Combination of Clindamycin Phosphate 1.2% and Benzoyl Peroxide 3.75% Aqueous Gel: Long-Term Use in Adult Females With Moderate Acne Vulgaris. 2017. Journal of Drugs in Dermatology: JDD	No relevant study design - not RCT
Kircik, L. H.Tretinoin microsphere gel pump 0.04% versus tazarotene cream 0.05% in the treatment of mild-to-moderate facial acne vulgaris. 2009. Journal of Drugs in Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kligman, A. M. F., J. E., Jr.,Plewig, G.Topical vitamin A acid in acne vulgaris. 1969. Archives of Dermatology	No relevant study design - not RCT
Kligman, A. M. P., G.,Mills, O. H., Jr.Topically applied tretinoin for senile (solar) comedones. 1971. Archives of Dermatology	No relevant study design - not RCT
Kligman, A. M.Comparison of a topical benzoyl peroxide gel, oral minocycline, oral doxycycline and a combination for suppression of P. acnes in acne patients. 1998. Journal of dermatological treatment	No relevant outcmoes reported - bacterial counts
Knutson, D. D. S., L. J.,Smoot, W. H.Meclocycline sulfosalicylate. Topical antibiotic agent for the treatment of acne vulgaris. 1981. Cutis	No relevant article type - non-systematic review
Ko, H. C. S., M.,Seo, S. H.,Oh, C. K.,Kwon, K. S.,Kim, M. B.Prospective, open-label, comparative study of clindamycin 1%/benzoyl peroxide 5% gel with adapalene 0.1% gel in Asian acne	Reported outcomes relevant for the network meta-analysis but not in

Reference	Reason for exclusion
patients: Efficacy and tolerability. 2009. Journal of the European Academy of Dermatology and Venereology	enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kobayashi, M. N., T.,Fukamachi, K.,Nakamura, M.,Tokura, Y.Efficacy of combined topical treatment of acne vulgaris with adapalene and nadifloxacin: A randomized study. 2011. Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Koltun, W. L., A. W.,Thiboutot, D.,Niknian, M.,Sampson-Landers, C.,Korner, P.,Marr, J.Efficacy and safety of 3 mg drospirenone/20 mcg ethinylestradiol oral contraceptive administered in 24/4 regimen in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled trial. 2008. Contraception	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Koltun, W. M., J. M.,Marr, J.,Kunz, M.Treatment of moderate acne vulgaris using a combined oral contraceptive containing ethinylestradiol 20 mug plus drospirenone 3 mg administered in a 24/4 regimen: A pooled analysis. 2011. European Journal of Obstetrics and Gynecology and Reproductive Biology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kotrajaras, R.Comparative study in the treatment of acne vulgaris with cyproterone acetate, tetracycline and vitamin A acid. 1982. Journal of the Medical Association of Thailand	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Krausz, A. F., A. J.Cutaneous hyperandrogenism: role of antiandrogen therapy in acne, hirsutism, and androgenetic alopecia. 2013. Journal of Drugs in Dermatology: JDD	No relevant article type - non-systematic review
Kriplani, A. T., J.,Agrawal, N.,Kulshrestha, V.,Ammini, A. C.,Kumar, G.A comparative study of Diane-35 plus spironolactone and Diane-35 plus finasteride in cases of hirsutism and acne. 2009. International journal of endocrinology and metabolism	No relevant study population - only 38% of participants have acne
Krishnan, G.Comparison of two concentrations of tretinoin solution in the topical treatment of acne vulgaris. 1976. Practitioner	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Kubeyinje, E. P.Topical tretinoin compared with topical clindamycin phosphate in the treatment of acne and acne-associated hyperpigmentation in Arabs. 1997. Journal of dermatological treatment	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Kubota, Y. M., A.,Shirahige, Y.,Nakai, K.,Katsuura, J.,Moriue, T.,Murakami, Y.,Matsunaka, H.,Yoneda, K.Effect of sequential application of topical adapalene and clindamycin phosphate in the treatment of Japanese patients with acne vulgaris. 2012. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kuflik, E. G.Benzoyl peroxide gel in acne therapy. 1976. Cutis	No relevant study design - not RCT
Kurokawa, I. A., H.,Nishijima, S.,Asada, Y.,Kawabata, S.Clinical and bacteriologic evaluation of OPC-7251 in patients with acne: A double-blind group comparison study versus cream base. 1991. Journal of the American Academy of Dermatology	Duplicate record
Kus, S. Y., D.,Aytug, A.Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris. 2005. Clinical and Experimental Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kwon, H. H. C., S. C.,Jung, J. Y.,Bae, Y. I.,Park, G. H.Comparison of novel dual mode vs conventional single pass of a 1450-nm diode laser in the treatment of acne vulgaris for Korean patients: A 20-week prospective, randomized, split-face study. 2018. Journal of Cosmetic Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kwon, H. H. L., J. B.,Yoon, J. Y.,Park, S. Y.,Ryu, H. H.,Park, B. M.,Kim, Y. J.,Suh, D. H.The clinical and histological effect of home-use, combination blue-red LED phototherapy for mild-to-moderate acne vulgaris in Korean patients: A double-blind, randomized controlled trial. 2013. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kwon, H. H. M., K. R.,Park, S. Y.,Yoon, J. Y.,Suh, D. H.,Lee, J. B.Daylight photodynamic therapy with 1.5% 3-butenyl 5-aminolevulinate gel as a convenient, effective and safe therapy in acne treatment: A double-blind randomized controlled trial. 2016. Journal of Dermatology	No relevant study population - sample includes mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Kwon, H. H. P., H. Y.,Choi, S. C.,Bae, Y.,Jung, J. Y.,Park, G. H.Novel device-based acne treatments: comparison of a 1450-nm diode laser and microneedling radiofrequency on mild-to-moderate acne vulgaris and seborrhoea in Korean patients through a 20-week prospective, randomized, split-face study. 2018. Journal of the European Academy of Dermatology and Venereology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Kwon, H. H. P., S. Y.,Yoon, J. Y.,Min, S.,Suh, D. H.Do tutorials on application method enhance adapalene-benzoyl peroxide combination gel tolerability in the treatment of acne?. 2015. Journal of Dermatology	No relevant comparator - compares efficacy of adding training module to intervention

Reference	Reason for exclusion
Kwon, I. K., S.,Lee, D.Photodynamic therapy using chlorophyll-a in the treatment of acne vulgaris: A randomized, single-blind, split-face study. 2014. Journal of Investigative Dermatology	No relevant article type - conference abstract
Kwon,Comparison of clinical and histological effects between lactobacillus-fermented Chamaecyparis obtusa and tea tree oil for the treatment of acne: an eight-week double-blind randomized controlled split-face study. 2014. NA	No relevant intervention and comparison - Lactobacillus-fermented Chamaecyparis obtusa vs tea tree oil
L. Ghoshal, S. Banerjee, S. Ghosh, D. Gangopadhyay and S. JanaComparative evaluation of effectiveness of adapalene and azithromycin, alone or in combination, in acne vulgaris. 2007. Indian Journal of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Lachnit-Fixson, U. K., J.Therapy of androgenization symptoms: double blind study of an antiandrogen preparation (SH B 209 AB) against neogynon (author's transl). 1977. Medizinische klinik	Not in English language
Lain, E., Day, D., Harper, J., Guenin, E.Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Impact of Gender and Race on Efficacy and Safety. 2019. Journal of drugs in dermatology : JDD	Not obtainable
Langner, A. B., G. C.,Stapor, V.,Wolska, H.,Fraczykowska, M.Isotretinoin cream 0.05% and 0.1% in the treatment of acne vulgaris. 1994. Journal of Dermatological Treatment	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Laquieze, S. C., J.,Rueda, M. J.Beneficial effect of a moisturizing cream as adjunctive treatment to oral isotretinoin or topical tretinoin in the management of acne. 2006. Journal of drugs in dermatology : JDD	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Lassus, A.Local treatment of acne. A clinical study and evaluation of the effect of different concentrations of benzoyl peroxide gel. 1981. Current Medical Research & Opinion	Not an RCT
Lee SH, Huh CH, Park KC, Youn SW.Effects of repetitive superficial chemical peels on facial sebum secretion in acne patients.. 2006. J Eur Acad Dermatol Venereol	No relevant outcomes repoted - sebum levels only
Lee, E. J. L., H. K.,Shin, M. K.,Suh, D. H.,Lee, S. J.,Kim, N. I.An open-label, split-face trial evaluating efficacy and safty of photopneumatic therapy for the treatment of acne. 2012. Annals of Dermatology	No relevant study design - not RCT
Lee, H. E. K., J. Y.,Kim, Y. H.,Yoo, S. R.,Moon, S. H.,Kim, N. I.,Park, C.,Kim, J. H.,Koh, H. J.,Park, W. S.,Ro, Y. S.A double-blind randomized controlled comparison of apddr-0901, a novel cosmeceutical formulation, and 0.1% adapalene gel in the treatment of mild-to-moderate acne vulgaris. 2011a. European Journal of Dermatology	No relevant intervention - intervention & class not available in the UK
Lee, H. J., Kim, J. Y., Park, K. D., Lee, W. J.Randomized controlled double-blind study of a cleanser composed of 5-aminolevulinic acid	No relevant intervention - cleanser

Reference	Reason for exclusion
and peptides on mild and moderate acne vulgaris. 2019a. Journal of Cosmetic Dermatology.	
Lee, J. W. Y., K. H.,Park, K. Y.,Han, T. Y.,Li, K.,Seo, S. J.,Hong, C. K.Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: A randomized, controlled comparative study. 2011b. British Journal of Dermatology	No relevant study population - insufficient details to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Lee, S. Y. C.The efficacy of full-spectrum light generated by electrical discharge between two carbon arc rods for the treatment of acne compared to 1% topical clindamycin. 2010. Lasers in Surgery and Medicine	No relevant article type - conference abstract
Lee, S. Y., Park, A. Y., Shin, J. Y., Lee, H. J., Kim, J. E., Lee, S. H., Lee, J. S.Comparison of the efficacy of azithromycin versus doxycycline in acne vulgaris. 2019b. Journal of the American Academy of Dermatology	No relevant artcile type - conference abstract
Lee, W. J. J., H. J.,Kim, J. Y.,Lee, S. J.,Kim, D. W.Effect of photodynamic therapy on inflammatory acne using 3% liposomal 5-aminolevulinic acid emulsion and intense-pulsed light: A pilot study. 2012. Journal of Dermatology	No relevant article type - letter to editor
Lekakh, O. M., A. M.,Novice, K.,Kamalpour, J.,Sadeghian, A.,Mondo, D.,Kalnicky, C.,Guo, R.,Peterson, A.,Tung, R.Treatment of Acne Vulgaris With Salicylic Acid Chemical Peel and Pulsed Dye Laser: A Split Face, Rater-Blinded, Randomized Controlled Trial. 2015. Journal of Lasers in Medical Sciences	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Lekwuttikarn, R. T., T.,Chatproedprai, S.,Wananukul, S.Randomized, controlled trial split-faced study of 595-nm pulsed dye laser in the treatment of acne vulgaris and acne erythema in adolescents and early adulthood. 2017. International Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Lemay, A. A., D. F.,Roberts, J. L.,Harrison, D. D.The efficacy of an oral contraceptive containing 20ug ethinyl estradiol and 100ug levonorgestrel for the treatment of moderate acne. 2000. Gynecological endocrinology	No relevant article type - conference abstract
Lesher, J. L., Jr.,Chalker, D. K.,Smith, J. G., Jr.,Guenther, L. C.,Ellis, C. N.,Voorhees, J. J.,Shalita, A. R.,Klauda, H. C.An evaluation of a 2% erythromycin ointment in the topical therapy of acne vulgaris. 1985. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Lester, R. S. S., G. D.,Light, M. J.Isotretinoin and tetracycline in the management of severe nodulocystic acne. 1985. International Journal of Dermatology	Dosage of tetracycline lower than BNF value

Reference	Reason for exclusion
Leu, F. S., U.,Fournet, M.,Truffat, C.Random sample study of the effect of two concentrations of retinoic acid on acne vulgaris. 1974. Medecine ET hygiene	Not in English language
Levesque, A. H., I.,Seite, S.,Rougier, A.,Bissonnette, R.Randomized trial comparing a chemical peel containing a lipophilic hydroxy acid derivative of salicylic acid with a salicylic acid peel in subjects with comedonal acne. 2011. Journal of cosmetic dermatology	No relevant intervention - lipohydroxy acid
Lew-Kaya, D. A. R., L. L.,Sefton, J.,Stern, K.Once-daily erythromycin 2% gel in the treatment of acne vulgaris: Two double-blind comparisons with tretinoin 0.01% gel. 1992. Advances in Therapy	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Leyden, J. G., G. L.Randomized facial tolerability studies comparing gel formulations of retinoids used to treat acne vulgaris. 2001. Cutis; cutaneous medicine for the practitioner	No relevant study population - participants did not have acne
Leyden, J. J. B., R. S.,Dunlap, F. E.,Ellis, C. N.,Connolly, M. A.,Levy, S. F.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. 2001. American Journal of Clinical Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Leyden, J. J. G., E. H.Evaluation of the antimicrobial effects in vivo of Triaz Gel (benzoyl peroxide special gel), Cleocin-T Lotion (clindamycin phosphate lotion), and Azelex Cream (azelaic acid cream) in humans. 1997. Journal of Dermatological Treatment	No relevant outcomes reported - bacterial counts
Leyden, J. J. G., R.,Nighland, M.Cumulative irritation potential of topical retinoid formulations. 2008. Journal of drugs in dermatology : JDD	No relevant study population - participants did not have acne
Leyden, J. J. H., J. G.,Jarratt, M. T.,Stewart, D. M.,Levy, S. F.The efficacy and safety of a combination benzoyl peroxide/clindamycin topical gel compared with benzoyl peroxide alone and a benzoyl peroxide/erythromycin combination product. 2001. Journal of Cutaneous Medicine and Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Leyden, J. J. K., L.,Yaroshinsky, A.Two randomized, double-blind, controlled trials of 2219 subjects to compare the combination clindamycin/tretinoin hydrogel with each agent alone and vehicle for the treatment of acne vulgaris. 2006. Journal of the American Academy of Dermatology	No relevant data reported - study reports combined results of 2 RCTs
Leyden, J. J. N., M.,Rossi, A. B.,Ramaswamy, R.Irritation potential of tretinoin gel microsphere pump versus adapalene plus benzoyl peroxide gel. 2010. Journal of Drugs in Dermatology	No relevant study population - participants did not have acne
Leyden, J. J. T., E. A.,Miller, B.,Ung, M.,Berson, D.,Lee, J.Once-daily tazarotene 0.1 % gel versus once-daily tretinoin 0.1 % microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. 2002. Cutis; cutaneous medicine for the practitioner	Not obtainable
Leyden, J. J. W., M.A novel gel formulation of clindamycin phosphate-tretinoin is not associated with acne flaring. 2008. Cutis	No relevant outcomes reported - reports 2-wk treatment-related flaring

Reference	Reason for exclusion
	outcomes of 12-week RCT reported in Schlessinger 2007
Leyden, J. J.Topical treatment for the inflamed lesion in acne, rosacea, and pseudofolliculitis barbae. 2004. Cutis	No relevant article type - introduction to supplement
Leyden, J. W., M.,Baldwin, E. K.Tolerability of clindamycin/tretinoin gel vs. tretinoin microsphere gel and adapalene gel. 2009. Journal of Drugs in Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Leyden, J., Levy, S.The development of antibiotic resistance in Propionibacterium acnes. 2001. Cutis	Not reported how many people were randomised in each arm; no tables available; also the outcome is bacteria counts which is not relevant
Li,Effects of Qingfei Liangxue Fa on sebum excretion rate and free fatty acid of patients with acne vulgaris. 2004. NA	No relevant intervention - complementary therapy
Liani, L. P., J. S.Evaluation of topical erythromycin and topical lactate with or without systemic ketoconazole in acne vulgaris. 1992. Indian journal of dermatology, venereology and leprology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Liddell, K.Benzoyl peroxide gel in the treatment of acne vulgaris. 1974. British Journal of Clinical Practice	Not obtainable
Lihong, S.He-Ne laser auricular irradiation plus body acupuncture for treatment of acne vulgaris in 36 cases. 2006. Journal of Traditional Chinese Medicine	No relevant intervention - laser plus acupuncture
Lim, C. C. P., D. G. C.,Adamson, J.A sustained release tetracycline preparation in acne vulgaris. 1974. Practitioner	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Lim, S. K. H., J. M.,Lee, Y. H.,Lee, Y.,Seo, Y. J.,Kim, C. D.,Lee, J. H.,Im, M.Comparison of Vitamin D Levels in Patients with and without Acne: a Case-Control Study Combined with a Randomized Controlled Trial. 2016. PloS one	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Lin, Z. R. Z., W.,You, S. F.,Xiao, Y.Clinical observation on pricking blood and acupoint injection in treating acne. 2016. Western journal of traditional chinese medicine [xi bu zhong yi yao za zhi]	Not in English language
Liu, H., Yu, H., Xia, J., Liu, L., Liu, G. J., Sang, H., Peinemann, F.Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc and fruit acid (alphaÃ¢Â€Â□hydroxy acid) for acne. 2020. Cochrane Database of Systematic Reviews	Systematic review - references were checked for relevance
Liu, L. H. F., X.,An, Y. X.,Zhang, J.,Wang, C. M.,Yang, R. Y.Randomized trial of three phototherapy methods for the treatment of	No relevant outcome data reported - interventions provided until >90%

Reference	Reason for exclusion
acne vulgaris in chinese patients. 2014. Photodermatology Photoimmunology and Photomedicine	improvement observed in participants
Lookingbill, D. P. A., B. B.,Ellis, C. N.,Jegasothy, B. V.,Lucky, A. W.,Ortiz- Ferrer, L. C.,Savin, R. C.,Shupack, J. L.,Stiller, M. J.,Zone, J. J.,Landis, J. R.,Ramaswamy, R.,Cherill, R. J.,Pochi, P. E.Inocoterone and acne: The effect of a topical antiandrogen: Results of a multicenter clinical trial. 1992. Archives of Dermatology	No relevant intervention - never marketed
Lookingbill, D. P. C., D. K.,Lindholm, J. S.,Katz, H. I.,Kempers, S. E.,Huerter, C. J.,Swinehart, J. M.,Schelling, D. J.,Klauda, H. C.Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: Combined results of two double-blind investigations. 1997. Journal of the American Academy of Dermatology	No relevant intervention - never marketed
Lu, J. L., Z.Acupuncture combined with cupping and circling moxibustion for 40 cases of acne. 2018. World Journal of Acupuncture - Moxibustion	No relevant intervention - acupuncture-cupping
Lubtikulthum, P. K., N.,Udompataikul, M.A comparative study on the effectiveness of herbal extracts vs 2.5% benzoyl peroxide in the treatment of mild to moderate acne vulgaris. 2019. Journal of Cosmetic Dermatology.	No relevant intervention - topical herbal extract
Lucky, A. W. C., S. I.,Funicella, T.,Jarratt, M. T.,Jones, T.,Reddick, M. E.Double-blind, vehicle-controlled, multicenter comparison of two 0.025% tretinoin creams in patients with acne vulgaris. 1998a. Journal of the American Academy of Dermatology	Outcomes reported in figures only
Lucky, A. W. C., S. I.,Jarratt, M. T.,Quigley, J. W.Comparative efficacy and safety of two 0.025% tretinoin gels: Results from a multicenter, double-blind, parallel study. 1998b. Journal of the American Academy of Dermatology	Outcomes reported in figures only
Lucky, A. W. H., T. A.,Olson, W. H.,Robisch, D. M.,Lebwohl, M.,Swinyer, L. J.Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. 1997. Journal of the American Academy of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Lucky, A. W. K., W.,Thiboutot, D.,Niknian, M.,Sampson-Landers, C.,Korner, P.,Marr, J.A combined oral contraceptive containing 3-mg drospirenone/20-mug ethinyl estradiol in the treatment of acne vulgaris: A randomized, double-blind, placebo-controlled study evaluating lesion counts and participant self-assessment. 2008. Cutis	Outcomes reported in figures only
Lucky, A. W. M., J. M.,Roberts, J.,Taylor, S.,Jones, T.,Ling, M.,Garrett, S.Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long-term (1 year) treatment. 2007. Journal of drugs in dermatology : JDD	No relevant study design - not RCT
Lucky, A. W. S., J.Comparison of micronized tretinoin gel 0.05% and tretinoin gel microsphere 0.1% in young adolescents with acne: A post hoc analysis of efficacy and tolerability data. 2011. Cutis	Outcomes reported in figures only
Lueangarun, S. S., K.,Tempark, T.,Managit, C.,Sithisarn, P.Clinical efficacy of 0.5% topical mangosteen extract in nanoparticle loaded gel in treatment of mild-to-moderate acne vulgaris: A 12-week, split-face, double-blinded, randomized, controlled trial. 2019. Journal of Cosmetic Dermatology.	Non relevant intervention – alpha-mangostin
Lyons, R. E.Comparative effectiveness of benzoyl peroxide and tretinoin in acne vulgaris. 1978. International Journal of Dermatology	No relevant study population - insufficient

Reference	Reason for exclusion
	details reported to determine severity of acne
Ma, L. X., L. H.,Yu, B.,Yin, R.,Chen, L.,Wu, Y.,Tan, Z. J.,Liu, Y. B.,Tian, H. Q.,Li, H. Z.,Lin, T.,Wang, X. L.,Li, Y. H.,Wang, W. Z.,Yang, H. L.,Lai, W.Low-dose topical 5-aminolevulinic acid photodynamic therapy in the treatment of different severity of acne vulgaris. 2013. Photodiagnosis and Photodynamic Therapy	No relevant study design - not RCT
Ma, X. H. Z., S. L.,Zhou, G. M.Clinical observation on treatment of female delayed acne vulgaris with qingre cuochuang tablet. 2004. Zhongguo zhong xi yi jie he za zhi zhongguo zhongxiyi jiehe zazhi = chinese journal of integrated traditional and western medicine	Not in English language
Ma, Y. L., Y.,Wang, Q.,Ren, J.,Xiang, L.Prospective study of topical 5-aminolevulinic acid photodynamic therapy for the treatment of severe adolescent acne in Chinese patients. 2015. Journal of Dermatology	No relevant study deisgn - not RCT
MacDonald, R. H. M., H.,Ray, S. K.Clinical trial of Actinac in acne. 1976. British Journal of Clinical Practice	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mackey, J. P.A small double-blind trial of an anovulant agent in acne vulgaris. 1975. Irish Medical Journal	No relevant study design - not RCT
Magin,Topical and oral CAM in acne: A review of the empirical evidence and a consideration of its context. 2006. NA	No relevant intervention - systematic review about complementary and alternative medicines for acne
Mahran, H. G., Drbala, K. M.Efficacy of twelve sessions of 905nm infrared laser on acne vulgaris. 2019. Annals of Clinical and Analytical Medicine	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Maiti, R. S., C. S.,Ashique Rahman, M. A.,Srinivasan, A.,Parida, S.,Hota, D.Efficacy and Safety of Tazarotene 0.1% Plus Clindamycin 1% Gel Versus Adapalene 0.1% Plus Clindamycin 1% Gel in Facial Acne Vulgaris: A Randomized, Controlled Clinical Trial. 2017. Clinical Drug Investigation	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Maloney, J. M. A., D. I.,Flack, M.,McLaughlin-Miley, C.,Sevilla, C.,Derman, R.Use of a low-dose oral contraceptive containing norethindrone acetate and ethinyl estradiol in the treatment of moderate acne vulgaris. 2001. Clinical journal of women's health	Not obtainable
Maloney, J. M. D. J., P.,Watson, D.,Niknian, M.,Lee-Rugh, S.,Sampson-Landers, C.,Korner, P.A randomized controlled trial of a low-dose combined oral contraceptive containing 3 mg drospirenone plus 20 mug ethinylestradiol in the treatment of acne vulgaris: Lesion counts, investigator ratings and subject self-assessment. 2009a. Journal of Drugs in Dermatology	Duplicate record
Maloney, J. M. D., P., Jr.,Watson, D.,Niknian, M.,Lee-Rugh, S.,Sampson-Landers, C.,Korner, P.A randomized controlled trial of a	No relevant study population - sample does

Reference	Reason for exclusion
low-dose combined oral contraceptive containing 3 mg drospirenone plus 20 microg ethinylestradiol in the treatment of acne vulgaris: lesion counts, investigator ratings and subject self-assessment. 2009b. Journal of Drugs in Dermatology: JDD	not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Maloney, J. M. D., P.,Watson, D.,Niknian, M.,Lee-Rugh, S.,Sampson-Landers, C.,Korner, P.Treatment of acne using A 3-milligram drospirenone/20-microgram ethinyl estradiol oral contraceptive administered in a 24/4 regimen: A randomized controlled trial. 2008. Obstetrics and Gynecology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mandekou-Lefaki, I. D., F.,Teknetzis, A.,Euthimiadou, R.,Karakatsanis, G.Low-dose schema of isotretinoin in acne vulgaris. 2003. International Journal of Clinical Pharmacology Research	No relevant study design - not RCT
Mandy, S.A.A comparison of the efficacy and safety of tretinoin cream 0.025% and 0.05%. 1990. Advances in Therapy	No relevant data reported - post hoc analysis of non-randomised comparison of 2 RCTs
Mandy, S.Tretinoin in acne vulgaris. 1975. Modern Problems in Paediatrics	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Mango, D. R., S.,Manna, P.,Miggiano, G. A.,Serra, G. B.Clinical and hormonal effects of ethinylestradiol combined with gestodene and desogestrel in young women with acne vulgaris. 1996. Contraception	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mansour, D. V., C.,Sommer, W.,Weisberg, E.,Taneepanichskul, S.,Melis, G. B.,SundstrÃ¶m-Poromaa, I.,Korver, T.Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17Î²-oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. 2011b. European journal of contraception & reproductive health care	Duplicate record
Mansour, D. V., C.,Sommer, W.,Weisberg, E.,Taneepanichskul, S.,Melis, G. B.,Sundstrom-Poromaa, I.,Korver, T.Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17beta-oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. 2011a. European Journal of Contraception and Reproductive Health Care	No relevant study population - participants did not have acne
Mansurul, A. M. I., A. Z. M.Effect of spironolactone on acne vulgaris - A double blind study. 2000. Bangladesh Journal of Dermatology, Venereology and Leprology	Not obtainable
Marazzi, P. B., G.,Donald, A.,Davies, H.Clinical evaluation of Double Strength IsotrexinTM versus Benzamycin in the topical treatment of	Duplicate record

Reference	Reason for exclusion
mild to moderate acne vulgaris. 2002b. Journal of Dermatological Treatment	
Marcinkiewicz, J. W.-P., A.,Walczewska, M.,Lipko-Godlewska, S.,Jachowicz, R.,Maciejewska, A.,Bialecka, A.,Kasprowicz, A.Topical taurine bromamine, a new candidate in the treatment of moderate inflammatory acne vulgaris: a pilot study. 2008. European Journal of Dermatology	No relevant intervention - taurine bromaminenot available in the UK
Marcinkiewicz, J.Taurine bromamine: a new therapeutic option in inflammatory skin diseases. 2009. Polskie Archiwum Medycyny Wewnetrznej	No relevant study design - not RCT
Marczyk, B. M., P.,Budzisz, E.,Rotsztejn, H.Comparative study of the effect of 50% pyruvic and 30% salicylic peels on the skin lipid film in patients with acne vulgaris. 2014. Journal of Cosmetic Dermatology	No relevant data reported - sebum secretion study
Mareledwane, N. G.A randomized, open-label, comparative study of oral doxycycline 100 mg vs. 5% topical benzoyl peroxide in the treatment of mild to moderate acne vulgaris. 2006. International Journal of Dermatology	No relevant data reported
Marous, Mr.R., Flaten, H.K., Sledge, B., Rietcheck, H.R., Dellavalle, R., Suneja, T., Dunnick, C.Complementary and Alternative Methods for Treatment of Acne Vulgaris: a Systematic Review. 2018. Current Dermatology Reports	No relevant intervention - systematic review about complementary and alternative medicines for acne
Marron, S. E. T.-A., L.,Boira, S. Anxiety, depression, quality of life and patient satisfaction in acne patients treated with oral isotretinoin. 2013. Acta Dermato-Venereologica	No relevant study design - not RCT
Marsden, J. R. L., M. F.,Ford, G. P.,Shuster, S.Effect of low dose cyproterone acetate on the response of acne to isotretinoin. 1984. British Journal of Dermatology	No relevant study design - not RCT
Matsunaga, K. L., Y. H.,Chan, R.,Kerrouche, N.,Paliargues, F.Adjunctive usage of a non-comedogenic moisturizer with adapalene gel 0.1% improves local tolerance: A randomized, investigator-blinded, split-face study in healthy Asian subjects. 2013. Journal of Dermatological Treatment	No relevant study population – participants did not have acne
Mazzarello, V. D., M. G.,Ferrari, M.,Piga, G.,Usai, D.,Zanetti, S.,Sotgiu, M. A.Treatment of acne with a combination of propolis, tea tree oil, and aloe vera compared to erythromycin cream: Two double-blind investigations. 2018. Clinical Pharmacology: Advances and Applications	No relevant intervention - a cream based on three natural extracts vs 3% erythromycin cream vs placebo cream but no useful data for comparison of erythromycin cream and placebo reported
Mazzarello, V., Gavini, E., Rassu, G., Donadu, M. G., Usai, D., Piu, G., Pomponi, V., Sucato, F., Zanetti, S., Montesu, M. A. Clinical Assessment of New Topical Cream Containing Two Essential Oils Combined with Tretinoin in the Treatment of Acne. 2020. Clinical, Cosmetic and Investigational Dermatology CCIDClin Cosmet Investig Dermatol	No relevant intervention - a galenic compound containing 2 essential oils (Myrtus communis L. and Origanum vulgare)
Mazzetti, A. M., L.,Gerloni, M.,Cartwright, M.A Phase 2b, Randomized, Double-Blind Vehicle Controlled, Dose Escalation Study Evaluating Clascoterone 0.1%, 0.5%, and 1% Topical Cream in Subjects With Facial Acne. 2019. Journal of drugs in dermatology : JDD	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mazzetti, A., Moro, L., Gerloni, M., Cartwright, M.Pharmacokinetic Profile, Safety, and Tolerability of Clascoterone (Cortexolone 17-alpha	Not obtainable

Reference	Reason for exclusion
propionate, CB-03-01) Topical Cream, 1% in Subjects With Acne Vulgaris: An Open-Label Phase 2a Study. 2019. Journal of Drugs in Dermatology: JDDJ Drugs Dermatol	
McGillis, T. J. R., M. J.,Reisner, R. M.,Sternberg, T. H.,Stirling, N. C.,Winer, L. H.Topical Vitamin A Acid in the Management of Comedo Acne. 1971. Cutis; cutaneous medicine for the practitioner	Not obtainable
McHugh, R. C. R., A.,Sangha, N. D.,McCarty, M. A.,Utterback, R.,Rohrback, J. M.,Osborne, B. E.,Fleischer, A. B., Jr.,Feldman, S. R.A topical azithromycin preparation for the treatment of acne vulgaris and rosacea. 2004. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
McKenzie, M. W. B., D. C.,Popovich, N. G.Topical clindamycin formulations for the treatment of acne vulgaris. An evaluation. 1981. Archives of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mehran, G., Sepasgozar, S., Rohaninasab, M., Goodarzi, A., Ghassemi, M., Fotooei, M., Behrangi, E.Comparison between the therapeutic effect of microneedling versus tretinoin in patients with comedonal acne: A randomized clinical trial. 2019. Iranian Journal of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Meigel, W. G., H.,Wokalek, H.Oral treatment of acne conglobata with isotretinoin. Results of the German Multicenter Study. 1983. Der hautarzt; zeitschrift fur dermatologie, venerologie, und verwandte gebiete	Not in English language
Merkviladze, N. G., T.,Tushurashvili, P.,Ekaladze, E.,Jojua, N.The efficacy of topical drugs in treatment of noninflammatory acne vulgaris. 2010. Georgian Medical News	No relevant study design - not RCT
Merritt, B. B., C. N.,Morrell, D. S.Use of isotretinoin for acne vulgaris. 2009. Pediatric Annals	No relevant study design - not RCT
Michaelsson, G. J., L.,Ljunghall, K.A double-blind study of the effect of zinc and oxytetracycline in acne vulgaris. 1977a. British Journal of Dermatology	No relevant comparison - compares oral zinc and tetracyclines
Michaelsson, G. J., L.,Vahlquist, A.Effects of oral zinc and vitamin A in acne. 1977b. Archives of Dermatology	No relevant comparison - compares oral zinc sulfate alone and in combination with vitamin A
Michaelsson, G.Oral zinc in acne. 1980. Acta dermato-venereologica	No relevant article type - non-systematic review
Mikhael, E. M. M., M. Y. Evaluation of the effect of topical atorvastatin solution for the treatment of papulopustular acne. 2013. International Journal of Current Pharmaceutical Research	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Milikan, L. E.A double-blind study of Betadine skin cleanser in acne vulgaris. 1976. Cutis	No relevant intervention - Betadine skin cleanser
Miller, J. A. J., H. S.T reatment of hirsutism and acne with cyproterone acetate. 1986a. Clinics in Endocrinology & Metabolism	No relevant article type - non-systematic review

Reference	Reason for exclusion
Miller, S. T. S., J. J.Low-dose doxycycline moderately effective for acne. 2003. Journal of Family Practice	No relevant study design - not RCT
Millikan, L. E. A., R.Use of Buf-Puf and benzoyl peroxide in the treatment of acne. 1981. Cutis	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mills Jr, O. H. M., R. R.,Kligman, A. M.Acne vulgaris. Oral therapy with tetracycline and topical therapy with vitamin A. 1972. Archives of dermatology	No relevant data - insufficient data reported
Mills Jr, O. T., C.,Cardin, C. W.,Smiles, K. A.,Leyden, J. J.Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. 2002. Acta Dermato-Venereologica	Outcomes reported in figures only
Mills, O. H., Jr.,Kligman, A. M.Treatment of acne vulgaris with topically applied erythromycin and tretinoin. 1978. Acta Dermato-Venereologica	No relevant study design - not RCT
Min, S. P., S. Y.,Yoon, J. Y.,Suh, D. H.Comparison of fractional microneedling radiofrequency and bipolar radiofrequency on acne and acne scar and investigation of mechanism: comparative randomized controlled clinical trial. 2015. Archives of Dermatological Research	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Mirnezami, M. R., H.Is Oral Omega-3 Effective in Reducing Mucocutaneous Side Effects of Isotretinoin in Patients with Acne Vulgaris?. 2018. Dermatology Research and Practice	No relevant intervention - oral omega-3
Mitra, A. S., G. I.Topical photodynamic therapy for non-cancerous skin conditions. 2006. Photodiagnosis and Photodynamic Therapy	Duplicate record
Miyachi, Y. M., F.,Mita, T.,Bai, L.,Ikoma, A.Efficacy and safety of a fixed dose combination gel of adapalene 0.1% and benzoyl peroxide 2.5% in Japanese patients with acne vulgaris-a multicenter, randomzed, double-blinded, active-controlled, parallel group phase III study. 2016. Skin research	Not English language
Mobacken, H. H., K.Topical treatment of acne vulgaris with clindamycin. 1985. Lakartidningen	Not in English language
Moftah, N. H. I., S. M.,Wahba, N. H.Intense pulsed light versus photodynamic therapy using liposomal methylene blue gel for the treatment of truncal acne vulgaris: a comparative randomized split body study. 2016. Archives of Dermatological Research	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mohammadi, S. F., S.,Pardakhty, A.,Khalili, M.,Mohebbi, A.,Yousefian, M. R.,Aflatoonian, M.A survey to compare the efficacy of niosomal erythromycin alone versus combination of erythromycin and zinc acetate in the treatment of acne vulgaris. 2017. Journal of Kerman University of Medical Sciences	Outcomes reported in figures only
Mohan Kumar, P., Savitha, A. K., Suthanthira Kannan, S. To compare the side effect profile of azithromycin pulse therapy with doxycycline in acne vulgaris treatment: An open labelled, randomised, parallel group,	No relevant study population - sample includes participants with

Reference	Reason for exclusion
hospital based study. 2019. Indian Journal of Public Health Research and Development	mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Mokhtari, F. F., G.,Basiri, A.,Farhadi, S.,Nilforoushzadeh, M.,Behfar, S.Comparison effect of azithromycin gel 2% with clindamycin gel 1% in patients with acne. 2016. Advanced Biomedical Research	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Mokhtari, F., Shajari, A., Iraji, F., Faghihi, G., Siadat, A. H., Sadeghian, G., Adibi, N.The effectiveness of adapalene 0.1% with intense pulsed light versus benzoyl peroxide 5% with intense pulsed light in the treatment of acne vulgaris: A comparative study. 2019. Journal of Research in Medical SciencesJ	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Moltz, L. K., E.Medium dose oral cyproterone acetate therapy in women with moderate hyperandrogenism. 1984. Geburtshilfe und frauenheilkunde	Not in English language
Moneib, H. T., A. A.,Youssef, S. S.,Fawzy, M. M.Randomized split-face controlled study to evaluate 1550-nm fractionated erbium glass laser for treatment of acne vulgaris-an image analysis evaluation. 2014. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Monib, K. M. E. D., Hussein, M. S.Nd:YAG laser vs IPL in inflammatory and noninflammatory acne lesion treatment. 2019. Journal of Cosmetic Dermatology.	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Monk, B. E. A., J. A.,Caldwell, I. W.,Green, B.,Pelta, D.,Leonard, J.,Du Vivier, A.,Johnson, K.,Tolowinska, I.Efficacy of low-dose cyproterone acetate compared with minocycline in the treatment of acne vulgaris. 1987. Clinical & Experimental Dermatology	No relevant intervention - suboptimal dose of minocycline only taken for 21 days each month
Montes, L. F.Acne vulgaris: treatment with topical benzoyl peroxide acetone gel. 1977. Cutis	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Moore, C. L., C.,Moltz, L.,Oettel, M.,Klinger, G.,Schreiber, G.Antiandrogenic properties of the dienogest-containing oral contraceptive Valette. 1999. Drugs of Today	Not obtainable
Moravvej, H. H., A. M.,Yousefi, M.,Givrad, S.Efficacy of doxycycline versus azithromycin in the treatment of moderate facial acne vulgaris. 2012. Iranian Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Morel, P. V., M. P.,Beylot, C.,Bonerandi, J. J.,Dreno, B.,Lehucher-Ceyrac, D.,Slimani, S.,Dupuy, P.Clinical efficacy and safety of a topical combination of retinaldehyde 0.1% with erythromycin 4% in acne vulgaris. 1999. Clinical and Experimental Dermatology	No relevant intervention - topical retinaldehyde gel
Morganti, P. B., E.,Guarneri, B.,Guarneri, F.,Fabrizi, G.,Palombo, P.,Palombo, M.Topical clindamycin 1% vs. linoleic acid-rich phosphatidylcholine and nicotinamide 4% in the treatment of acne: A multicentre-randomized trial. 2011. International Journal of Cosmetic Science	No relevant data reported
Morganti, P. R., S. D.,Bruno, C.,Cardillo, A.Ethyl lactate and benzoyl peroxide in acne vulgaris. 1988. Journal of Applied Cosmetology	No relevant study population - insufficient details to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Mugglestone, C. J. R., E. L.The treatment of acne with an anti-androgen/oestrogen combination. 1982. Clinical & Experimental Dermatology	Dosage of tetracycline lower than BNF value
Muhlemann, M. F. C., G. D.,Cream, J. J.,Wise, P.Oral spironolactone: An effective treatment for acne vulgaris in women. 1986. British Journal of Dermatology	No relevant data reported - randomised cross-over trial, data for first phase not reported separately from data from second phase
Murff, H. J.Combination therapies are more effective than monotherapy for mild to moderate acne. 2008. Journal of Clinical Outcomes Management	No relevant article type - commentary on an RCT
Naieni, F. F. A., H.Comparison of three different regimens of oral azithromycin in the treatment of acne vulgaris. 2012. Journal of isfahan medical school	Not in English language
Nandimath, M. K. R., N. B.Comparision of clinical efficacy of topical clindamycin with adapalene and adapalene alone in treatment of mild to moderate facial acne vulgaris. 2013. International Journal of Pharma and Bio Sciences	Not obtainable
Narurkar, V. A. B., K. R.,Cohen, J. L.An open-label trial examining the efficacy and safety of a pre- and postprocedure topical five-product system (Clinique Medical Optimizing Regimen) specifically formulated to complement laser/light-based facial cosmetic procedures. 2010. Journal of Cosmetic & Laser Therapy	No relevant study population - participants scheduled to undergo facial physical treatment cosmetic procedure
Nelson, R. M. R., A. E.Hirsutism and acne treated by an androgen antagonist. 1970. Obstetrics & Gynecology	No relevant study design - not RCT

Reference	Reason for exclusion
Ng, C. H. T., M. M.,Celi, E.,Tate, B.,Schweitzer, I.Prospective study of depressive symptoms and quality of life in acne vulgaris patients treated with isotretinoin compared to antibiotic and topical therapy. 2002. Australasian Journal of Dermatology	No relevant study design - not RCT
Ng, P. P. G., C. L.Treatment outcome of acne vulgaris with oral isotretinoin in 89 patients. 1999. International Journal of Dermatology	No relevant study design - not RCT
Niazi, S. S., A.Comparison of efficacy of fixed low-dose regimens (daily vs alternate day) of oral isotretinoin in mild to moderate acne vulgaris. 2015. Journal of Pakistan Association of Dermatologists	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Nicklas, C. R., R.,Cardenas, C.,Hasson, A.Comparison of efficacy of aminolaevulinic acid photodynamic therapy vs. adapalene gel plus oral doxycycline for treatment of moderate acne vulgaris-A simple, blind, randomized, and controlled trial. 2018. Photodermatology photoimmunology and photomedicine	Duplicate record
Nielsen, P. G.Treatment of female acne vulgaris with a cream containing the antiandrogen canrenone. 1983. Dermatologica	No relevant article type - letter to editor
Nighland, M. G., R.Tretinoin microsphere gel in facial acne vulgaris: a meta-analysis. 2008. Journal of drugs in dermatology : JDD	No relevant data reported - reports pooled results from 3 trials combined
NilFroushzadeh, M. A. S., A. H.,Baradaran, E. H.,Moradi, S.Clindamycin lotion alone versus combination lotion of clindamycin phosphate plus tretinoin versus combination lotion of clindamycin phosphate plus salicylic acid in the topical treatment of mild to moderate acne vulgaris: a randomized control trial. 2009. Indian journal of dermatology, venereology and leprology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Niren, N. M. T., H. M.The Nicomide Improvement in Clinical Outcomes Study (NICOS): results of an 8-week trial. 2006. Cutis	No relevant study design - not RCT
Nitzan, Y. B. C., A. D.Zinc in skin pathology and care. 2006. Journal of Dermatological Treatment	Duplicate record
Nofal, E. N., A.,Gharib, K.,Nasr, M.,Abdelshafy, A.,Elsaid, E.Combination chemical peels are more effective than single chemical peel in treatment of mild-to-moderate acne vulgaris: A split face comparative clinical trial. 2018. Journal of Cosmetic Dermatology	No relevant study design - not RCT
Nordin, K. F., T.,Rylander, C.Ro 11-1430, a new retinoic acid derivative for the topical treatment of acne. 1981. Dermatologica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Norris, J. F. H., B. R.,Basey, A. J.,Cunliffe, W. J.A comparison of the effectiveness of topical tetracycline, benzoyl-peroxide gel and oral oxytetracycline in the treatment of acne. 1991. Clinical & Experimental Dermatology	No relevant intervention - topical tetracycline and 250 mg of oral oxytetracycline

Reference	Reason for exclusion
Nyirady, J. G., R. M.,Nighland, M.,Berger, R. S.,Jorizzo, J. L.,Kim, Y. H.,Martin, A. G.,Pandya, A. G.,Schulz, K. K.,Strauss, J. S.A comparative trial of two retinoids commonly used in the treatment of acne vulgaris. 2001. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Nyirady, J. N., M.,Payonk, G.,Pote, J.,Phillips, S.,Grossman, R.A comparative evaluation of tretinoin gel microsphere, 0.1%, versus tretinoin cream, 0.025%, in reducing facial shine. 2000. Cutis; cutaneous medicine for the practitioner	No relevant study population - sample includes people with facial oiliness
Ochsendorf, F.Clindamycin phosphate 1.2% / tretinoin 0.025%: a novel fixed-dose combination treatment for acne vulgaris. 2015. Journal of the European Academy of Dermatology & Venereology	No relevant study design - not RCT
Oh, S. H. R., D. J.,Han, E. C.,Lee, K. H.,Lee, J. H.A comparative study of topical 5-aminolevulinic acid incubation times in photodynamic therapy with intense pulsed light for the treatment of inflammatory acne. 2009. Dermatologic Surgery	Split face study - but randomised treatments not compared directly in the same participants.
Olafsson, J. H. G., J.,Eggertsdottir, G. E.,Kristjansson, F.Doxycycline versus minocycline in the treatment of acne vulgaris: A double-blind study. 1989. Journal of Dermatological Treatment	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Olivier, S. D., A.,Bierschwale, H.,Archer, D.Efficacy of a low-dose oral contraceptive (20mcg ethinyl estradiol/100 mcg levonorgestrel) for the treatment of moderate acne. 2003. International journal of obstetrics & gynecology	No relevant article type - conference abstract
Olson, W. H. L., J. S.,Robisch, D. M.The duration of response to norgestimate and ethinyl estradiol in the treatment of acne vulgaris. 1998. International Journal of Fertility and Women's Medicine	No relevant data reported - reports combined results from Redmond 1997 and Lucky 1997 trials
Oprica, C. E., L.,Hagstromer, L.,Nord, C. E.Clinical and microbiological comparisons of isotretinoin vs. tetracycline in acne vulgaris. 2007. Acta Dermato-Venereologica	No relevant data - insufficient data reported
Orafidiya, L. O. A., E. O.,Oyedele, A. O.,Babalola, O. O.,Onayemi, O.Preliminary clinical tests on topical preparations of Ocimum gratissimum linn leaf essential oil for the treatment of acne vulgaris. 2002. Clinical Drug Investigation	No relevant study population - no information about severity of acne reported and study is not relevant for PCOS, maintenance or refractory treatments
Orafidiya,The effect of aloe vera gel on the anti-acne properties of the essential oil of Ocimum gratissimum Linn leaf - A preliminary clinical investigation. 2004. NA	No relevant intervention - Ocimum oil lotion and aloe gel
Orringer, J. S. K., S.,Hamilton, T.,Schumacher, W.,Cho, S.,Hammerberg, C.,Fisher, G. J.,Karimipour, D. J.,Johnson, T. M.,Voorhees, J. J.Treatment of acne vulgaris with a pulsed dye laser: A randomized controlled trial. 2004. Journal of the American Medical Association	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Orringer, J. S. K., S.,Maier, L.,Johnson, T. M.,Sachs, D. L.,Karimipour, D. J.,Helfrich, Y. R.,Hamilton, T.,Voorhees, J. J.A randomized, controlled, split-face clinical trial of 1320-nm Nd:YAG laser therapy in the treatment of acne vulgaris. 2007. Journal of the American Academy of Dermatology	No relevant study population - sample includes people mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Orringer, J. S. S., D. L.,Bailey, E.,Kang, S.,Hamilton, T.,Voorhees, J. J.Photodynamic therapy for acne vulgaris: A randomized, controlled, split-face clinical trial of topical aminolevulinic acid and pulsed dye laser therapy. 2010. Journal of Cosmetic Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Owens, D. W.Clinical evaluation of topical vitamin A acid in therapy of acne vulgaris. 1973. Texas Medicine	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Ozgen, Z. Y. G., O.A randomized, double-blind comparison of nadifloxacin 1% cream alone and with benzoyl peroxide 5% lotion in the treatment of mild to moderate facial acne vulgaris. 2013. Marmara Medical Journal	No relevant intervention - nadifloxacin 1% cream not available in the UK
Ozkan, M. D., G.,Sabuncu, I.,Saracoglu, N.,Akgun, Y.,Urer, S. M.Clinical efficacy of topical clindamycin phosphate and azelaic acid on acne vulgaris and emergence of resistant coagulase-negative staphylococci. 2000. Turkish Journal of Medical Sciences	Duplicate record
Ozolins, M. E., E. A.,Avery, A.,Cunliffe, W. J.,O'Neill, C.,Simpson, N. B.,Williams, H. C.Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne. 2005. Health technology assessment (Winchester, England)	No relevant article type - executive summary of Ozolins 2004 trial
PÃ©rez LÃ³pez, M. M. V., J. M.A new salt of erythromycin (A-137 or erythromycin lauryl sulfate) in the topical treatment of acne. 1982. Medicina cutanea ibero-latino-americana	Not in English language
Packman, A. M. B., R. H.,Dunlap, F. E.,Kraus, S. J.,Webster, G. F.Treatment of acne vulgaris: Combination of 3% erythromycin and 5% benzoyl peroxide in a gel compared to clindamycin phosphate lotion. 1996. International Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Padilla, R. S. M., J. M.,Becker, L. E.Topical tetracycline hydrochloride vs. topical clindamycin phosphate in the treatment of acne: a comparative study. 1981. International Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Pai, I. F. W., Y. C.,Lu, Y. C.Clinical trial of cyproterone acetate-ethinyl oestradiol compound on androgen dependent skin disorders. 1982.	Not in English language

Reference	Reason for exclusion
Taiwan i Hsueh Hui Tsa Chih - Journal of the Formosan Medical Association	
Palacios, S. W., L.,Parke, S.,Machlitt, A.,Romer, T.,Bitzer, J.Efficacy and safety of a novel oral contraceptive based on oestradiol (oestradiol valerate/dienogest): A Phase III trial. 2010. European Journal of Obstetrics and Gynecology and Reproductive Biology	No relevant study population - participants did not have acne
Palatsi, R. H., E.,Liukko, P.,Malmiharju, T.,Mattila, L.,Riihiluoma, P.,Ylostalo, P.Serum total and unbound testosterone and sex hormone binding globulin (SHBG) in female acne patients treated with two different oral contraceptives. 1984. Acta Dermato-Venereologica	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Palatsi, R. R., M.,Kivinen, S.Pituitary function and DHEA-S in male acne and DHEA-S, prolactin and cortisol before and after oral contraceptive treatment in female acne. 1986. Acta Dermato-Venereologica	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Pandey, D. A., S.Efficacy of isotretinoin and antihistamine versus isotretinoin alone in the treatment of moderate to severe acne: A randomised control trial. 2019. Kathmandu University Medical Journal	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Panzer, J. D. P., W.,Meek, T. J.,Derbes, V. J.,Atkinson, W.Acne treatment: A comparative efficacy trial of clindamycin and tetracycline. 1977. Cutis	No relevant data - insufficient data reported
Pariser, D. B., A.,Fried, R.,Jarratt, M. T.,Kempers, S.,Kircik, L.,Lucky, A. W.,Rafal, E.,Rendon, M.,Weiss, J.,et al.,Tretinoin gel microsphere pump 0.04% plus 5% benzoyl peroxide wash for treatment of acne vulgaris: morning/morning regimen is as effective and safe as morning/evening regimen. 2010. Journal of drugs in dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Pariser, D. C., L. E.,Johnson, L. A.,Gottschalk, R. W.Adapalene 0.1% gel compared to tazarotene 0.1% cream in the treatment of acne vulgaris. 2008. Journal of drugs in dermatology : JDD	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Pariser, D. M., Green, L. J., Lain, E. L., Schmitz, C., Chinigo, A. S., McNamee, B., Berk, D. R.Safety and tolerability of sarecycline for the treatment of acne vulgaris: results from a phase III, multicenter, open-label study and a phase I phototoxicity study. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant study design - participants were not randomised on entry to the study and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Park, K. Y. K., E. J.,Seo, S. J.,Hong, C. K.Comparison of fractional, nonablative, 1550-nm laser and 595-nm pulsed dye laser for the treatment of facial erythema resulting from acne: A split-face, evaluator-blinded, randomized pilot study. 2014. Journal of Cosmetic and Laser Therapy	No relevant study population - sample includes people with acne erythema
Parker, F.A comparison of clindamycin 1% solution versus clindamycin 1% gel in the treatment of acne vulgaris. 1987. International Journal of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Pastrana-Ruiz, M. E. V.-M., M. E.,Hojyo-Tomoka, M. T.,Dom inguez-Soto, L.Antibiotics for the treatment of acne. Double-blind comparative study with a 1% solution of clindamycin phosphate versus 500 mg oral tetracycline in patients with moderate acne. 1989. Dermatologia revista mexicana	Not in English language
Patel, V. B. M., A. N.,Marfatia, Y. S.Preparation and comparative clinical evaluation of liposomal gel of benzoyl peroxide for acne. 2001a. Drug Development and Industrial Pharmacy	No relevant study design - not RCT
Patel, V. B. M., A.,Marfatia, Y. S.Clinical assessment of the combination therapy with liposomal gels of tretinoin and benzoyl peroxide in acne. 2001b. AAPS PharmSciTech	No relevant study design - not RCT
Paver, K.Complications from combined oral tetracycline and oral corticoid therapy in acne vulgaris. 1970. Medical Journal of Australia	Not obtainable
Pavithra, G. U., G. M.,Rukmini, M. S.A randomized controlled trial of topical benzoyl peroxide 2.5% gel with a low glycemic load diet versus topical benzoyl peroxide 2.5% gel with a normal diet in acne (grades 1-3). 2018. Indian Journal of Dermatology, Venereology & Leprology	No relevant study population - insufficient details reported to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Peachey, R. D. C., B. L.Topical retinoic acid in the treatment of acne vulgaris. 1971. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Peck, G. L. O., T. G.,Butkus, D.,Pandya, M.,Arnaud-Battandier, J.,Gross, E. G.,Windhorst, D. B.,Cheripko, J.Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. 1982b. Journal of the American Academy of Dermatology	No relevant data - insufficient data reported
Peck, G. L. O., T. G.,Butkus, D.Isotretinoin versus placebo in the treatment of cystic acne. 1982a. Journal of the American Academy of Dermatology	Duplicate record
Pedace, F. J. S., R.Topical retinoic acid in acne vulgaris. 1971. The British journal of dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Peereboom-Wynia, J. D. R. C., P. J. G.,Bernsen, R.A new alcohol-free preparation of benzoyl peroxide gel (Basiron) for acne vulgaris. A	Not in English language

Reference	Reason for exclusion
double blind trial. 1984. TGO - Tijdschrift voor Therapie Geneesmiddel en Onderzoek	
Peker, M. T., H. B.,Arca, E.,Erbil, A. H.,Gur, A. R.Efficacy of topical erythromycin, tetracycline and clindamycin in the treatment of acne vulgaris. 2004. Deri hastaliklari ve frengi arsivi	Not in English language
Perez, M. A., F.,De Moragas, J. M.A double blind study comparing clindamycin-phosphate versus oral tetracycline in acne treatment. 1987b. Medicina cutanea ibero-latino-americana	Not in English language
Perez, M. A., F.,De Moragas, J. M.Comparative double-blind study of topical clindamycin phosphate and oral tetracycline in the treatment of acne. 1987a. Medicina cutanea ibero-latino-americana	Not in English language
Petit, L. P.-F., C.,Uhoda, E.,Vroome, V.,Cauwenbergh, G.,Pierard, G. E.Coping with mild inflammatory catamenial acne: a clinical and bioinstrumental split-face assessment. 2004. Skin Research & Technology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Pierard-Franchimont, C. G., V.,Arrese, J. E.,Martalo, O.,Braham, C.,Slachmuylders, P.,Pierard, G. E.Lymecycline and minocycline in inflammatory acne: A randomized, double-blind intent-to-treat study on clinical and in vivo antibacterial efficacy. 2002. Skin Pharmacology and Applied Skin Physiology	Antibiotic dosages lower than BNF values
Pierard-Franchimont, C. H., F.,Fraiture, A. L.,Fumal, I.,Pierard, G. E.Split-face clinical and bio-instrumental comparison of 0.1% adapalene and 0.05% tretinoin in facial acne. 1999. Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Pinto, C. S., F.,Orellana, J. J.,Gonzalez, S.,Hasson, A.Efficacy of red light alone and methyl-aminolaevulinate-photodynamic therapy for the treatment of mild and moderate facial acne. 2013. Indian Journal of Dermatology, Venereology & Leprology	No relevant study design - not RCT
Pisani, M. G., V.,Grimaldi, F. F.Treatment of acne vulgaris with an ointment containing azelaic acid (12%), L-carnitine (2%), enoxolone (1%): double-blind study versus placebo. TRATTAMENTO DELL'ACNE VOLGARE CON UNA CREMA A BASE DI ACIDO AZELAICO (12%), L-CZRNITINA (2%), ENOXOLONE (1%): STUDIO IN DOPPIO CIECO VERSUS PLACEBO. 1991. Chron dermatol	Not in English language
Plewig, G. D., H.,Pfleger, M.,Michelsen, S.,Kligman, A. M.Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne. 2004. Journal der Deutschen Dermatologischen Gesellschaft	Not in English language
Plewig, G. H., K. T.,Nenoff, P.Clinical and bacteriological evaluation of nadifloxacin 1% cream in patients with acne vulgaris: A double-blind, phase III comparison study versus erythromycin 2% cream. 2006. European Journal of Dermatology	No relevant intervention - nadifloxacin 1% cream not available in the UK
Plewig, G.Dermabrasion for nodular cutaneous elastosis with cysts and comedones. 1972. Archives of Dermatology	Not obtainable
Plewig, G.Vitamin A acid. Topical treatment in acne vulgaris. 1969. Pennsylvania Medicine	No relevant population - insufficient information to

Reference	Reason for exclusion
	determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Pochi, P. E. B., F. K.,Ellis, C. N.,Stoughton, R. B.,Whitmore, C. G.,Saatjian, G. D.,Sefton, J.Erythromycin 2 percent gel in the treatment of acne vulgaris. 1988. Cutis	Not obtainable
Podfigurna, 2019Clinical, hormonal and metabolic parameters in women with PCOS with different combined oral contraceptives (containing chlormadinone acetate versus drospirenone). 2019. Journal of Endocrinological Investigation	Duplicate of Podfigurna 2020
Polakova, K. F., A.,Sayag, M.,Jourdan, E.Adermocosmetic containing bakuchiol, Ginkgo biloba extract and mannitol improves the efficacy of adapalene in patients with acne vulgaris: Result from a controlled randomized trial. 2015. Clinical, Cosmetic and Investigational Dermatology	No relevant intervention - bakuchiol, Ginkgo biloba extract, and mannitol complex
Pollock, B. T., D.,Stringer, M. R.,Bojar, R. A.,Goulden, V.,Stables, G. I.,Cunliffe, W. J.Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: A study of clinical efficacy and mechanism of action. 2004. British Journal of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Ponzio, H. A. B., R. T.,Bozko, M. P.Clinical evaluation of a line of products for the control of acne in teenagers. 1994. Anais brasileiros de dermatologia	Not in English language
Poulos, E. T. T., F. J.Acne vulgaris. Double blind trial comparing tetracycline and clindamycin. 1976. Archives of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Prasad, S. M., A.,Kubavat, A.,Kelkar, A.,Modi, A.,Swarnkar, B.,Bajaj, B.,Vedamurthy, M.,Sheikh, S.,Mittal, R.Efficacy and safety of a nano-emulsion gel formulation of adapalene 0.1% and clindamycin 1% combination in acne vulgaris: A randomized, open label, active-controlled, multicentric, phase IV clinical trial. 2012. Indian Journal of Dermatology, Venereology and Leprology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Prendiville, J. S. L., R. A.,Russell-Jones, R.A comparison of dapsone with 13-cis retinoic acid in the treatment of nodular cystic acne. 1988. Clinical and Experimental Dermatology	No relevant data reported - group numbers not reported
Pria, S. D. G., R. B.,Mahesh, V. B.An antiandrogen in acne and idiopathic hirsutism. 1969. Journal of Investigative Dermatology	No relevant study design - not RCT
Priano, L. B., S.,Isola, V.,Grazioli, I.,Melzi, G.,Massone, L.Topical spironolactone 5% versus benzoylperoxide 5% + miconazole 2% in the therapy of acne: double-blind, controlled study to evaluate the efficacy and the eventual systemic absorption. 1993. Giornale italiano di dermatologia e venereologia	Not in English language
Prince, R. A. B., D. A.,Hepler, C. D.,Feldick, H. G.Clinical trial of topical erythromycin in inflammatory acne. 1981. Drug Intelligence & Clinical Pharmacy	No relevant study population - sample includes people with mild to severe acne and study

Reference	Reason for exclusion
	is not relevant for PCOS, maintenance or refractory treatments
Prince, R. A. H., J. M.,Maroc, J. A.Comparative trial of benzoyl peroxide versus benzoyl peroxide with urea in inflammatory acne. 1982. Cutis	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Privitera, G. B., S.,Del Mastro, S.Clinical and pharmacokinetic evaluation of josamycin in the treatment of inflammatory acne. 1989. Journal of Chemotherapy	No relevant study deisgn - not RCT
Rafanelli, A. G., I.,Melzi, G.A controlled study spironolactone vs progesterone in the topical treatment of acne. 1993. Giornale italiano di dermatologia e venereologia	Not in English language
Rafiei R, Yaghoobi RAzithromycin versus tetracycline in the treatment of acne vulgaris.. 2006. J Dermatolog Treat	No relevant intervention - suboptimal dose of tetracycline
Raimer, S. M., J. M.,Bourcier, M.,Wilson, D.,Papp, K.,Siegfried, E.,Garrett, S.Efficacy and safety of dapsone gel 5% for the treatment of acne vulgaris in adolescents. 2008. Cutis	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Rajka, G.On therapeutic approaches to some special types of acne. 1985. Acta Dermato-Venereologica. Supplementum	No relevant study deisgn - not RCT
Raoof, J., Hooper, D., Moore, A., Zaiac, M., Sullivan, T., Kircik, L., Lain, E., Jankicevic, J., Stuart, I.FMX101 4% topical minocycline foam for the treatment of moderate-to-severe acne vulgaris: efficacy and safety from a Phase III randomized, doubleblind, vehicle-controlled study. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant article type - conference abstract
Raoof, T. J. H., D.,Moore, A.,Zaiac, M.,Sullivan, T.,Kircik, L.,Lain, E.,Jankicevic, J.,Stuart, I.Efficacy and Safety of a Novel Topical Minocycline Foam for the Treatment of Moderate-to-Severe Acne Vulgaris: A Phase 3 Study. 2019. Journal of the American Academy of Dermatology.	No relevant intervention - FMX101 4% topical minocycline foam not available in the UK
Raoof, T. J., Hooper, D., Moore, A., Zaiac, M., Sullivan, T., Kircik, L., Lain, E., Jankicevic, J., Stuart, I.Efficacy and safety of a novel topical minocycline foam for the treatment of moderate to severe acne vulgaris: A phase 3 study. 2020. Journal of the American Academy of Dermatology	No relevant intervention - FMX101 4% topical minocycline foam not available in the UK
Rapaport, M. P., S. M.,Reisner, R. M.Evaluation of topical erythromycin and oral tetracycline in acne vulgaris. 1982. Cutis; cutaneous medicine for the practitioner	No relevant intervention - suboptimal dose of tetracycline
Rassai, S. R., E.,Ramirez-Fort, M. K.,Feily, A.Adjuvant Narrow Band UVB Improves the Efficacy of Oral Azithromycin for the Treatment of Moderate to Severe Inflammatory Facial Acne Vulgaris. 2014. Journal of Cutaneous & Aestheic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS,

Reference	Reason for exclusion
	maintenance and refractory treatments
Rea, S. T., S.,Frittelli, V.,Gunnarsson, R.A feasibility study for a triple-blind randomized controlled trial investigating the effects of oral isotretinoin on mood and quality of life in patients with acne vulgaris. 2017. Clinical and experimental dermatology	No releavant study design - not RCT
Rea, S. T., S.,Frittelli, V.,Gunnarsson, R.A feasibility study for a triple-blind randomized controlled trial investigating the effects of oral isotretinoin on mood and quality of life in patients with acne vulgaris. 2018. Clinical and Experimental Dermatology	Duplicate record
Rebillo, T. H., J. L.Skin surface glycerol levels in acne vulgaris. 1978. Journal of Investigative Dermatology	No relevant study design - not RCT
Redmond, G. P. G., G. P.,Gupta, M. K.,Bedocs, N. M.,Parker, R.,Skibinski, C.,Bergfeld, W.Treatment of androgenic disorders with dexamethasone: dose-response relationship for suppression of dehydroepiandrosterone sulfate. 1990. Journal of the American Academy of Dermatology	No relevant study population - sample includes people with hirsuitism or alopecia, only 11% participants with acne
Reinel, D. B., H.A new drug combination for the topical treatment of acne. Miconazole 2% + benzoyl peroxide 5% versus benzoyl peroxide 5%--a double-blind study. 1985. Zeitschrift fur hautkrankheiten	Not in English language
Richter, C. T., C.,Hillmann, K.,Dobos, G.,Stroux, A.,Kottner, J.,Blume-Peytavi, U.Reduction of Inflammatory and Noninflammatory Lesions with Topical Tyrothricin 0.1% in the Treatment of Mild to Severe Acne Papulopustulosa: A Randomized Controlled Clinical Trial. 2016. Skin Pharmacology and Physiology	No relevant intervention - topical Tyrothricin;nNo relevant study population - sample includes people with mild to severe acne
Richter, J. R. F., L. R.,Kiistala, U. O.,Jung, E. G.Efficacy of the fixed 1.2% clindamycin phosphate, 0.025% tretinoin gel formulation (Velac) and a proprietary 0.025% tretinoin gel formulation (Aberela) in the topical control of facial acne. 1998b. Journal of the European Academy of Dermatology and Venereology	Duplicate record
Rietschel, R. L. D., S. H.Benzoyl peroxide reactions in an acne study group. 1982. Contact Dermatitis	No relevant data reported - pharmokinetic study
Rietschel, R. L. D., S. H.Clindamycin phosphate used in combination with tretinoin in the treatment of acne. 1983. International Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Rist, T. D., M. W.Study design and selection criteria in the BEST study. 2003. Cutis	No relevant data reported
Rivkin, L. R., M.Clinical evaluation of a new erythromycin solution for acne vulgaris. 1980. Cutis	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Riyanto, P. S., P.,Lelyana, R.Advantage of soybean isoflavone as antiandrogen on acne vulgaris. 2015. Dermato-Endocrinology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Robinson, S. K., Z.,Tang, M. M.Metformin as an adjunct therapy for the treatment of moderate to severe acne vulgaris: A randomized open-labeled study. 2019. Dermatologic Therapy	Dosage of tetracycline lower than BNF value
Robledo Aguilar, A. L. B., E.,del Pino Gamboa, J.,Sambricio Guiu, F.,Rodriguez Pichardo, A.,Sotillo Gago, I.,Chaparro Martinez, A.,Garcia Aparicio, P. G.Multicentric comparative study of the efficacy and tolerance of clindamycin phosphate 1% topical solution and tetracycline topical solution for the treatment of acne vulgaris. 1988. Current therapeutic research - clinical and experimental	No relevant intervention - tetracycline topical solutio not available in the UK
Rocha, M. A. D. G., L. R. S.,Sanudo, A.,Bagatin, E.Modulation of Toll Like Receptor-2 on sebaceous gland by the treatment of adult female acne. 2017a. Dermato-endocrinology	No relevant study design - not RCT
Rocha, M. C., K. H. M.,Carvalho, V. M.,Bagatin, E.ADT-G as a promising biomarker for peripheral hyperandrogenism in adult female acne. 2017b. Dermato-endocrinology	No relevant data reported - pharmokinetic study
Rocha, M. S., A.,Bagatin, E.The effect on acne quality of life of topical azelaic acid 15% gel versus a combined oral contraceptive in adult female acne: A randomized trial. 2017c. Dermato-endocrinology	No relevant data reported - quality of life data only
Rojanamatin, J. C., P.Treatment of inflammatory facial acne vulgaris with intense pulsed light and short contact of topical 5-aminolevulinic acid: a pilot study. 2006. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Romiti, N.Use of the aromatic retinoid Ro-11-1430 for acne therapy. 1978. Pharmatherapeutica	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Ruamrak, C. L., N.,Natakankitkul, S.Comparison of clinical efficacies of sodium ascorbyl phosphate, retinol and their combination in acne treatment. 2009. International Journal of Cosmetic Science	No relevant study population - sample includes people with mild to severe acne; No relevant intervention - topical sodium ascorbyl phosphate
Ruxton,A novel topical ingredient derived from seaweed significantly reduces symptoms of acne vulgaris: a general literature review. 2013. NA	No relevant intervention - marine-derived ingredients for acne
Ryou, J. H. L., S. J.,Park, Y. M.,Kim, H. O.,Kim, H. S.Acne-photodynamic therapy with intra-lesional injection of 5-aminolevulinic acid. 2009. Photodermatology, Photoimmunology & Photomedicine	No relevant study design - not RCT
Sadick, N. S. L., Z.,Laver, L.Treatment of mild-to-moderate acne vulgaris using a combined light and heat energy device: Home-use clinical study. 2010c. Journal of Cosmetic and Laser Therapy	No relevant article type - conference abstract
Sadick, N., Edison, B. L., John, G., Bohnert, K. L., Green, B.An Advanced, Physician-Strength Retinol Peel Improves Signs of Aging and Acne Across a Range of Skin Types Including Melasma and Skin of Color. 2019. Journal of Drugs in Dermatology: JDDJ Drugs Dermatol	Not obtainable
Sadick, N.An open-label, split-face study comparing the safety and efficacy of levulan kerastick (aminolevulonic acid) plus a 532 nm KTP	Reported outcomes relevant for the network meta-analysis but not in

Reference	Reason for exclusion
laser to a 532 nm KTP laser alone for the treatment of moderate facial acne. 2010a. Journal of Drugs in Dermatology	enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Saihan, E. M. B., J. L.,Meyrick, G.,Speller, D. C.,Thornton, E.,Chestney, V.The effect of a topical antibiotic preparation in acne vulgaris--a controlled clinical and laboratory study. 1981. British Journal of Clinical Practice	No relevant intervention - actinac discontinued in the UK
Salagnac, V. L., F.,De, L. O.,Le, C. Y.,Kalis, B.Topical treatment of actinic ageing with vitamin A acid at various concentrations. TRAITEMENT DU VIEILLISSEMENT ACTINIQUE PAR LA VITAMINE A ACIDE TOPIQUE A DIFFERENTES CONCENTRATIONS. 1991. REV. FR. GYNECOL. OBSTET.	Not in English language
Sampaio, S. A. P. M., H. C. B.,Freitas, T. H. P.,Totoli, Sasm,Martins, MrfcA multicenter trial comparing the efficacy and tolerance of isotretinoin gel 0,05% and tretinoin cream 0.05% in the treatment of acne vulgaris. 1997. Revista brasileira de medicina	Not in English language
Sanam, M. Z., O.Desogestrel+ethinylestradiol versus levonorgestrel +ethinylestradiol: Which one has better affect on acne, hirsutism, and weight change. 2011. Saudi Medical Journal	No relevant study population - participants did not have acne
Santos, M. A. B., V. G.,Santos, G.Effectiveness of photodynamic therapy with topical 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone in the treatment of acne vulgaris: comparative study. 2005. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Santos-Caetano, J. P. C., M. R.A Randomized Controlled Tolerability Study to Evaluate Reformulated Benzoyl Peroxide Face Washes for Acne Vulgaris. 2019. Journal of drugs in dermatology : JDD	No relevant intervention - intervention is washed off the face
Sardesai Vkambli, V.Comparison of efficacy of topical clindamycin and nicotinamide combination with plain clindamycin for the treatment of acne vulgaris and acne resistant to topical antibiotics. 2003. Indian journal of dermatology, venereology and leprology	No relevant study design - not RCT
Sauer, G. C.Prospective study on the safety of long-term tetracycline therapy for acne. 1981. Cutis	No relevant study design - not RCT
Sayyafan, M. S. R., M.,Salmanpour, R.Clinical assessment of topical erythromycin gel with and without zinc acetate for treating mild-to-moderate acne vulgaris. 2019. Journal of Dermatological Treatment.	No relevant study design - not RCT
Sayyafran, 2019 Clinical assessment of topical erythromycin gel with and without zinc acetate for treating mild-to-moderate acne vulgaris. 2019. Journal of Dermatological Treatment	Duplication of Sayyafan 2019
Schachner, L. E., W.,Kittles, C.,Mertz, P.Topical erythromycin and zinc therapy for acne. 1990a. Journal of the American Academy of Dermatology	No relevant data - insufficient data reported
Schachner, L. P., A.,Kittles, C.A clinical trial comparing the safety and efficacy of a topical erythromycin-zinc formulation with a topical clindamycin formulation. 1990b. Journal of the American Academy of Dermatology	No relevant data - insufficient data reported
Scheinfeld, N.ABSORICA (isotretinoin): a new form. 2013. SKINmed	No relevant study design - not RCT
Schlessinger, J. M., A.,Gold, M.,Leonardi, C.,Eichenfield, L.,Plott, R. T.,Leyden, J.,Wortzman, M.Clinical safety and efficacy studies of a	No relevant study population - sample

Reference	Reason for exclusion
novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. 2007. Journal of drugs in dermatology : JDD	includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Schutte, H. C., W. J.,Forster, R. A.The short-term effects of benzoyl peroxide lotion on the resolution of inflamed acne lesions. 1982. British Journal of Dermatology	No relevant study population - sample includes people with mild to severe acne
Schwanitz, H. J. M., E.Internal versus topical tetracycline therapy of acne. 1984. Zeitschrift fur hautkrankheiten	Not in English language
Scott, A. M., Stehlik, P., Clark, J., Zhang, D., Yang, Z., Hoffmann, T., Mar, C. D., Glasziou, P.Blue-Light Therapy for Acne Vulgaris: A Systematic Review and Meta-Analysis. 2019. Annals of Family Medicine	Systematic review - references were checked for relevance
Semprini, A., Braithwaite, B., Corin, A., Sheahan, D., Tofield, C., Helm, C., Montgomery, B., Fingleton, J., Weatherall, M., Beasley, R. Randomised controlled trial of topical kanuka honey for the treatment of acne. 2016. BMJ Open	No relevant intervention - compairson of addition of topical 90% medicalgrade kanuka honey and 10% glycerine to standard antibacterial soap wash with antibacterial soap wash alone
Sen, A. K., S.,Chatterjee, R. N.,Sarkar, M.,Bhattacharjee, S.,Ram, A. K.Acomparativestudyof efficacy and safetyoftopical clindamycingelversus combination of clindamycingeland benzoylperoxidecreamin patients ofmildtomoderateacnevulgaris. 2013. Indian Journal of Pharmacology	No relevant article type - conference abstract
Shafiq, Y. N., B. S.,Rizwani, G. H.,Usman, M.,Shah, B. A.,Aslam, M.,Hina, B.Anti-acne activity of Casuarina equisetifolia bark extract: a randomized clinical trial. 2014. Bangladesh journal of pharmacology	No relevant intervention - Casuarina equisetifolia bark extract (5% cream)
Shaheen, J. A. K., M.,Kareem, A.,Ahmad, M.,Ansari, N. U. H.,Ahmad, I.Clinical evaluation of roxithromyin in acne vulgaris: Comparison of daily versus alternate day regimen. 2005. Journal of Pakistan Association of Dermatologists	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Shahid, J. K., T.Tretinoin cream versus benzoyl peroxide(10%) gel in the tropical treatment of mild acne vulgaris. 1996. Biomedica	Not obtainable
Shahlita, A. R. S., E. B.,Bauer, E.Topical erythromycin v clindamycin therapy for acne. A multicenter, double-blind comparison. 1984. Archives of Dermatology	No relevant study population - insufficient information to determine severity of acne
Shahmoradi, Z. I., F.,Siadat, A. H.,Ghorbaini, A.,Nilforoushzadeh, M. A.Comparison of topical 5% nicotinamid and 2% clindamycin gels in the treatment of the mild to moderate acne vulgaris: a double-blinded randomized clinical trial. 2015. Journal of isfahan medical school	Not in English language
Shahmoradi, Z. I., F.,Siadat, A. H.,Ghorbaini, A.Comparison of topical 5% nicotinamid gel versus 2% clindamycin gel in the treatment of the mild-moderate acne vulgaris: A double-blinded randomized clinical trial. 2013. Journal of Research in Medical Sciences	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS,

Reference	Reason for exclusion
	maintenance and refractory treatments
Shalita, A. M., B.,Menter, A.,Abramovits, W.,Loven, K.,Kakita, L.Tazarotene cream versus adapalene cream in the treatment of facial acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. 2005. Journal of drugs in dermatology : JDD	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Shalita, A. R. B., D. S.,Thiboutot, D. M.,Leyden, J. J.,Parizadeh, D.,Sefton, J.,Walker, P. S.,Gibson, J. R.Effects of tazarotene 0.1% cream in the treatment of facial acne vulgaris: Pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. 2004. Clinical Therapeutics	No relevant data reported - reports pooled result from 2 trials combined
Shalita, A. R. C., D. K.,Parish, L. C.,Bernstein, J. E.,Evans, C. S.The effects of topical nicotinamide on acne vulgaris. 1992. Journal of investigative dermatology	No relevant article type - conference abstract
Shalita, A. R. R., E. S.,Anderson, D. N.,Yavel, R.,Landow, S.,Lee, W. L.Compared efficacy and safety of tretinoin 0.1% microsphere gel alone and in combination with benzoyl peroxide 6% cleanser for the treatment of acne vulgaris. 2003. Cutis	No relevantinternvention - facial cleanser; No relevant study population - insufficient information to determine seveirty of acne and study is not relevant for PCOS, maintenance or refractory treatments
Shalita, A. R.Comparison of a salicylic acid cleanser and a benzoyl peroxide wash in the treatment of acne vulgaris. 1989. Clinical therapeutics	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Shalita, A. R.Comparison of a salicylic acid cleanser and a benzoyl peroxide wash in the treatment of acne vulgaris: COMPARACAO ENTRE SISTEMA DE LIMPEZA COM ACIDO SALICILICO E SOLUCAO DE PEROXIDO DE BENZOILA NO TRATAMENTO DO ACNE VULGARIS. 1998. Revista brasileira de medicina	Not in English language
Shalita, A. W., J. S.,Chalker, D. K.,Ellis, C. N.,Greenspan, A.,Katz, H. I.,Kantor, I.,Millikan, L. E.,Swinehart, T.,Swinyer, L.,et al.,A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. 1996. Journal of the American Academy of Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Sharma, A. D. G., P. D.,Sundaram, M.,Janaki, V. R.,Rege, V. L.,Bilimoria, F. E.,Arora, J.Topical lincomycin gel in acne vulgaris: A multicentric placebo controlled study. 2003. Indian Journal of Dermatology, Venereology and Leprology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS,

Reference	Reason for exclusion
	maintenance or refractory treatments
Sharquie,Treatment of acne vulgaris with 2% topical tea lotion. 2006. NA	No relevant intervention - 2% tea lotion
Sheehan-Dare, R. A. P.-S., J. W.,Cunliffe, W. J.A comparative study between topical clindamycin and oral minocycline in the treatment of acne vulgaris. 1989. Round table series - royal society of medicine	Duplicate record
Sheehan-Dare, R. A. P.-S., J.,Cunliffe, W. J.A double-blind comparison of topical clindamycin and oral minocycline in the treatment of acne vulgaris. 1990. Acta Dermato-Venereologica	No relevant data - insufficient data reported
Shen, W. T., Wu, Y., He, H. Q., Yu, Y., Qin, H. H., Fei, J. B., Wang, G. J.Efficacy and safety of artemether emulsion for the treatment of mild-to-moderate acne vulgaris: a randomized pilot study. 2020. Journal of Dermatological Treatment	No relevant intervention - artemether
Shetti, S. A. N., H. N.,Hanumantharaya, N.A randomized, open-label, comparative study of efficacy of low-dose continuous versus low-dose intermittent oral isotretinoin therapy in moderate-to-severe acne vulgaris. 2017. National Journal of Physiology, Pharmacy and Pharmacology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Shie Morteza, M., Hayati, Z., Namazi, N., Abdollahimajd, F.Efficacy and safety of oral silymarin in comparison with oral doxycycline and their combination therapy in the treatment of acne vulgaris. 2019. Dermatologic Therapy	No relevant intervention - silymarin
Shin JU, Lee SH, Jung JY, Lee JH.A split-face comparison of a fractional microneedle radiofrequency device and fractional carbon dioxide laser therapy in acne patients.. 2012. J Cosmet Laser Ther	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Shwetha, H. G., A.A comparative study of efficacy and safety of combination of topical 1% clindamycin and 0.1% adapalene with 1% clindamycin and 2.5% benzoyl peroxide in mild to moderate acne in a tertiary care hospital. 2013. Indian Journal of Pharmacology	No relevant article type - conference abstract
Sidgiddi, 2019Efficacy of oral isotretinoin in combination with desloratadine in the treatment of common vulgaris acne in Vietnamese Patients. 2019. Open Access Macedonian Journal of Medical Sciences	Duplication of Van 2019
Sidgiddi, S., Allenby, K., Okumu, F., Gautam, A.Bioavailability, Pharmacokinetics, and Transepidermal Water Loss of Short Contact Tazarotene Lotion 0.1% Versus Tazarotene (Tazorac^R) Cream 0.1. 2019. The Journal of Clinical & Aesthetic DermatologyJ Clin Aesthet Dermatol	The paper reports 2 studies, both do not meet inclusion criteria: the first one describes a non-relevant comparison and the second one does not reported severity of acne
Simpson, N. B. B., P. E.,Forster, R. A.,Cunliffe, W. J.The effect of topically applied progesterone on sebum excretion rate. 1979. British Journal of Dermatology	No relevant data reported - pharmokinetic study

Reference	Reason for exclusion
Simpson, N. B. M., K. A.5% Aluminium chloride hexahydrate and sebum excretion rate. 1982. Acta Dermato-Venereologica	Duplicate record
Singhi, M. G. B. R.Comparison of oral azithromycin pulse with daily doxycycline in the treatment of acne vulgaris. 2003. Indian journal of dermatology, venereology and leprology	No relevant study design - not RCT
Skidmore, R. K., R.,Walker, C.,Thomas, J.,Bradshaw, M.,Leyden, J.,Powala, C.,Ashley, R.Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. 2003. Archives of Dermatology	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Smit, F.Minocycline versus doxycycline in the treatment of acne vulgaris. A double-blind study. 1978. Dermatologica	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Smith, E. B. P., R. S.,McCabe, J. M.,Becker, L. E.Benzoyl peroxide lotion (20%) in acne. 1980a. Cutis	Duplicate record
Smith, J. G., Jr.,Chalker, D. K.,Wehr, R. F.The effectiveness of topical and oral tetracycline for acne. 1976. Southern Medical Journal	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Smith, M. A., Waterworth, P. M., & Curwen, M. P.A controlled trial of oral antibiotics in the treatment of acne vulgaris. 1962. British journal of dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Soldo-Belic, A. C., V.,Vujic-Podlipec, D.,Oremovic, L.,Sviben-Radovcic, Z.,Kostovic, K.,Nola, I.,Mateljic, V.Advantages of liposome-encapsulated 1% clindamycin solution versus 1% clindamycin solution in the therapy of acne vulgaris. 1999. Acta Dermatovenerologica Croatica	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Spellman, M. C. P., S. H.Efficacy and safety of azelaic acid and glycolic acid combination therapy compared with tretinoin therapy for acne. 1998. Clinical therapeutics	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments

Reference	Reason for exclusion
St Surin-Lord, S., Schlesinger, T. E., Guenin, E.Novel tretinoin 0.05% lotion for the oncedaily treatment of moderatetosevere acne vulgaris in a preadolescent and adolescent population. 2019. Journal of Clinical and Aesthetic Dermatology	No relevant data reported - reports pooled data of 2 trials combined
Stainforth, J. M.-H., S.,Papworth-Smith, J. W.,Eady, E. A.,Cunliffe, W. J.,Norris, J. F. B.,Simpson, N. B.,Cork, M. J.A single-blind comparison of topical erythromycin/zinc lotion and oral minocycline in the treatment of acne vulgaris. 1993. Journal of Dermatological Treatment	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Stankler, L.Pustular acne vulgaris. Rotational oral antibacterial therapy for 1 year. 1979. British Journal of Clinical Practice	No relevant study design - not RCT
Stein Gold, L., D., S.,Weiss, J.,Draelos, Z. D.,Ellman, H.,Stuart, I. A.A novel topical minocycline foam for the treatment of moderate-to-severe acne vulgaris: Results of 2 randomized, double-blind, phase 3 studies. 2019. Journal of the American Academy of Dermatology	No relevant intervention - FMX101 4% is a topical minocycline foam not available in the UK
Stein Gold, L., Pariser, D. M., Guenin, E.Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate and Severe Acne Vulgaris in Females: Effect of Age on Efficacy and Tolerability. 2019. Journal of drugs in dermatology : JDD	Not obtainable
Stein Gold, L., T., J.,Cruz-Santana, A.,Papp, K.,Poulin, Y.,Schlessinger, J.,Gidner, J.,Liu, Y.,Graeber, M.A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. 2009. Cutis	No relevant data reported - a repeat publication of Gollnick 2009
Stein Gold, L..,Werschler, W. P., & Mohawk, J.Â Adapalene/benzoyl peroxide gel 0.3%/2.5%: effective acne therapy regardless of age or gender. 2017. Journal of drugs in dermatology	No relevant data reported - post hoc analysis by gender and age of Stein Gold & Weiss 2016.
Stein Gold, L.Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and benzoyl peroxide (3.75%) aqueous gel in moderate and severe acne vulgaris subpopulations. 2015. Journal of Drugs in Dermatology	No relevant data reported - post hoc analysis by acne severity of Pariser 2014
Stein Gold, L.Efficacy and tolerability of fixed-combination acne treatment in adolescents. 2013. Cutis	No relevant data reported - publication from Thiboutot 2008
Stinco, G. P., F.,Valent, F.,Errichetti, E.,Di Meo, N.,Trevisan, G.,Patrone, P.Efficacy, tolerability, impact on quality of life and sebostatic activity of three topical preparations for the treatment of mild to moderate facial acne vulgaris. 2016. Giornale italiano di dermatologia e venereologia	Not in English language
Stoughton, R. B. C., R. C.,Gange, R. W.,Walter, J. F.Double-blind comparison of topical 1 percent clindamycin phosphate (Cleocin T) and oral tetracycline 500 mg/day in the treatment of acne vulgaris. 1980. Cutis	No relevant study design - not RCT
Stoughton, R. B. R., W.Topical clindamycin in the control of acne vulgaris. 1976. Cutis	No relevant article type - non-systematic review
Strauss, J. S. G., A. B.,Jones, T.,Koo, J. Y.,Leyden, J. J.,Lucky, A.,Pappas, A. A.,McLane, J.,Leach, E. E.Concomitant administration of vitamin E does not change the side effects of isotretinoin as used in acne vulgaris: a randomized trial. 2000. Journal of the American Academy of Dermatology	No relevant intervention - isotretinoin with vitamin E
Strauss, J. S., Leyden, J. J., Lucky, A. W., Lookingbill, D. P., Drake, L. A., Hanifin, J. M., Lowe, N. J., Jones, T. M., Stewart, D. M., Jarratt, M. T., Katz, I., Pariser, D. M., Pariser, R. J., Tschen, E., Chalker, D. K., Rafal, E. S., Savin, R. P., Roth, H. L., Chang, L. K., Baginski, D. J.,	No relevant comparison - micronized isotretinoin vs standard isotretinoin

Reference	Reason for exclusion
Kempers, S., McLane, J., Eberhardt, D., Leach, E. E., Bryce, G., Hong, J.A randomized trial of the efficacy of a new micronized formulation versus a standard formulation of isotretinoin in patients with severe recalcitrant nodular acne. 2001. Journal of the American Academy of DermatologyJ Am Acad Dermatol	
Stuttgen, G. I., H.,Mahrle, G.Oral vitamin A acid in treatment of dermatoses with pathologic keratinization. 1977. International Journal of Dermatology	No relevant study design - not RCT
Stuttgen, G.Oral vitamin A acid therapy. 1975. Acta Dermato-Venereologica. Supplementum	No relevant study design - not RCT
Sun, X., Qian, F., He, Y., Gu, X., Di, W.Safety and Efficacy of Combined Oral Contraceptive Ethinyl Estradiol/Drospirenone (YAZ) in Chinese Women: A Single-Arm, Open-Label, Multicenter, Post-Authorization Study. 2020. Advances in Therapy	No relevant study design - not a RCT
Sutono, T.Efficacy of Garcinia mangostana L. (mangosteen rind extract) to reduce acne severity. 2013. Medical Journal of Indonesia	No relevant intervention - extract of mangosteen rind
Swinyer, L. J. S., T. A.,Britt, M. R.Topical agents alone in acne. A blind assessment study. 1980. JAMA	No relevant intervention - suboptimal doses
Taaffe, A. C., W. J.,Cove, J.Topical erythromycin in acne - a double-blind study. 1981. British Journal of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Tabasum, H. A., T.,Anjum, F.,Rehman, H.The effect of Unani antiacne formulation (Zimade Muhasa) on acne vulgaris: A singleblind, randomized, controlled clinical trial. 2014. Journal of Pakistan Association of Dermatologists	No relevantstudy population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Takigawa, M. T., Y.,Shimada, S.,Furukawa, F.,Noguchi, N.,Ito, T.Clinical and bacteriological evaluation of adapalene 0.1% gel plus nadifloxacin 1% cream versus adapalene 0.1% gel in patients with acne vulgaris. 2013. Journal of Dermatology	No relevant intervention - adapalene 0.1% gel plus nadifloxacin 1% cream not available in the UK
Tan, J. G., H. P. M.,Loesche, C.,Ma, Y. M.,Gold, L. S.Synergistic efficacy of adapalene 0.1%-benzoyl peroxide 2.5% in the treatment of 3855 acne vulgaris patients. 2011. Journal of Dermatological Treatment	No relevant data reported - pooled analysis of Thiboutout 2007, Stein Gold 2009, and Gollnick 2009
Tan, J. G., L. S.,Schlessinger, J.,Brodell, R.,Jones, T.,Cruz, A.,Kerrouche, N.,Jarratt, M.Short-term combination therapy and long-term relapse prevention in the treatment of severe acne vulgaris. 2012a. Journal of Drugs in Dermatology	Study design does not meet protocol eligibility criteria - combines individual patient data from 2 RCTs
Tan, J. G., L. S.,Schlessinger, J.,Brodell, R.,Jones, T.,Dhuin, J. C.,Jarratt, M.Combination of adapalene-benzoyl peroxide and oral doxycycline is efficacious in short-term therapy: Maintenance with adapalene-benzoyl peroxide prevents relapse in treatment of severe acne vulgaris. 2012b. Pediatric Dermatology	No relevant article type - conference abstract
Tang, X., Li, C., Ge, S., Chen, Z., Lu, L.Efficacy of photodynamic therapy for the treatment of inflammatory acne vulgaris: A systematic review and meta-analysis. 2020. Journal of Cosmetic DermatologyJ	Systematic review - references were checked for relevance
Tanghetti, E. A., Werschler, W. P., Lain, T., Guenin, E., Martin, G., Pillai, R.Tazarotene 0.045% Lotion for Once-Daily Treatment of	Not obtainable

Reference	Reason for exclusion
Moderate-to-Severe Acne Vulgaris: Results from Two Phase 3 Trials. 2020. Journal of drugs in dermatology : JDD	
Tanghetti, E. D., S.,Green, L.,Del Rosso, J.,Draelos, Z.,Leyden, J.,Shalita, A.,Glaser, D. A.,Grimes, P.,Webster, G.,Barnett, P.,Le Gall, N.Randomized comparison of the safety and efficacy of tazarotene 0.1% cream and adapalene 0.3% gel in the treatment of patients with at least moderate facial acne vulgaris. 2010. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis by sex of Draelos 2007
Tanghetti, E. H., J. C.,Oefelein, M. G.The efficacy and tolerability of dapsone 5% gel in female vs male patients with facial acne vulgaris: Gender as a clinically relevant outcome variable. 2012. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis by sex of Draelos 2007
Tanghetti, E. H., J.,Baldwin, H.,Kircik, L.,Bai, Z.,Alvandi, N.Once-Daily Topical Dapsone Gel, 7.5%: Effective for Acne Vulgaris Regardless of Baseline Lesion Count, With Superior Efficacy in Females. 2018. Journal of drugs in dermatology : JDD	No relevant data reported - post hoc analysis by sex of Stein Gold 2016
Tangjaturonrusamee, C. R., P.,Ditre, C. M.Comparison of pneumatic broadband light plus adapalene gel 0.3% versus adapalene gel 0.3% monotherapy in the treatment of mild to moderate acne. 2016. Cutis	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Tanzi, E. L. A., T. S.Comparison of a 1450-nm Diode Laser and a 1320-nm Nd:YAG Laser in the Treatment of Atrophic Facial Scars: A Prospective Clinical and Histologic Study. 2004. Dermatologic Surgery	Duplicate record
Tao, S. Q. X., R. S.,Li, F.,Cao, L.,Fan, H.,Fan, Y.,Yang, L. J.Efficacy of 3.6% topical ALA-PDT for the treatment of severe acne vulgaris. 2016. European Review for Medical & Pharmacological Sciences	No relevant study design - not RCT
Taub, A. F.A comparison of intense pulsed light, combination radiofrequency and intense pulsed light, and blue light in photodynamic therapy for acne vulgaris. 2007. Journal of drugs in dermatology : JDD	No relevant data reported - number of participants assigned to each group not reported
Tay, C. H.Treatment of acne vulgaris with topical vitamin A acid. 1978. Singapore Medical Journal	No relevant study design - not RCT
Taylor, S. C. C.-B., F. E.,McMichael, A.,Downie, J. B.,Rodriguez, D. A.,Alexis, A. F.,Callender, V. D.,Alvandi, N.Efficacy, safety, and tolerability of topical dapsone gel, 7.5% for treatment of acne vulgaris by Fitzpatrick skin phototype. 2018. Journal of Drugs in Dermatology	No relevant data reported - post-hoc analysis of Eichenfeld 2016 & Stein Gold 2016 trials
Taylor, S. C.Utilizing combination therapy for ethnic skin. 2007. Cutis	No relevant data reported - subgroup analysis by skin type of Kircik 2007
Thappa, D. M. D., J.Nodulocystic acne: Oral gugulipid versus tetracycline. 1994. Journal of Dermatology	No relevant intervention - Guggulsterone
Thiboutot, D. A., D. F.,Lemay, A.,Washenik, K.,Roberts, J.,Harrison, D. D.A randomized, controlled trial of a low-dose contraceptive containing 20 mug of ethinyl estradiol and 100 mug of levonorgestrel for acne treatment. 2001. Fertility and Sterility	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS,

Reference	Reason for exclusion
	maintenance and refractory treatments
Thiboutot, D. A., S.,Soto, P.Efficacy and tolerability of adapalene 0.3% gel compared to tazarotene 0.1% gel in the treatment of acne vulgaris. 2008. Journal of drugs in dermatology : JDD	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Thiboutot, D. M. K., L.,McMichael, A.,Cook-Bolden, F. E.,Tyring, S. K.,Berk, D. R.,Chang-Lin, J. E.,Lin, V.,Kaoukhov, A.Efficacy, safety, and dermal tolerability of dapsone gel, 7.5% in patients with moderate acne vulgaris: A pooled analysis of two phase 3 trials. 2016. Journal of Clinical and Aesthetic Dermatology	No relevant population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Thomas, D. R. R., S.,Smith, E. B.Comparison of topical erythromycin 1.5 percent solution versus topical clindamycin phosphate 1.0 percent solution in the treatment of acne vulgaris. 1982. Cutis	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Thomsen, R. J. S., A.,Knutson, D.,Strauss, J. S.Topical clindamycin treatment of acne. Clinical, surface lipid composition, and quantitative surface microbiology response. 1980. Archives of Dermatology	No relevant intervention - topical 1% clindamycin hydrochloride hydrate not licensed in the UK
Thorneycroft, I. H. S., F. Z.,Bradshaw, K. D.,Ballagh, S. A.,Nichols, M.,Weber, M. E.Effect of low-dose oral contraceptives on androgenic markers and acne. 1999. Contraception	No relevant study population - sample includes women with and without acne, no further details reported
Thuangtong, R. T., C.,Rattanaumpawan, P.,Ditre, C. M.Comparison of salicylic acid 30% peel and pneumatic broadband light in the treatment of mild to moderately severe facial acne vulgaris. 2017. Cutis; cutaneous medicine for the practitioner	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Ting, W.Randomized, observer-blind, split-face study to compare the irritation potential of 2 topical acne formulations over a 14-day treatment period. 2012. Cutis; cutaneous medicine for the practitioner	No relevant study population - insufficient information to determine severity of acne
Toossi, P. F., M.,Malekzad, F.,Mohtasham, N.,Kimyai-Asadi, A.Subantimicrobial-dose doxycycline in the treatment of moderate facial acne. 2008. Journal of drugs in dermatology : JDD	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS,

Reference	Reason for exclusion
	maintenance or refractory treatments
Trice, E. R.Treatment of acne vulgaris with Secomat -S lotion. 1966. Virginia Medical Monthly	No relevant study design - not RCT
Tschen, E. H. K., H. I.,Jones, T. M.,Monroe, E. W.,Kraus, S. J.,Connolly, M. A.,Levy, S. F.A combination benzoyl peroxide and clindamycin topical gel compared with benzoyl peroxide, clindamycin phosphate, and vehicle in the treatment of acne vulgaris. 2001. Cutis; cutaneous medicine for the practitioner	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Tuchin, V. V. G., E. A.,Bashkatov, A. N.,Simonenko, G. V.,Odoevskaya, O. D.,Altshuler, G. B.A Pilot Study of ICG Laser Therapy of Acne Vulgaris: Photodynamic and Photothermolysis Treatment. 2003. Lasers in Surgery and Medicine	No relevant data reported - sebum excretion data
Tucker, S. B. T., R.,Cochran, R.,Flannigan, S. A.Comparison of topical clindamycin phosphate, benzoyl peroxide, and a combination of the two for the treatment of acne vulgaris. 1984. British Journal of Dermatology	No relevant data - insufficient data reported
Tucker, S. B. T., T.,Cochran, R.Comparison of topical clindamycin phosphate, benzoyl peroxide and a combination of the two, for the treatment of acne vulgaris. 1990. Indian journal of dermatology, venerology and leprology	Duplicate record
Tunca, M. A., A.,Ozmen, I.,Erbil, H.Topical nadifloxacin 1% cream vs. topical erythromycin 4% gel in the treatment of mild to moderate acne. 2010. International Journal of Dermatology	No relevant intervention - topical nadifloxacin 1% cream not available in the UK
Turan, A. S., H.,Baskan, E. B.,Turan, H.,Aydogan, K.Efficacy of topical sodium sulfacetamide in the treatment of mild and moderate acne vulgaris: a randomized, comparative study. 2012. Turkderm deri hastaliklari ve frengi arsivi	Not in English language
Tye, M. J. L., E.Acne treated with wet compresses followed by corticosteroid cream. 1968. Arizona Medicine	No relevant study design - not RCT
Tzung, T. Y. W., K. H.,Huang, M. L.Blue light phototherapy in the treatment of acne. 2004. Photodermatology Photoimmunology and Photomedicine	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Uebelhoer, N. S. B., M. A.,Dover, J. S.,Arndt, K. A.,Rohrer, T. E.Comparison of stacked pulses versus double-pass treatments of facial acne with a 1,450-nm laser. 2007. Dermatologic Surgery	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Uede, M. K., C.,Yonei, N.,Furukawa, F.,Yamamoto, Y.Persistent effects of adapalene gel after chemical peeling with glycolic acid in patients with acne vulgaris. 2013. Open dermatology journal	Participants were not selected on their complete/partial response to the first treatment
Ullah, G. N., S. M.,Bhatti, Z.,Ahmad, M.,Bangash, A. R.Comparison of oral azithromycin with oral doxycycline in the treatment of acne vulgaris. 2014. Journal of Ayub Medical College, Abbottabad : JAMC	No relevant study population - insufficient information to determine

Reference	Reason for exclusion
	severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Ustuner, P. G., A. T.,Demirbilek, M.Clinical and bacteriological evaluation of nadifloxacin 1% cream versus erythromycin 4% gel in the treatment of mild-to-moderate facial acne vulgaris: a randomized study. 2015. Turkiye klinikleri journal of medical sciences	No relevant intervention - nadifloxacin 1% cream not available in the UK
Vali, A. F., G.,Zaghian, N.,Koosha, M.The efficacy of topical solution of 0.3% ciprofloxacin in treatment of mild to moderate acne vulgaris. 2009. Iranian Red Crescent Medical Journal	No relevant intervention - topical ciprofloxacin cream
Van der Meeren, H. L. M. V. d. S., J. G.,Stijnen, T.Dose-response relationship in isotretinoin therapy for conglobate acne. 1983. Dermatologica	Relevant outcomes only reported graphically - cannot extract useful data
Van Neste, D. T., D.,Decroix, J.Imidazoles and benzoyl peroxide: A comparative trial of two treatment schedules. 1986. Dermatologica	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
van Wayjen, R. G. v. d. E., A.Experience in the long-term treatment of patients with hirsutism and/or acne with cyproterone acetate-containing preparations: efficacy, metabolic and endocrine effects. 1995. Experimental & Clinical Endocrinology & Diabetes	No relevant study design - not RCT
Van, d. V., dMHLM,Stijnen, T.The treatment of acne conglobata with 13-cis retinoic acid (isotretinoin). 1983. Nederlands tijdschrift voor geneeskunde	Not in English language
Van, T. N. D. T., L.,Nguyen Trong, H.,Chau Van, T.,Trinh Minh, T.,Thi Minh, P. P.,Dinh Huu, N.,Tran Cam, V.,Le Huyen, M.,Tran Hau, K.,Gandolfi, M.,Satolli, F.,Feliciani, C.,Tirant, M.,Vojvodic, A.,Lotti, T.Efficacy of oral isotretinoin in combination with desloratadine in the treatment of common vulgaris acne in Vietnamese Patients. 2019. Open Access Macedonian Journal of Medical Sciences	No relevant internvention - oral Desloratadine; also no relevant study population - insufficient information to determine severity of acne
Vartiainen, M. d. G., H.,Broekmeulen, C. J.Comparison of the effect on acne with a combiphasic desogestrel-containing oral contraceptive and a preparation containing cyproterone acetate. 2001. European Journal of Contraception & Reproductive Health Care	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Vasarinsh, P.Benzoyl Peroxide- Sulfur Lotions in Acne Vulgaris- A Controlled Study. 1969. Cutis; cutaneous medicine for the practitioner	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Vaswani, N. P., R. K.,Bhutani, L. K.,Ramachandran, K.Topical therapy of acne vulgaris with retinoic acid and erythromycin lotion. 1989. Indian journal of dermatology, venerology and leprology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments

Reference	Reason for exclusion
Vaswani, N. P., R. K.Treatment of acne vulgaris with anti-androgens. 1990. Indian journal of dermatology, venerology and leprology	No relevant intervention - cimetidine
Vatanchi, M. F., G.,Siegel, D.Updates on novel research in laser and photodynamic therapy for treatment of acne vulgaris. 2017. Journal of the american academy of dermatology	Duplicate record
Venier, A. C., P.,Salvatori, S.,Varricchio, M. C.Topical treatment of acne vulgaris with clindamycin phosphate solution (double blind clinical trial). 1985. Chronica dermatologica	Not in English language
Verma, K. C. S., A. S.,Dhamija, S. K.Oral zinc sulphate therapy in acne vulgaris: a double-blind trial. 1980. Acta Dermato-Venereologica	No relevant study population - insufficient details to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Vermeulen, A. R., R.Effects of cyproterone acetate plus ethinylestradiol low dose on plasma androgens and lipids in mildly hirsute or acneic young women. 1988. Contraception	No relevant study population - sample includes people with hirsuitism or acne but no details of acne participants provided and study is not relevant for PCOS, maintenance or refractory treatments
Verschoore, M. L., A.,Wolska, H.,Jablonska, S.,Czernielewski, J.,Schaefer, H.Efficacy and safety of CD 271 alcoholic gels in the topical treatment of acne vulgaris. 1991. British Journal of Dermatology	No relevant intervention - CD 271 alcoholic gel
Verschoore, M. P., M.,Czernielewski, J.,Sorba, V.,Clucas, A.Adapalene 0.1% gel has low skin-irritation potential. 1997. Journal of the American Academy of Dermatology	No relevant study population - participants did not have acne
Voravutinon, N. R., J.,Sadhwani, D.,Iyengar, S.,Alam, M.A comparative split-face study using different mild purpuric and subpurpuric fluence level of 595-nm pulsed-dye laser for treatment of moderate to severe acne vulgaris. 2016. Dermatologic Surgery	No relevant study design - not RCT
Wahab, M. A. R., M. H.,Monamie, N. S.,Jamaluddin, M.,Khondker, L.,Afroz, W.Isotretinoin versus weekly pulse dose azithromycin in the treatment of acne- A comparative study. 2008. Journal of Pakistan Association of Dermatologists	No relevant comparison - azithromycin
Walton, S. C., W. J.,Lookingbill, P.,Keczkes, K.Lack of effect of topical spironolactone on sebum excretion. 1986. British Journal of Dermatology	No relevant article type - letter to editor
Wang, A. P., Tu, P., Ji, S. Z., Wu, Y., Shen, Y., Zhu, X. J.Clinical efficacy of benzoyl peroxide gel with different concentrations in acne vulgaris. 2003. Chinese journal of dermatology	Not in English language
Wang, H. W. L., T.,Zhang, L. L.,Guo, M. X.,Stepp, H.,Yang, K.,Huang, Z.,Wang, X. L.Prospective study of topical 5-aminolevulinic acid photodynamic therapy for the treatment of moderate to severe acne vulgaris in Chinese patients. 2012. Journal of Cutaneous Medicine & Surgery	No relevant study design - not RCT
Wang, J. H. W., B.,Zheng, R. D.Effective observation on external using tretinoin cream treating common acne (Chinese). 2001. China journal of leprosy & skin diseases	Not in English language
Wang, Q. Y., D.,Liu, W.,Chen, J.,Lin, X.,Cheng, S.,Li, F.,Duan, X.Use of optical fiber imported intra-tissue photodynamic therapy for	No relevant data - insufficient data reported

Reference	Reason for exclusion
treatment of moderate to severe acne vulgaris. 2016. Medical Science Monitor	
Wang, S. Q. C., J. T.,Flor, M. E.,Zelickson, B. D.Treatment of inflammatory facial acne with the 1,450 nm diode laser alone versus microdermabrasion plus the 1,450 nm laser: A randomized, split-face trial. 2006. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Wangsuwan, S., Meephansan, J.Comparative study of photodynamic therapy with riboflavin-tryptophan gel and 13% 5-aminolevulinic acid in the treatment of mild to moderate acne vulgaris. 2019. Clinical, Cosmetic and Investigational Dermatology	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Wanitphakdeedecha, R. I., T.,Phothong, W.,Eimpunth, S.,Manuskiatti, W.Local and systemic effects of low-level light therapy with light-emitting diodes to improve erythema after fractional ablative skin resurfacing: a controlled study. 2019. Lasers in Medical Science	Duplicate record
Wanitphakdeedecha, R., Tavechodperathum, N., Tantrapornpong, P., Suphatsathienkul, P., Techapichetvanich, T., Eimpunth, S., Manuskiatti, W.Acne treatment efficacy of intense pulsed light photodynamic therapy with topical licochalcone A, l-carnitine, and decanediol: A spilt-face, double-blind, randomized controlled trial. 2020. Journal of Cosmetic DermatologyJ	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Waranuch, N. P., P.,Yakaew, S.,Nakyai, W.,Grandmottet, F.,Onlom, C.,Srivilai, J.,Viyoch, J.Antiacne and antiblotch activities of a formulated combination of Aloe barbadensis leaf powder, Garcinia mangostana peel extract, and Camellia sinensis leaf extract. 2019. Clinical, Cosmetic and Investigational Dermatology CCID	No relevant intervention - a combination of Aloe barbadensis leaf extract, Garcinia mangostana peel extract, and Camellia sinensis leaf extract
Warren, M. R., J.,Arbit, D.,Sevilla, C.,Flack, M.The effects on weight of a low-dose oral contraceptive in the treatment of women with moderate acne vulgaris. 2001. Fertility and sterility	No relevant article type - conference abstract
Webster, G. C., D. I.,Quiring, J.,Vogelson, C. T.,Slade, H. B.A combined analysis of 2 randomized clinical studies of tretinoin gel 0.05% for the treatment of acne. 2009. Cutis; cutaneous medicine for the practitioner	No relevant dat reported - reports pooled results of 2 trials combined
Webster, G. F. G., L.,Poulin, Y. P.,Solomon, B. A.,Loven, K.,Lee, J.A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. 2002. Cutis; cutaneous medicine for the practitioner	Not obtainable
Webster, G. F.Safety and efficacy of Tretin-X compared with Retin-A in patients with mild-to-severe acne vulgaris. 2006. Skinmed	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS,

Reference	Reason for exclusion
	maintenance or refractory treatments
Webster, G. R., P.,Gold, M. H.,Mraz, S.,Calvarese, B.,Chen, D.Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and low concentration benzoyl peroxide (2.5%) aqueous gel in moderate or severe acne subpopulations. 2009. Journal of Drugs in Dermatology	No relevant data reported - pblication from Thiboutot 2008
Webster, G. T., D. M.,Chen, D. M.,Merikle, E.Impact of a fixed combination of clindamycin phosphate 1.2%-benzoyl peroxide 2.5% aqueous gel on health-related quality of life in moderate to severe acne vulgaris. 2010. Cutis	No relevant data reported - reports quality of life outcomes
Weiss, J. G., L. S.,Leoni, M.,Rueda, M. J.,Liu, H.,Tanghetti, E.Customized single-agent therapy management of severe inflammatory acne: A randomized, double-blind, parallel-Group, controlled study of a new treatment - Adapalene 0.3%-benzoyl peroxide 2.5% gel. 2015. Journal of Drugs in Dermatology	No relevant data reported - subgroup analysis of people with severe acne participating in Stein Gold 2016
Weiss, J. S. G., L.,Leoni, M.,Rueda, M. J.,Liu, H.,Tanghetti, E.Customized Single-agent Therapy Management of Severe Inflammatory Acne: A Randomized, Double-blind, Parallel-group, Controlled Study of a New Treatment--Adapalene 0.3%-Benzoyl Peroxide 2.5% Gel. 2015. Journal of Drugs in Dermatology: JDD	Duplicate record
Weissmann, A. W., A.,Plewig, G.Reduction of bacterial skin flora during oral treatment of severe acne with 13-cis retinoic acid. 1981. Archives of Dermatological Research	No relevant study design - not RCT
Weltert, Y. C., S.,Gibaud, C.,Courau, S.,Pechenart, P.,Sirvent, A.,Girard, F.Double-blind clinical assessment of the efficacy of a 4% nicotinamide gel (Exfoliac NC Gel) versus a 4% erythromycin gel in the treatment of moderate acne with a predominant inflammatory component. [French, English]. 2004. Nouvelles Dermatologiques	Not in English language
Wen, X. L., Y.,Hamblin, M. R.Photodynamic therapy in dermatology beyond non-melanoma cancer: An update. 2017. Photodiagnosis and Photodynamic Therapy	Duplicate record
Wexler, L.Two controlled studies of a topical steroid preparation in the treatment of acne vulgaris. 1968. Applied Therapeutics	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Wiegell, S. R. W., H. C.Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. 2006a. Journal of the American Academy of Dermatology	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Wilhelm, K. P. W., D.,Neumeister, C.,Zsolt, I.,Schwantes, U.Lack of irritative potential of nadifloxacin 1% when combined with other topical anti-acne agents. 2012. Clinical and Experimental Dermatology	No relevant study population - participants did not have acne and study is not relevant for PCOS, maintenance or refractory treatments
Wilkinson, R. D. A., J. E.,Murray, J. J.,Craig, G. E.Benzoyl peroxide and sulfur: foundation for acne management. 1966. Canadian Medical Association Journal	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS,

Reference	Reason for exclusion
	maintenance or refractory treatments
Winkler, U. H. F., H.,Mulders, J. A.Cycle control, quality of life and acne with two low-dose oral contraceptives containing 20 microg ethinylestradiol. 2004a. Contraception	Duplicate record
Winkler, U. H. F., H.,Mulders, JapaCycle control, quality of life and acne with two low-dose oral contraceptives containing 20 mug ethinylestradiol. 2004b. Contraception	No relevant study population - participants did not have acne
Wishart, J. M.An open study of Triphasil and Diane 50 in the treatment of acne. 1991. The Australasian journal of dermatology	No relevant population - insufficient information reported about acne severity and study is not relevant for PCOS, maintenance or refractory treatments
Witkowski, J. A. P., L. C.Chlorhydroxyquin-Benzoyl Peroxide Lotion in the Treatment of Acne - An Objective Evaluation. 1969. Cutis; cutaneous medicine for the practitioner	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Wolf, J. E., Jr.Safety and tolerability in the MORE trial. 2006. Cutis	No relevant study design - not RCT
Wong, R. C. K., S.,Heezen, J. L.Oral ibuprofen and tetracycline for the treatment of acne vulgaris. 1984. Journal of the American Academy of Dermatology	No relevant comparison
Woolery-Lloyd, H. B., L.,Ikeno, H.Sodium L-ascorbyl-2-phosphate 5% lotion for the treatment of acne vulgaris: a randomized, double-blind, controlled trial. 2010. NA	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Worret, I. A., W.,Zahradnik, H. P.,Andreas, J. O.,Binder, N.Acne resolution rates: Results of a single-blind, randomized, controlled, parallel phase III trial with EE/CMA (Belara) and EE/LNG (Microgynon). 2001. Dermatology	No relevant data reported
Xia, J. H., G.,Hu, D.,Geng, S.,Zeng, W.Concomitant use of 1,550-nm nonablative fractional laser with low-dose isotretinoin for the treatment of acne vulgaris in asian patients: A randomized split-face controlled study. 2018. Dermatologic Surgery	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Xing,Fire needle therapy for moderate-severe acne: A PRISMA systematic review and meta-analysis of randomized controlled trials. 2019. NA	No relevant intervention - systematic review about fire needle therapy
Xu, H. L.Supplemented Raising and Sinking powder for treating ninety cases with acne due to blood heat stagnation. 2015b. Henan traditional chinese medicine [henan zhong yi]	No relevant intervention - supplemented raising and sinking powder combined with isotretinoin erythromycin gel

Reference	Reason for exclusion
Xu,Supplemented Raising and Sinking powder for treating ninety cases with acne due to blood heat stagnation. 2015a. NA	Duplicate record
Yang, G. L. Z., M.,Wang, J. M.,He, C. F.,Luo, Y.,Liu, H. Y.,Gao, J.,Long, C. Q.,Bai, J. R.Short-term clinical effects of photodynamic therapy with topical 5-aminolevulinic acid for facial acne conglobata: an open, prospective, parallel-arm trial. 2013. Photodermatology, Photoimmunology & Photomedicine	No relevant study design - not RCT
Yang, Z., Zhang, Y., Lazic Mosler, E., Hu, J., Li, H., Zhang, Y., Liu, J., Zhang, Q.Topical benzoyl peroxide for acne. 2020. Cochrane Database of Systematic Reviews	Systematic review - references were checked for relevance
Yeung, C. K. S., S. Y.,Bjerring, P.,Yu, C. S.,Kono, T.,Chan, H. H.A comparative study of intense pulsed light alone and its combination with photodynamic therapy for the treatment of facial acne in Asian skin. 2007. Lasers in Surgery and Medicine	No relevant study population - insufficient information to determine severity of acne and study is not relevant for PCOS, maintenance or refractory treatments
Yilmaz, O. S., N.,Yuksel, E. P.,Aydin, F.,Ozden, M. G.,Canturk, T.,Turanli, A.Evaluation of 532-nm KTP laser treatment efficacy on acne vulgaris with once and twice weekly applications. 2011. Journal of Cosmetic & Laser Therapy	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Yong, C. C.Benzoyl peroxide gel therapy in acne in Singapore. 1979. International Journal of Dermatology	No relevant study population - sample includes 11% people with 11% acne
Yoon, J. H. P., E. J.,Kwon, I. H.,Kim, C. W.,Lee, G. S.,Hann, S. K.,Kim, K. H.,Kim, K. J.Concomitant use of an infrared fractional laser with low-dose isotretinoin for the treatment of acne and acne scars. 2014. Journal of dermatological treatment	No relevant intervention - laser treatment for acne scarring
Yoon, J. Y. K., H. H.,Min, S. U.,Thiboutot, D. M.,Suh, D. H.Epigallocatechin-3-gallate improves acne in humans by modulating intracellular molecular targets and inhibiting P. acnes. 2013. Journal of Investigative Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Yu, Z. S., J.,Lew-Kaya, D.,Walker, P.,Yu, D.,Tang-Liu, D. D.Pharmacokinetics of tazarotene cream 0.1% after a single dose and after repeat topical applications at clinical or exaggerated application rates in patients with acne vulgaris or photodamaged skin. 2003. Clinical Pharmacokinetics	No relevant study population - sample includes people with acne or photodamage - relevant outcomes not reported separately
Zachariae, H.Topical vitamin-A-acid in acne. 1980. Acta dermato-venereologica	No relevant study design - not RCT
Zander, E. W., S.Treatment of acne vulgaris with salicylic acid pads. 1992. Clinical Therapeutics	Duplicate record
Zarate, A. M., V. B.,Greenblatt, R. B.Effect of an antiandrogen, 17-alpha-methyl-B-nortestosterone, on acne and hirsutism. 1966. Journal of Clinical Endocrinology & Metabolism	No relevant study design - not RCT

Reference	Reason for exclusion
Zeichner, J. A. H., M.,Linkner, R. V.,Wong, V.Efficacy and safety of tretinoin 0.025%/clindamycin phosphate 1.2% gel in combination with benzoyl peroxide 6% cleansing cloths for the treatment of facial acne vulgaris. 2013. Journal of Drugs in Dermatology	No relevant study population - sample includes people with mild to severe acne and study is not relevant for PCOS, maintenance or refractory treatments
Zeichner, J. A. P., R. V.,Haddican, M.,Wong, V.Efficacy and safety of a ceramide containing moisturizer followed by fixed-dose clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel in the morning in combination with a ceramide containing moisturizer followed by tretinoin 0.05% gel in the evening for the treatment of facial acne vulgaris. 2012. Journal of Drugs in Dermatology: JDD	No relevant study design - not RCT
Zeichner, J. A., Harper, J. C., Roberts, W. E., Guenin, E., Bhatt, V., Pillai, R.Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. 2019. Journal of Clinical and Aesthetic Dermatology	Not obtainable
Zeichner, J. A.The Efficacy and Tolerability of a Fixed Combination Clindamycin (1.2%) and Benzoyl Peroxide (3.75%) Aqueous Gel in Adult Female Patients with Facial Acne Vulgaris. 2015. The Journal of Clinical & Aesthetic Dermatology	Reports post hoc analysis of >=25 years old for Pariser 2014
Zeichner, J.Strategies to minimize irritation and potential iatrogenic post-inflammatory pigmentation when treating acne patients with skin of color. 2011. Journal of Drugs in Dermatology: JDD	Duplicate record
Zeng, R., Liu, Y., Zhao, W., Yang, Y., Wu, Q., Li, M., Lin, T.A split-face comparison of a fractional microneedle radiofrequency device and fractional radiofrequency therapy for moderate-to-severe acne vulgaris. 2020. Journal of Cosmetic Dermatology.	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Zeng, X. L., W. L.,Zhao, T.Effects of Chinese medical facial mask comprehensive therapy in treating acne vulgaris. 2012b. Zhongguo zhong xi yi jie he za zhi zhongguo zhongxiyi jiehe zazhi = chinese journal of integrated traditional and western medicine	Duplicate record
Zeng,Effects of Chinese medical facial mask comprehensive therapy in treating acne vulgaris. 2012a. NA	Not in English language
Zhang, J., Zhang, X., He, Y., Wu, X., Huang, J., Huang, H., Lu, C.Photodynamic therapy for severe facial acne vulgaris with 5% 5-aminolevulinic acid vs 10% 5-aminolevulinic acid: A split-face randomized controlled study. 2020. Journal of Cosmetic DermatologyJ	Duplicate publication
Zhang, X. M.Clinical observations on the efficacy of autohemotherapy plus pricking-cupping bloodletting in treating common acne. 2015. Shanghai journal of acupuncture and moxibustion [shang hai zhen jiu za zhi]	Not in English language
Zhou, B. R. Z., T.,Bin Jameel, A. A.,Xu, Y.,Guo, S. L.,Wang, Y.,Permatasari, F.,Luo, D.The efficacy of conditioned media of adipose-derived stem cells combined with ablative carbon dioxide fractional resurfacing for atrophic acne scars and skin rejuvenation. 2016b. Journal of Cosmetic and Laser Therapy	No relevant study population - sample includes people with acne scars
Zhou, L.Pipa Qingfei Decoction combined with External Application of Acne Tincture in Treating Acne for 120 Cases. 2016c. Chinese	Duplicate record

Reference	Reason for exclusion
medicine modern distance education of china [zhong guo zhong yi yao xian dai yuan cheng jiao yu]	
Zhou, Y. Q. Y., R. J.The Curative Effect Observation of Tretinoin Capsule Combined with Tretinoin Cream in Treating Acne Vulgaris (Chinese). 2000. Chinese journal of dermatovenereology	Not in English language
Zhou,Pipa Qingfei Decoction combined with External Application of Acne Tincture in Treating Acne for 120 Cases. 2016a. NA	Not obtainable
Zhu, X. J. T., P.,Zhen, J.,Duan, Y. Q.Adapalene gel 0.1%: effective and well tolerated in the topical treatment of acne vulgaris in Chinese patients. 2001. Cutis; cutaneous medicine for the practitioner	Reported outcomes relevant for the network meta-analysis but not in enough detail to include in the analysis. Outcomes were not relevant for pairwise comparisons - including PCOS, maintenance and refractory treatments
Zouboulis, C. C. F., T. C.,Wohlrab, J.,Barnard, J.,Alio, A. B.Study of the efficacy, tolerability, and safety of 2 fixed-dose combination gels in the management of acne Vulgaris. 2009. Cutis	No relevant study population - sample does not meet the inclusion criteria for mild-to-moderate or moderate-to-severe acne and study is not relevant for PCOS, maintenance or refractory treatments

1

2 **Economic studies and studies reporting utility data**

3 **Table 24: Excluded economic studies and reasons for their exclusion**

Economic studies	Reason for exclusion
Borgonjen RJ, de Lange JA, van de Kerkhof PCM. Guideline-based clinical decision support in acne patients receiving isotretinoin: improving adherence and cost-effectiveness. J Eur Acad Dermatol Venereol. 2017; 31(10): ve440-e442	Intervention outside scope (clinical decision support)
Bossuyt L, Bosschaert J, Richert B, Cromphaut P, Mitchell T, Al Abadie M, Henry I, Bewley A, Poyner T, Mann N, Czernielewski J. Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. Eur J Dermatol 2003; 13(2):130-5	Only intervention costs (drug acquisition) considered
Czilli T, Tan J, Knezevic S, Peters C. Cost of Medications Recommended by Canadian Acne Clinical Practice Guidelines. J Cutan Med Surg. 2016; 20(6): 542-545	Only intervention costs (drug acquisition) considered
Haddock ES, Eichenfield LF. High-dose isotretinoin: Bigger dents in wallets? J Am Acad Dermatol. 2016 Aug;75(2):e75-6	Letter
Hansen, L. A., Vermeulen, L. C., Bland, S., & Wetterneck, T. B. (2007). Guideline for Low-Cost Antimicrobial Use in the Outpatient Setting. American Journal of Medicine, 120(4), 295-302	Not an economic evaluation - identification of drugs with low acquisition cost that are effective
Joish VN, Boklage S, Lynen R, Schmidt A, Lin J. Use of drospirenone/ ethinyl estradiol (DRSP/EE) among women with acne reduces acne treatment-related resources. J Med Econ. 2011; 14(6): 681-9	Retrospective analysis of administrative data

Economic studies	Reason for exclusion
Lee YH, Liu G, Thiboutot DM, Leslie DL, Kirby JS. A retrospective analysis of the duration of oral antibiotic therapy for the treatment of acne among adolescents: investigating practice gaps and potential cost-savings. J Am Acad Dermatol. 2014; 71(1): 70-6	Retrospective analysis of administrative data
Leyden JJ, Tanghetti EA, Miller B, Ung M, Berson D, Lee J. Once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.1% microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. Cutis 2002; 69(2 Suppl):12-9	Only intervention costs (drug acquisition) considered
Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, Williams HC. Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne. Health Technol Assess 2005; 9(1)	Average CE ratios reported, no incremental analysis and not possible to estimate ICERs as costs per intervention not reported
Ozolins M, Eady EA, Avery AJ, Cunliffe WJ, Po AL, O'Neill C, Simpson NB, Walters CE, Carnegie E, Lewis JB, Dada J, Haynes M, Williams K, Williams HC. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet 2004; 364(9452): 2188-95	Average CE ratios reported, no incremental analysis and not possible to estimate ICERs as costs per intervention not reported
Penna P, Meckfessel MH, Preston N. Fixed-Dose Combination Gel of Adapalene and Benzoyl Peroxide plus Doxycycline 100 mg versus Oral Isotretinoin for the Treatment of Severe Acne: Efficacy and Cost Analysis. Am Health Drug Benefits. 2014; 7(1):37-45	Only drug acquisition costs considered; efficacy based on naïve synthesis of RCT arm data
Rosamilia LL. Economic stewardship in acne management. Cutis. 2018; 102(1): 8-9	Not an economic evaluation
Rubin CB, Lipoff JB. Primary Nonadherence in Acne Treatment: The Importance of Cost Consciousness. JAMA Dermatol. 2015; 151(10):1144-5	Letter - not an economic evaluation
Straight CE, Lee YH, Liu G, Kirby JS (2015). Duration of oral antibiotic therapy for the treatment of adult acne: a retrospective analysis investigating adherence to guideline recommendations and opportunities for cost-savings. Journal of the American Academy of Dermatology, 72(5), 822-827	Retrospective analysis of administrative data
Tassavor M, Payette MJ. Estimated cost efficacy of U.S. Food and Drug Administration-approved treatments for acne. Dermatol Ther. 2019; 32(1): e12765	Letter - description of costs associated with different pharmacological interventions (drug + lab testing + clinician visit costs)
Webster GF, Guenther L, Poulin YP, Solomon BA, Loven K, Lee J. A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. Cutis. 2002 Feb;69(2 Suppl):4-11	Only intervention costs (drug acquisition) considered
Yuwnate AH, Chandane RD, Sah RK, et al. Efficacy and cost-effective analysis of benzyl benzoate, permethrin, and ivermectin in the treatment of scabies and azithromycin versus doxycycline in the treatment of acne vulgaris. Natl J Physiol Pharm Pharmacol. 2019; 9(10): 977-982	Economic evaluation conducted in India
Zeitany AE, Bowers EV, Morrell DS. High-dose isotretinoin has lower impact on wallets: A cost analysis of dosing approaches. J Am Acad Dermatol. 2016; 74(1):174-6	Letter; cost analysis using data based on a letter reporting a retrospective analysis

1 **Table 25: Excluded studies reporting utility data and reasons for their exclusion**

Studies reporting utility data	Reason for exclusion
Afsar FS, Seremet S, Demirlendi Duran H, Karaca S, Mumcu Sonmez N. Sexual quality of life in female patients with acne. Psychol Health Med. 2020; 25(2):171-178	No utility data for acne health states
Altunay IK, Özkur E, Dalgard FJ, et al. Psychosocial Aspects of Adult Acne: Data from 13 European Countries. Acta Derm Venereol. 2020 Feb 5;100(4):adv00051	No utility data reported
Balkrishnan R, Kulkarni AS, Cayce K, Feldman SR. Predictors of healthcare outcomes and costs related to medication use in patients with acne in the United States. Cutis. 2006 Apr;77(4): 251-5	No utility data reported
Dreno B, Bordet C, Seite S, Taieb C, 'Registre Acné' Dermatologists. Acne relapses: impact on quality of life and productivity. J Eur Acad Dermatol Venereol. 2019; 33(5): 937-43	No utility data reported
Seidler AM, Bayoumi AM, Goldstein MK, Cruz PD Jr, Chen SC. Willingness to pay in dermatology: assessment of the burden of skin diseases. J Invest Dermatol. 2012; 132(7):1785-90	Utility data obtained from people valuing their own health state
VanBeek MJ. Integrating patient preferences with health utilities: a variation on health-related quality of life. Arch Dermatol. 2008; 144(8): 1037-41	Editorial - no utility data reported

2

3

Appendix L – Research recommendations

Research recommendations for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Research question - physical modalities

What is the effectiveness of physical modalities (such as light devices) in the treatment of acne vulgaris or persistent acne vulgaris-related scarring?

Why this is important

Physical treatments for acne are popular with people because they have the benefit of treating a local area without systemic effects. They can be used in people with co-morbidities or side effects where other treatments are unsuitable. They are currently available in the private sector but there is no standardisation of treatment modalities or duration. Many different physical therapies have been described for acne including:

- Comedone extraction
- Phototherapy – including UVB, intense pulsed light, blue and red light
- Photochemical therapy (e.g. photodynamic therapy)
- Laser
- Photopneumatic therapy (e.g. intense pulsed light + vacuum)
- Photothermal therapy (eg gold nanoparticles +light or laser)

Physical treatments are also used for acne scarring. These include:

- Punch excision
- CO2 laser
- Dermabrasion
- Radiofrequency (e.g. fractional microneedling, bipolar)

Further research is required to determine the most effective physical treatments for acne and acne scarring. This could open the way to wider availability in the NHS.

Table 26: Research recommendation rationale

Research question	What is the effectiveness of physical modalities (such as light devices) in the treatment of acne vulgaris or persistent acne vulgaris-related scarring?
Why is this needed	
Importance to 'patients' or the population	Physical treatments for acne are popular with people because they have the benefit of treating a local area without systemic effects. They can be used in people with co-morbidities or side effects where other treatments are unsuitable. There is evidence from small studies that physical therapies including various light sources with or without addition of chemical or physical photosensitiser may be effective in all grades of acne. There is also some evidence to support CO2 laser treatment for acne scarring. However, the studies are too small or of insufficient quality to allow recommendations to be made.
Relevance to NICE guidance	Currently physical treatments for acne vulgaris cannot be recommended. Weak recommendation can be made for CO2 laser for acne scarring, but stronger evidence is required to allow a stronger recommendation. which would lead to wider availability on NHS.

Research question	What is the effectiveness of physical modalities (such as light devices) in the treatment of acne vulgaris or persistent acne vulgaris-related scarring?
Relevance to the NHS	Acne vulgaris is the most common skin condition affecting the majority of teenagers and young adults. Acne scarring leads to lifelong psychological distress for some people. Physical treatments for acne could provide an alternative for people unwilling or unable to use other treatment modalities. With more evidence of effectiveness and cost effectiveness these treatments may become available on the NHS. Physical treatments for acne scarring may benefit the NHS by reducing psychological morbidity.
National priorities	There are 2 national priorities, one is to improve young people's mental health and another is to reduce antibiotic prescribing to prevent resistance. • Improving the mental health of young people is a national priority. Improving acne can have a positive impact on mental health. Rates of depression and suicide are increasing in the under 25-year-old age group, especially amongst men 20-25 years old. (suicides in the UK 2019 ons.gov.uk). In 2018 the government produced a paper 'Transforming children's and young people's mental health provision', including improving services for those 16-25 years old. This aligns with a need to understand support required for young people with acne vulgaris https://www.gov.uk/government/consultations/transforming-children-and-young-peoples-mental-health-provision-a-green-paper/quick-read-transforming-children-and-young-peoples-mental-health-provision • Acne has traditionally been treated with long courses of antibiotics. If any particular type of physical treatment could be identified as having a positive impact on acne vulgaris then it may lead to a decreased need for antibiotics. Antibiotic resistance is rising in the UK and the government wants to optimise antibiotic prescribing to prevent the development of superbugs. Keeping people well informed would therefore help to address this priority (Tackling antimicrobial resistance 2019–2024 The UK's five-year national action plan Published 24 January 2019. HM Government) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf
Current evidence base	It is hard to draw conclusions from the current evidence. There are a lack of existing randomised controlled trials in physical treatments for acne and acne scarring, and those which have been done have been variable quality on small numbers of participants.
Equality	Access to any recommended physical treatments for acne or acne scarring currently differs across the country and according to socioeconomic group. They are mainly available in the private sector.
Feasibility	Physical treatments need to be supervised, even if they are delivered at home. There would be significant NHS costs associated with setting up provision for physical treatments, but this may be offset by benefits. A time commitment from particpants would be required.
Other comments	Not applicable

Table 27: Research recommendation characteristics table - (a) relates to acne management and (b) persistent acne vulgaris-related scarring management

Criterion	Explanation
Population	a) Adults with acne vulgaris b) Adults with persistent acne-related scarring
Intervention	a) any physical intervention for acne, for example: • Blue light therapy weekly for 3 months b) any physical intervention for acne scarring, for example • CO2 laser single or multiple treatments
Comparison	(a) no treatment or another active treatment. b) no treatment for acne scarring
Outcome	a) Participant reported improvement, clinician reported improvement in lesion count b) Participant reported improvement, clinician reported improvement in scar appearance a) Recurrence a&b) Side effects: participant and clinician reported, including pigmentary changes and scarring
Study design	Randomised controlled trial
Timeframe	a) • 3-6 months (intervention) • 6 month (follow-up) b) • Intervention period • 6 and 12 month follow up
Additional information	Ideally longer term follow-up data collection would also be useful.

Research question - chemical peels

What is the effectiveness of chemical peels in the treatment of acne vulgaris or persistent acne vulgaris-related scarring?

Why this is important

Chemical peels are used to remove the surface of the skin. Peels may be 'superficial' for treatment of acne vulgaris, removing the dead layer of skin, or 'deeper' for atrophic scar management. They are usually applied repeatedly as a course of treatment. Chemical peels are currently not used as standard treatment in the NHS but are available to buy by the public and can be provided by private aesthetic practitioners. The use of chemical peels has potential to change acne and acne scarring management, as an alternative to those who cannot use, tolerate, or are resistant, to other treatments. Therefore, further research is needed to establish its effectiveness.

Table 28: Research recommendation rationale

Research question	What is the effectiveness of chemical peels in the treatment of acne vulgaris or persistent acne vulgaris-related scarring?
Why is this needed	

Research question	What is the effectiveness of chemical peels in the treatment of acne vulgaris or persistent acne vulgaris-related scarring?
Importance to 'patients' or the population	The use of chemical peels has potential to change acne and acne scarring management, as an alternative to those who cannot use, tolerate, or are resistant, to other treatments. Therefore further research is required to increase the robustness of the evidence
Relevance to NICE guidance	Chemical peels are currently not routinely offered as a treatment of acne vulgaris or acne associated scarring in the NHS and there is insufficient evidence to make a strong recommendation.
Relevance to the NHS	Acne vulgaris is the most common skin condition affecting the majority of teenagers and young adults. Acne scarring leads to lifelong psychological distress for some people. Chemical peels for acne could provide an alternative for people unwilling or unable to use other treatment modalities. With more evidence of effectiveness and cost effectiveness these treatments may become available on the NHS. Chemical peels for acne scarring may benefit the NHS by reducing psychological morbidity
National priorities	• Acne has traditionally been treated with long courses of antibiotics. If chemical peels would be effective in the management of acne vulgaris then it may lead to a decreased need for antibiotics. Antibiotic resistance is rising in the UK and the government wants to optimise antibiotic prescribing to prevent the development of superbugs. Keeping people well informed would therefore help to address this priority (Tackling antimicrobial resistance 2019–2024 The UK's five-year national action plan Published 24 January 2019. HM Government) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf • There are safety concerns about the use of oral retinoids (https://www.gov.uk/government/publications/isotretinoin-for-severe-acne-uses-and-effects) so provision of alternative therapy would be welcome if safe and effective. • Improving the mental health of young people is a national priority. If chemical peels are safe and effective to improve acne it may help improve self-esteem and confidence. Rates of depression and suicide are increasing in the under 25-year-old age group, especially amongst men 20-25 years old. (suicides in the UK 2019 ons.gov.uk). In 2018 the government produced a paper 'Transforming children's and young people's mental health provision', including improving services for those 16-25 years old. More effective acne treatment can have a positive impact on mental wellbeing and therefore addresses this priority. https://www.gov.uk/government/consultations/transforming-children-and-young-peoples-mental-health-provision-a-green-paper/quick-read-transforming-children-and-young-peoples-mental-health-provision
Current evidence base	There was no evidence for the use of chemical peels, either alone or combined, in moderate to severe acne treatment. There was some evidence that chemical peels may be effective in the treatment of mild to moderate acne. However, there was a low number of studies with small sample size. None of the studies compared effectiveness of chemical peels against placebo. The evidence base for chemical peels in treatment of acne associated scarring was low to very low quality with small sample size and limited follow-up time.
Equality	None specified

Research question	What is the effectiveness of chemical peels in the treatment of acne vulgaris or persistent acne vulgaris-related scarring?
Feasibility	This research is feasible
Other comments	Not applicable

Table 29: Research recommendation characteristics table – (a) relates to acne management and (b) persistent acne vulgaris-related scarring management

Criterion	Explanation
Population	a) Adults with acne vulgaris b) Adults with persistent acne-related scarring
Intervention	a) Chemical peels for the treatment acne b) Chemical peels for the treatment of acne associated scarring
Comparison	Any other peel Any other treatment Placebo
Outcome	a) Participant reported improvement, clinician reported improvement in lesion count b) Participant reported improvement, clinician reported improvement in scar appearance a) Recurrence a&b) Side effects: participant and clinician reported, including pigmentary changes and scarring
Study design	Randomised controlled parallel or split-face trial
Timeframe	Likely treatment over 3 months with follow up to 3 years
Additional information	Not applicable

Research question – hormone-modifying agents in the treatment of acne

What is the effectiveness of hormone modifying agents in the treatment of acne vulgaris?

Why this is important

Hormone modifying agents are used in the management of acne based on clinical expertise and experience. These treatments may be beneficial for people requiring long-term maintenance or those who do not wish to take oral antibiotics or isotretinoin. There is currently limited evidence of efficacy and long-term safety.

Hormone modifying agents may include:

- Oral spironolactone
- Oral cyproterone acetate (alone or combined with ethinyl oestradiol)
- Oral combined oral contraceptive preparations containing drospirenone or other anti-androgenic progesterones
- Oral metformin (indirect antiandrogenic effect)
- Topical clascoterone

Further research is required to determine the efficacy of hormone modifying agents in the treatment of acne vulgaris.

1 **Table 30: Research recommendation rationale**

Research question	What is the effectiveness of hormone modifying agents in the treatment of acne vulgaris?
Why is this needed	
Importance to 'patients' or the population	Hormone modifying agents may be an alternative option for people with acne who do not wish to take or have contraindications to oral antibiotics or isotretinoin. It can be used long-term with minimal monitoring and can form part of the maintenance treatment in acne. There is insufficient evidence from the review to make recommendations though it is used in clinical practice for selective patients.
Relevance to NICE guidance	Hormone modifying agents are currently not included in the recommendations for acne management. More research and high-quality evidence may lead to widening the recommendation on acne management and help individuals access these treatments as part of their care.
Relevance to the NHS	Acne vulgaris is the most common skin condition affecting the majority of teenagers and young adults. In some people, acne may persist or develop in adulthood. Hormone modifying agents could provide an alternative option in the treatment of acne, which requires minimal monitoring and may be offered in primary care and for maintenance treatment.
National priorities	There are 2 national priorities, one is to improve young people's mental health, and another is to reduce antibiotic prescribing to prevent resistance. There is also an MHRA review underway regarding isotretinoin prescribing due to concerns about safety. • Improving the mental health of young people is a national priority. Improving acne can have a positive impact on mental health. Rates of depression and suicide are increasing in the under 25-year-old age group, especially amongst men 20-25 years old. (suicides in the UK 2019 ons.gov.uk). In 2018 the government produced a paper 'Transforming children's and young people's mental health provision', including improving services for those 16-25 years old. This aligns with a need support young people with acne vulgaris, highlighting the importance of timely treatment and its impact on the person's mental wellbeing. https://www.gov.uk/government/consultations/transforming-children-and-young-peoples-mental-health-provision-a-green-paper/quick-read-transforming-children-and-young-peoples-mental-health-provision • Antibiotic resistance is rising in the UK and the government wants to optimise antibiotic prescribing to prevent the development of multi-drug resistant pathogens. If hormone modifying agents have been shown to be an effective treatment in acne, this will lead to reduction in antibiotic prescribing. (Tackling antimicrobial resistance 2019–2024 The UK's five-year national action plan Published 24 January 2019. HM Government) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf • Hormone modifying agents may be an alternative treatment option for individuals who do not wish to or have contraindications to isotretinoin. This is important as there is currently an ongoing review by the MHRA on the safety of isotretinoin.

Research question	What is the effectiveness of hormone modifying agents in the treatment of acne vulgaris?
Current evidence base	There is limited evidence available for the use of hormone modifying agents in the treatment of acne. The trials were small, with differing primary outcomes and were of varying quality. It is hard to draw conclusions from the current evidence.
Equality	The use of hormone modifying agents in the treatment of acne currently differs across the country and may be more readily available in the private sector. Oral hormone modifying agents which are anti-androgenic are used in females. Topical hormone modifying agents have been shown to be safe in males and children aged 9 and above.
Feasibility	Hormone modifying agents are low cost, and available in primary care. Minimal monitoring is required for long-term use.
Other comments	Not applicable

Table 31: Research recommendation characteristics table - (a) relates to acne management in adult females and (b) acne management in adult or adolescent

Criterion	Explanation
Population	a) Adult females with acne vulgaris b) Adults or adolescents with acne vulgaris
Intervention	a) Any oral or topical anti-androgen, for example: • Spironolactone • Oral cyproterone acetate • Topical clascoterone b) Any topical anti-androgen, for example • Topical clascoterone
Comparison	No treatment or another active treatment.
Outcome	• Participant reported improvement, clinician reported improvement in lesion count • Recurrence • Side effects: participant and clinician reported, including pigmentary changes and scarring
Study design	Randomised controlled trial
Timeframe	Intervention period • 6 months (intervention) • 6 month (follow-up)
Additional information	Ideally longer term follow-up data collection would also be useful.

Appendix M – Network Meta-analysis report from the NICE Guidelines Technical Support Unit (TSU)

Network meta-analysis report for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Prepared by: NICE Guidelines TSU, Bristol (Caitlin Daly and Nicky J. Welton)

Introduction

The purpose of this analysis was to estimate the comparative effectiveness of various interventions for treating people with mild to moderate acne.

The outcomes included in this analysis were efficacy, discontinuation for any reason, and discontinuation due to side effects. Risk of scarring was considered, but there was insufficient evidence to conduct a network meta-analysis (NMA).

Methods

Inclusion of split-face trials

Split-face randomised controlled trials (RCTs) were eligible for inclusion in the efficacy analysis if they provided data on the difference in percentage change from baseline acne lesion counts and its corresponding standard error, which appropriately accounted for within-patient correlation.

Split-face RCTs were not eligible for the discontinuation for any reason outcome, as the discontinuation results could not be attributed to a particular treatment.

Split-face RCTs (Tangjaturonrusamee 2016, Zheng 2019) were eligible for the discontinuation due to side effects outcome. However, this required the estimation of additional parameters to account for censoring, and there were insufficient data to estimate this. Consequently, split-face RCTs were not included in the discontinuation due to side effects analysis.

Efficacy: intention to treat (ITT) vs. Completers Data

In the efficacy analysis, summary data from an ITT analysis were prioritised over a completer analysis within RCTs. If ITT data were available the sample size of each treatment arm k of trial i, $n_{i,k}$ was the number randomised to arm k, but if ITT data were not available, the number of completers was used as the sample size for each arm in the analysis.

Prioritization of Efficacy Data

Let $x_{j,i,k}$ and $y_{j,i,k}$ be the lesion counts at baseline and follow-up, respectively, for individual j, treatment arm k of trial i. Let $p_{j,i,k} = \frac{(x_{j,i,k} - y_{j,i,k})}{x_{j,i,k}} = 1 - \frac{y_{j,i,k}}{x_{j,i,k}}$ be the proportionate reduction in lesion counts. To be included in the analysis of efficacy data, parallel RCTs had to provide enough data to calculate one of the following prioritised sets of summary count data:

a. The mean percent change from baseline (pCFB) count, $\overline{P}_{i,k} = \frac{1}{n_{i,k}} \sum_{j=1}^{n_{i,k}} p_{j,i,k}$, and its standard error, $se_{\overline{P}_{i,k}}$, for each treatment arm k,

OR

the mean difference in percent change from baseline count between treatment arms 1 and k, $MD_{\bar{P}_{i,k}} = \bar{P}_{i,k} - \bar{P}_{i,1}$, and its standard error, $se\left(MD_{\bar{P}_{i,k}}\right)$. Trials with more than 2 arms also needed to provide a measure of the covariance between the relative effects, $Cov\left(MD_{\bar{P}_{i,j}}, MD_{\bar{P}_{i,k}}\right), j \neq k$.

b. The mean baseline count, $\bar{X}_{i,k} = \frac{1}{n_{i,k}} \sum_{j=1}^{n_{i,k}} x_{j,i,k}$, the mean change from baseline (CFB), $\bar{C}_{i,k} = \frac{1}{n_{i,k}} \sum_{j=1}^{n_{i,k}} \left(x_{j,i,k} - y_{j,i,k}\right)$, and their corresponding standard errors, $se_{\bar{X}_{i,k}}, se_{\bar{C}_{i,k}}$, respectively, for each treatment arm k.

c. The mean baseline count, $\bar{X}_{i,k}$, the mean count at follow-up, $\bar{Y}_{i,k} = \frac{1}{n_{i,k}} \sum_{j=1}^{n_{i,k}} y_{j,i,k}$, their corresponding standard errors, $se_{\bar{X}_{i,k}}, se_{\bar{Y}_{i,k}}$, respectively, for each treatment arm k, and the correlation between the baseline and follow-up means, ρ.

An exception to the above prioritised list was made if a trial reported inflammatory and non-inflammatory counts, in which case (b) and (c) were prioritised to enable inclusion of the combined inflammatory and non-inflammatory counts, see 'Efficacy: combining lesion counts'.

As mentioned earlier, split-face trials had to provide enough data to calculate the mean difference in pCFB count between treatment arms 1 and k, $MD_{\bar{P}_{i,k}}$, where the standard error, $se\left(MD_{\bar{P}_{i,k}}\right)$, had accounted for within-patient variability.

Each trial included in the analysis contributed data on one of the following prioritised lesion types, where lesions at the top of the list were preferred:

i. Total lesion count
ii. Inflammatory count
iii. Pustule count
iv. Papule count
v. Nodule count
vi. Cyst count
vii. Non-inflammatory count

Trials that only reported efficacy measures based on a scale, rather than lesion counts, were also considered. To include these data in the analysis of efficacy counts, we required reliable evidence from trials reporting summary data on both lesion counts and validated scales to model the relationship between the two. However, there were insufficient data to model this relationship, and so no studies reporting efficacy measures based on a scale were included.

Efficacy: Combining Lesion Counts

Where RCTs did not report total lesion counts, but reported counts for multiple types of lesions, an effort was made to try to combine these counts across lesion types. For example, adding a sub- script l for lesion type to all notation and using a superscript $total$ to indicate the summary for total lesion counts, summaries for total lesion counts can be obtained from sub-types at baseline:

1
$$\bar{X}_{i,k}^{total} = \sum_{l=1}^{n_{types}} \bar{X}_{i,k,l}$$

$$\left(se_{\bar{X}_{i,k}}^{total}\right)^2 = \sqrt{\sum_{l=1}^{n_{types}} \left(se_{\bar{X}_{i,k,l}}^2\right) + 2\sum_{l \neq m} \mathrm{cov}(\bar{X}_{i,k,l}, \bar{X}_{i,k,m})}$$

2 The same approach was used to obtain mean change from baseline, $\bar{C}_{i,k}^{total}$, and follow-up,
3 $\bar{Y}_{i,k}^{total}$, for total lesion counts by combining summaries for sub-types.

4 In all cases, assumptions about the correlation between the outcomes on the different
5 lesions were required to properly estimate the standard errors. No RCT included in the
6 analysis reported this, and no other reliable source of evidence in the literature was found.
7 As such, we derived the correlations between lesion counts in trials reporting the SDs for
8 each lesion type and the SD for their total. This was possible for inflammatory and non-
9 inflammatory counts, where the correlation may be calculated as (Casella 2002):

10
$$\rho = \frac{\left(sd^{total}\right)^2 - \left(sd^{\text{inflammatory}}\right)^2 - \left(sd^{\text{non-inflammatory}}\right)^2}{2sd^{\text{inflammatory}}sd^{\text{non-inflammatory}}}.$$

11 We observed a wide variation of correlations across studies and outcomes. We preferred the
12 correlation values between baseline counts, as the variation in these counts is not subjected
13 to other sources of variation that arise during treatment. The median of the correlations
14 between the inflammatory and non-inflammatory baseline counts was 0.26, and this value
15 was assumed for baseline, follow-up and CFB counts.

16 The correlation between pustules and papules counts could also be derived from one RCT
17 (Poli 2005), which reported summary statistics for these lesion types, and reported their sum
18 as the inflammatory count (Casella 2002):

19
$$\rho = \frac{\left(sd^{\text{inflammatory}}\right)^2 - \left(sd^{\text{pustules}}\right)^2 - \left(sd^{\text{papules}}\right)^2}{2sd^{\text{pustules}}sd^{\text{papules}}}.$$

20 However, this was a small study (total sample size = 81) and it was unclear if the correlations
21 derived in this study were representative of the population. As such, we did not combine
22 pustule and papule counts.

23 ***Efficacy Data Imputation***

24 Some RCTs reported the median baseline, follow-up, CFB, or pCFB counts, rather than the
25 mean. In these trials, we assumed that the counts were normally distributed such that the
26 mean count was approximately equal to the median count.

27 Where a trial did not directly report information to calculate the standard error of the mean
28 outcome (baseline, follow-up, CFB, or pCFB counts) the standard deviations (SDs), $sd_{i,k}$,
29 were derived based on other information reported in the trial as described below and
30 standard errors obtained as $se_{i,k} = sd_{i,k} \Big/ \sqrt{n_{i,k}}$.

31 **Imputing SDs based on Interquartile Range (IQR)**

32 (for RCTs: Seaton 2003, Charakida 2007)

Let $IQR_{i,k}$ represent the interquartile range, i.e., the difference between the first and third quartile lesion counts, in treatment arm k. Then, assuming that the counts are normally distributed (Wiebe 2006),

$$sd_{i,k} \approx \frac{IQR_{i,k}}{1.35}.$$

Imputing SDs based on Range

(for RCT: Wiegell 2006)

Let $\min_{i,k}, \max_{i,k}$ represent the minimum and maximum lesion counts, respectively, in treatment arm k. Then, assuming that the counts are normally distributed (Wiebe 2006),

$$sd_{i,k} \approx \frac{\max_{i,k} - \min_{i,k}}{4}.$$

Imputing SDs based on Confidence Interval Limits

If a RCT reported the $100(1-\alpha)\%$ confidence interval (CI) limits for arm-level summaries or a mean difference, the standard error would be derived as

$$se_{i,k} = \frac{\text{upper limit}_{i,k} - \text{lower limit}_{i,k}}{2z_{1-\alpha/2}},\ se\left(MD_{i,k}\right) = \frac{\text{upper limit}_{i,k} - \text{lower limit}_{i,k}}{2z_{1-\alpha/2}}.$$

where $z_{1-\alpha/2}$ is the $1-\alpha/2$ quantile of the standard normal distribution. When a CI corresponded to a MD, the SDs of both treatment groups were assumed to be equal and were imputed from the standard error of the mean difference,

$$sd_{i,1} = sd_{i,k} = \frac{se\left(MD_{i,k}\right)}{\sqrt{\frac{1}{n_{i,1}} + \frac{1}{n_{i,k}}}}.$$

If a RCT (Shalita 2005) only reported one of the $100(1-\alpha)\%$ CI limits for arm-level summaries or a mean difference, the standard error was derived as

$$se_{i,k} = \frac{\left|\text{mean} - \text{limit}_{i,k}\right|}{z_{1-\alpha/2}},\ se\left(MD_{i,k}\right) = \frac{\left|MD_{i,k} - \text{limit}_{i,k}\right|}{z_{1-\alpha/2}}.$$

Imputing SDs based on p-values

If an exact p-value was reported, then the SD is inferred exactly. If an RCT reported a p-value in the form of "<0.05", then SDs were imputed assuming a p-value = 0.05 (or the upper limit of the specified range). This is a conservative approach as this provides an upper limit for the SD. If an RCT reported a p-value as "significant", but did not state the significance level, a p-value of 0.05 was assumed. If an RCT reported a p-value as "non-significant" or in the form of ">0.05", then no p-value was assumed, and thus a SD could not be imputed.

P-values corresponding to between-group comparisons

[for RCTs: Katsambas 1989 study A, Mills 1992, Henderson 1995, Redmond 1997, Sommer 1997, Shalita 1999, Lucky 2001, Rizer 2001, Cunliffe 2002b, Wolf 2003, Alirezai 2005, Thiboutout 2006, Iraji 2007, Thiboutout 2007, Gollnick 2009, Tirado-Sanchez 2009, Eichenfield 2013, Ragab 2014, Bernhardt 2016, Xu 2016, Dayal 2017, Dayal 2020 (non UK studies: Chalker 1987, Shalita 1996, Webster 2001, Berger 2007b, Plewig 2009, Eichenfield 2016]

Where an RCT only provided information on uncertainty in the form of p-values corresponding to hypothesis tests of mean differences, $MD_{i,k}$, the corresponding standard errors for parallel RCTs were derived as

$$se\left(MD_{i,k}\right)=\frac{\left|MD_{i,k}\right|}{t^{-1}\left(\text{p-value}_{i,k}, df=n_{i,1}+n_{i,k}-2\right)},$$

where $t^{-1}\left(\cdot, df\right)$ is the the inverse quantile of a t distribution with df degrees of freedom. This imputation assumes p-values correspond to a one-sided t-test (Wiebe 2006, Altman 2011). The SDs were assumed to be equal across treatment arms, giving

$$sd_{i,1}=sd_{i,k}=\frac{se\left(MD_{i,k}\right)}{\sqrt{\frac{1}{n_{i,1}}+\frac{1}{n_{i,k}}}}.$$

In multi-arm trials, all possible SDs were imputed from the reported p-values and an average of the imputed SDs across arms was used as the imputed SD for each arm in the analysis. This approach was used to impute the standard deviation of the reference treatment in two multi-arm RCTs (Thibotout 2006, Gollnick 2009) for the baseline model used in the economic analysis (see Appendix J).

In some parallel group RCTs (Mills 1986 study I, Mills 1986 study II, Mills 1986 study III, Handstead 1985, and the non-UK RCT Spellman 1998) reporting the mean baseline and follow-up counts, only a p-value corresponding to the mean difference in the CFB counts was reported. In these cases, the standard error of the mean difference in CFB counts was first calculated, and the SDs of the CFB count were derived as described above assuming these were equal across treatment arms. The SDs of the baseline counts were then imputed, assuming the baseline and follow-up SDs were equal,

$$sd_{X_{i,k}}=sd_{Y_{ik}}=\frac{sd_{C_{i,k}}}{\sqrt{2\left(1-\rho\right)}}$$

where ρ was the assumed correlation between the baseline and follow-up counts.

In split-face RCTs (Na 2007, Jung 2009, Kwon 2019), we only needed to derive the standard error of the mean difference in percentage change from baseline counts, as this was what was required for the analysis. Again, the p-values were assumed to correspond to a one-sided t-test:

$$se\left(MD_{\bar{P}_i}\right)=\frac{\left|MD_{\bar{P}_i}\right|}{t^{-1}\left(\text{p-value}_i, df=n_i-1\right)}.$$

Imputing Follow-up and pCFB SDs based on Baseline SDs

One RCT (Tu 2001) reported mean pCFB counts, but the only measure of uncertainty reported in the trial were the SDs of the baseline counts. To impute the pCFB SDs, a weighted linear regression model was fitted to data from RCTs that reported both baseline SDs and pCFB SDs, regardless of the type of lesion count. The weights for each arm k in study i were calculated as $w_{i,k} = \frac{n_{i,k}}{\sum_i \sum_k n_{i,k}}$. This gave the following regression equation (R^2 = 0.15) from which the pCFB SDs were imputed:

$$sd_{P_{i,k}} = 0.4676 sd_{X_{i,k}} + 28.1267$$

for each treatment arm k.

Similarly, another RCT (Chottawornsak 2019) reported mean baseline and follow-up counts, but the only measure of uncertainty reported in that trial were the SDs of baseline counts. The follow-up SDs were imputed using a weighted linear regression model, fitted to data from RCTs that reported both baseline SDs and follow-up SDs, regardless of the type of lesion count. The weights for each arm k in study i were calculated as $w_{i,k} = \frac{n_{i,k}}{\sum_i \sum_k n_{i,k}}$. This gave the following regression equation (R^2 = 0.56) from which the follow-up SDs were imputed:

$$sd_{Y_{i,k}} = 0.65735 sd_{X_{i,k}} + 2.07803$$

for each treatment arm k.

Imputing SEs in split-face RCTs based on assumed within-patient correlation

In two split-face RCTs (Barolet 2010, Zheng 2019), the pCFB SDs were reported for treatment arm k. In these trials, we calculated the standard error of the mean difference in pCFB as

$$se\left(MD_{\bar{P}_i}\right) = \sqrt{sd_{i,1}^2 + sd_{i,2}^2 - 2\rho sd_{i,1} sd_{i,2}}$$

where $\rho = 0.7247$ was the assumed within-patient correlation, estimated from another RCT, Choi 2010, that reported individual patient data.

Imputing Correlation between Baseline and Follow-up Counts

None of the RCTs reporting mean baseline and follow-up counts reported the correlation between the baseline and follow-up counts. Instead, this was imputed in all trials by calculating the correlation between the baseline and follow-up counts in RCTs that reported all of the SDs for baseline, follow-up and CFB counts:

$$\rho = \frac{sd_{B_{i,k}}^2 + sd_{F_{i,k}}^2 - sd_{C_{i,k}}^2}{2 sd_{B_{i,k}} sd_{F_{i,k}}}.$$

The median correlation reported in these RCTs was 0.50 regardless of lesion type, and 0.52 when restricting to RCTs reporting total lesion types. We used 0.52 in our analyses as this was based on the prioritised lesion type in our analysis.

Additional Derivations

One 4-arm RCT (Papageorgiou 2000) reported the mean pCFBs in inflammatory counts with 95% CIs for just 2 of the 4 treatments (Blue Light LED, Blue + Red light), and relative effects, $MD_{\bar{P}_{i,k}}$, with CIs for three of the treatments vs. Blue + Red light. To obtain the mean pCFB counts for the two remaining treatments (Placebo [physical], Benzoyl Peroxide), we applied the mean pCFB count for Blue + Red light, $\overline{P}_{i,1}$, to the mean differences of these treatments vs. Blue + Red light, $MD_{\bar{P}_{i,k}}$,

$$\overline{P}_{i,k} = \overline{P}_{i,1} + MD_{\bar{P}_{i,k}} .$$

The pCFB SDs for Blue Light LED and Blue + Red Light were derived based on their 95% CIs (see 'Imputing SDs based on confidence interval limits'). Assuming that the SDs in the other two treatment arms were equal, we imputed them as the average of the SDs for Blue Light LED and Blue + Red Light.

In one 4-arm RCT (Shalita 2005) the lower limit of one of the mean differences, as well as a p-value for another mean difference, was reported. The SDs corresponding to these two sources of uncertainty were derived, and the average of the SDs was imputed as the SD for all arms, assuming they were equal.

Network meta-analysis

In order to take all trial information into consideration network meta-analyses (NMA) were conducted. NMA is a generalisation of standard pairwise meta-analysis for A versus B trials, to data structures that include, for example, A versus B, B versus C, and A versus C trials (Lu 2004, Caldwell 2005, Dias 2013a). A basic assumption of NMA methods is that direct and indirect evidence estimate the same parameter, that is, the relative effect between A and B measured directly from an A versus B trial, is the same as the relative effect between A and B estimated indirectly from A versus C and B versus C trials. NMA techniques strengthen inference concerning the relative effect of two treatments by including both direct and indirect comparisons between treatments, and, at the same time, allow simultaneous inference on all treatments while respecting randomisation (Lu 2004; Caldwell 2005).

Simultaneous inference on the relative effects of all treatments is possible whenever treatments are part of a single "network of evidence", that is, every treatment is linked to at least one of the other treatments under assessment. The correlation between the random effects of multi-arm trials (i.e. those with more than 2 arms) in the network is taken into account in the analysis (Dias 2013a). In a NMA, we assume that intervention A is similar (in dose, administration etc.) when it appears in the A versus B and A versus C studies and also that the participants included in each trial are similar in terms of characteristics that may modify relative treatment effects (Dias 2018).

A Bayesian framework was used to estimate all parameters, using Markov chain Monte Carlo simulation methods implemented in OpenBUGS 3.2.3 for efficacy and WinBUGS 1.4.3 for both discontinuation outcomes (Lunn 2000 & 2013). Codes for all outcomes are provided in supplement 3. Data used in every analysis described in this appendix are provided in supplement 4.

Efficacy

The mean pCFB counts were assumed to have a normal likelihood:

$$\overline{P}_{i,k} \sim N\left(\theta_{i,k}, se^2_{\overline{P},i,k}\right)$$

where $\theta_{i,k}$ is the proportional change from baseline.

In RCTs reporting mean baseline and CFB counts, we assumed that the baseline counts were not correlated with the CFB counts, and thus the likelihoods were

$$\begin{aligned}\overline{X}_{i,k} &\sim N(\mu_{X_{i,k}}, se^2_{\overline{X}_{i,k}}) \\ \overline{C}_{i,k} &\sim N\left(\theta_{i,k}\mu_{X_{i,k}}, se^2_{\overline{C}_{i,k}}\right)\end{aligned}.$$

where $\mu_{X_{i,k}}$ is the mean CFB count in study i arm k.

In RCTs reporting mean baseline and follow-up counts, noting that the baseline and follow-up means are correlated, a bivariate normal likelihood was given for these data:

$$\begin{pmatrix}\overline{X}_{i,k} \\ \overline{Y}_{i,k}\end{pmatrix} \sim N\left(\begin{pmatrix}\mu_{\overline{X}_{i,k}} \\ \mu_{\overline{X}_{i,k}}(1-\theta_{i,k})\end{pmatrix}, \begin{pmatrix}se^2_{\overline{X}_{i,k}} & \rho se_{\overline{X}_{i,k}} se_{\overline{Y}_{i,k}} \\ \rho se_{\overline{X}_{i,k}} se_{\overline{Y}_{i,k}} & se^2_{\overline{Y}_{i,k}}\end{pmatrix}\right).$$

The treatments were assumed to act additively on the proportional change from baseline, $\theta_{i,k}$, so the NMA model is given directly to $\theta_{i,k}$:

$$\theta_{i,k} = \mu_i + \delta_{i,k}$$

where μ_i are the trial-specific baseline effects and $\delta_{i,k}$ are the trial-specific treatment effects, measuring the difference in the mean proportionate reduction in lesion counts, where positive values represent a reduction in counts, and negative values represent an increase in counts. These differences were modelled as fixed effects:

$$\delta_{i,k} = d_{t_{i,k}} - d_{t_{i,1}}$$

or random effects:

$$\delta_{i,k} \sim Normal\left(d_{t_{i,k}} - d_{t_{i,1}}, \tau^2\right)$$

where d_k are the basic parameters measuring the difference in mean proportionate reduction in lesion counts for treatment k vs. treatment 1, such that $d_1 = 0$, and τ is the between-study SD.

Non-informative Normal (0, 100^2) priors were assigned to the trial-specific baseline effects, as well as the mean lesion counts at baseline, while a Uniform(0, 25) prior was assigned to the between-study standard deviation in the random effects models (Dias 2011a), and was sufficiently wide so that the posterior distribution was not constrained. The treatment effects were informed by class effects, see 'Class effect models'. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic and was satisfactory by 60,000 simulations for both outcomes (Gelman 1992, Brooks 1998). A further simulation sample of 120,000 iterations post-convergence was obtained on which all reported results were based.

Supplement 5 provides the list of studies included in the efficacy NMA of treatments for people with mild to moderate acne with details on the types of efficacy data used, and the list of studies excluded from the efficacy NMA, although they reported efficacy data, with reasons for exclusion.

Discontinuation for any Reason or due to Side Effects

RCTs with zero or 100% events in all arms were excluded from the analyses of both discontinuation outcomes because these studies provide no evidence on relative effects (Dias 2011a). For studies with zero or 100% events in at least one, but not all arms, we planned to analyse the data without continuity corrections where computationally possible. Where this was not possible, we used a continuity correction where we added 0.5 to both the number of events and the number of non-events, which has been shown to perform well when there is an approximate 1:1 randomisation ratio across intervention arms (Sweeting 2004).

The number of participants who discontinued for any reason out of the total randomised to arm k were modelled with a binomial likelihood and logit link (Dias 2011a & 2018). Similarly, the number of participants who discontinued due to side effects out of the total randomised to arm k were modelled with a binomial likelihood and logit link (Dias 2011a & 2018).

For both outcomes, non-informative Normal(0, 100^2) priors were assigned to the trial-specific baseline effects, while a Uniform(0, 5) prior was assigned to the between-study standard deviation in the random effects models (Dias 2011a). The treatment effects were informed by class effects, see 'Class effect models'. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic and was satisfactory by 60,000 simulations for both outcomes (Gelman 1992, Brooks 1998). A further simulation sample of 120,000 iterations post-convergence was obtained on which all reported results were based.

Class Effect Models

Classes of treatments are groups of interventions which are thought to have similar modes of action (Dias 2108). Class models (Dias 2018) were used so that strength could be borrowed across treatments in the same class and to connect disconnected networks.

For all outcomes, both fixed and random class effects models were fitted. The random class effects model assumes that the relative effects of treatments within a class are exchangeable. That is, that the effects of treatments in a class are distributed around a common class mean, m_{D_k}, with a within-class variance, τ_k^2,

$$d_k \sim Normal\left(m_{D_k}, \tau_k^2\right)$$

where D_k identifies the class that treatment k belongs to. Treatment effects are shrunk towards a class mean and can borrow strength from other elements of the class.

Where there were less than 5 treatments within a class, the relative treatment effects were assumed to come from a normal distribution with a class mean and variance being borrowed from another similar class in the model, where possible. The following variance sharing rules were used:

- Treatments within classes that only differed by duration or a zinc acetate dihydrate add-on shared a within-class variance:
  - Efficacy: benzoyl peroxide [topical], lincosamide [topical], azelaic acid [topical], macrolide [topical], fusidic acid [topical], retinoid - total cumul dose < 120mg/kg (single course) [oral]
  - Discontinuation for any reason: benzoyl peroxide [topical], lincosamide [topical], azelaic acid [topical], macrolide [topical], fusidic acid [topical], benzoyl peroxide [topical] + lincosamide [topical]
  - Discontinuation due to side effects: placebo, benzoyl peroxide [topical], lincosamide [topical], macrolide [topical], fusidic acid [topical]
- Efficacy:

- Retinoid [topical], other topical acids [topical], benzoyl peroxide [topical] + retinoid [topical], lincosamide [topical] + retinoid [topical] shared a within-class variance
- Chemical peels [physical], photochemical + photothermal therapy, and photodynamic therapy shared a within-class variance
- Tetracycline [oral] and macrolide [oral] shared a within-class variance

- Discontinuation for any reason:
  - Retinoid [topical], benzoyl peroxide [topical] + retinoid [topical], lincosamide [topical] + retinoid [topical], retinoid [topical] + macrolide [topical] shared a within-class variance
  - Tetracycline [oral] and macrolide [oral] shared a within-class variance
  - Photochemical + photothermal therapy borrowed variance from other topical acids [topical]
- Discontinuation due to side effects:
  - Retinoid [topical], other topical acids [topical], benzoyl peroxide [topical] + retinoid [topical], lincosamide [topical] + retinoid [topical], retinoid [topical] + macrolide [topical] shared a within-class variance
  - Tetracycline [oral] and macrolide [oral] shared a within-class variance

The fixed class effects model assumes treatments within a class D_k have identical relative effects,

$$d_k = m_{D_k}.$$

Non-informative Normal(0, 100^2) priors were assigned to the class mean effects, as well as the effects of treatments not belonging to a class, while Uniform(0, 50) and Uniform(0, 5) priors were assigned to the within-class SDs in the random class effects models for efficacy and the discontinuation outcomes, respectively (Dias 2011a).

Two scenarios were considered: one where the different types of placebo within the placebo class were assumed to have exchangeable effects and one where they were assumed to have identical effects, regardless of the assumptions made for the other classes.

Note that evidence on treatments which were not licensed in the UK, but belonged to a class considered in the network, was initially included in the analyses to help estimate the class effects. However, because fixed class effects models were selected (as described in Results), this evidence was removed so that the resulting estimates were driven by treatments available in the UK.

Model Critique

When considering models for NMA, there are several aspects of the data that will impact the choice of parameters included in the model. Two important assumptions must be made in NMA regarding heterogeneity and consistency. Heterogeneity concerns the differences in treatment effects between trials within each treatment contrast, while consistency concerns the differences between the direct and indirect evidence informing the treatment contrasts (Dias 2011b & 2013b). A further assumption made in the analyses of the efficacy and discontinuation outcomes concerned the within-class variability, where the treatment effects within a class may be assumed to be identical or exchangeable.

Several models were considered for the base-case analyses, all of which assumed consistency:

1) **Fixed study, fixed class effects** model. This is the simplest model available to estimate the treatment effects, where treatments within classes are assumed to have identical effects and there is no heterogeneity between trials estimating the same treatment effects.

2) **Random study, fixed class effects** model. Treatments within classes are assumed to have identical effects, but any beyond chance differences between trial-specific estimates of the same treatment contrasts are captured by the between-study SD.
3) **Fixed study, random class effects** model. Treatments within classes are assumed to have exchangeable effects and there is no heterogeneity between trials estimating the same treatment effects.
    a. The effects of different types of placebo were assumed to be identical.
    b. The effects of different types of placebo were assumed to be exchangeable.
4) **Random study, random class effects** model. Treatments within classes are assumed to have exchangeable effects and any beyond chance differences between trial-specific estimates of the same treatment contrasts are captured by the between-study SD.
    a. The effects of different types of placebo were assumed to be identical.
    b. The effects of different types of placebo were assumed to be exchangeable.

When critiquing NMA models, it is good practice to assess and compare the fit of both fixed and random effects models, as differences may provide evidence of potential between-study heterogeneity. The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess the goodness of fit of each model (Spiegelhalter 2002). Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point) (Spiegelhalter 2002).

In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean deviance and the effective number of parameters, and thus penalizes model fit with model complexity (Spiegelhalter 2002). Lower values are preferred and typically differences of at least 3 points are considered meaningful (Spiegelhalter 2002).

Inconsistency Checks

Inconsistency was assessed by comparing the chosen base-case model assuming consistency to an “inconsistency”, or unrelated mean effects, model (Dias 2011b & 2013b). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that inconsistency can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 distinct trials (van Valkenhoef 2016). The consistency and inconsistency models were compared based on their posterior residual deviance and DIC. Where the base-case model assumes random study effects, if the inconsistency model has smaller heterogeneity (measured by the posterior median between-study SD) compared to the consistency model, then this indicates potential inconsistency in the data.

To visually assess if specific data-points are contributing to inconsistency, we plotted contributions to the posterior mean residual deviance for each data-point for the inconsistency model versus the consistency model. Points lying below the line of equality indicate data-points contributing to inconsistency.

We performed further checks for evidence of inconsistency through node-splitting both at the class-level and at the intervention level using the R2OpenBUGS package in R (Sturtz 2005) (see code in supplement 4). This method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared (Dias 2010a, van Valkenhoef 2016). Note that there were a small number of instances where a multi-arm trial

contained the node of interest twice. In these situations, one arm was randomly removed in order to approximate the direct and indirect estimates.

Subgroup and Sensitivity Analyses

Female and Male networks

When evidence on treatments that were only appropriate for females (e.g., co-cyprindiol [oral], combined oral contraceptives [oral]) indirectly contributed to other comparisons in the network, a separate analysis was conducted for males based on a sub-network with female only treatments removed. If the evidence on female only treatments did not indirectly inform other comparisons, then no re-analysis of the NMA was necessary and the treatment rankings for males was based on the subset treatments appropriate for males.

Bias-Adjustment Models

To assess and explain the presence of bias in the included evidence, models which adjusted for bias were fitted (Dias 2018). For each domain on the Cochrane Risk of Bias Tool (version 2) that had sufficient variability in the ratings, bias adjustment models were fitted to downweight trials at high or unclear risk of bias (Welton 2009, Dias 2010b):

$$\theta_{i,k} = \mu_i + \left(\delta_{i,k} + \beta_{i,k} x_{i,k} bias_{i,j}\right)$$

where $\beta_{i,k}$ is trial-specific bias of the treatment in arm k relative to the treatment in arm 1,

$$x_{i,k} = \begin{cases} -1 & \text{if } k \text{ vs. 1 is an active vs. inactive comparison} \\ 0 & \text{if } k \text{ vs. 1 is an active vs. active or inactive vs. active comparison} \\ 1 & \text{if } k \text{ vs. 1 is an inactive vs. active comparison} \end{cases},$$

and

$$bias_{i,j} = \begin{cases} 1 & \text{if study } i \text{ is at high or unclear risk of bias on domain } j \\ 0 & \text{otherwise} \end{cases}.$$

In addition, small study bias was also investigated (Dias 2018, Moreno 2009a & 2009b),

$$\theta_{i,k} = \mu_i + \left(\delta_{i,k} + \beta_{i,k} x_{i,k} \Big/ \sqrt{N_i}\right)$$

where N_i is the number of patients in trial i, or number of observations in the case of a split-face trial.

Age-adjusted analyses

A meta-regression adjusting for age was planned if at least 90% of the included trials for the efficacy outcome reported enough information on age to determine the proportion of participants less than ≤25 years of age and those >25 years of age. In studies reporting efficacy, 80.4% of the studies reported sufficient age data, and since the inclusion criteria were not met for the primary efficacy outcome, the age-adjusted analyses were not carried out.

Results

Efficacy

Initially this analysis was carried out on 111 trials of 46 classes and 90 interventions of varying durations which may or may not have been licensed in the UK, where the unlicensed interventions (e.g. tretinoin alone) were included to help the estimation of the class effects. However, because there was not enough evidence to inform the within-class variability, and the random study effects, fixed class effect model provided good fit (Table 32), the analysis was re-run with the non-UK licensed interventions being removed, where 90 trials of 41 classes and 78 interventions were included (Figure 17, Figure 18, Table 33). The random study effects, fixed class effects model was selected as the base-case model, as the posterior residual deviance indicated good model fit and there was not enough evidence to inform the within-class variability (Table 34).

Table 32: Model fit statistics for efficacy with non-UK licensed interventions included

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]
FE, fixed class	---	1768.0	3207.0
RE, fixed class	**9.52 (7.93, 11.54)**	**325.0**	**1829.0**
FE, random class (placebos coded the same)	---	792.8	2256.0
FE, random class (placebos coded separately)	---	790.7	2253.0
RE, random class (placebos coded the same)	8.52 (6.76, 10.71)	324.8	1829.0
RE, random class (placebos coded separately)	9.70 (8.24, 11.55)	328.1	inestimable

Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; RE, random study effects; SD, standard deviation; UME, unrelated mean effects
a Posterior mean residual deviance compared to 327 total data points
b Lower values of DIC preferred

Figure 17: Network diagram of direct evidence between classes included in efficacy analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular class.

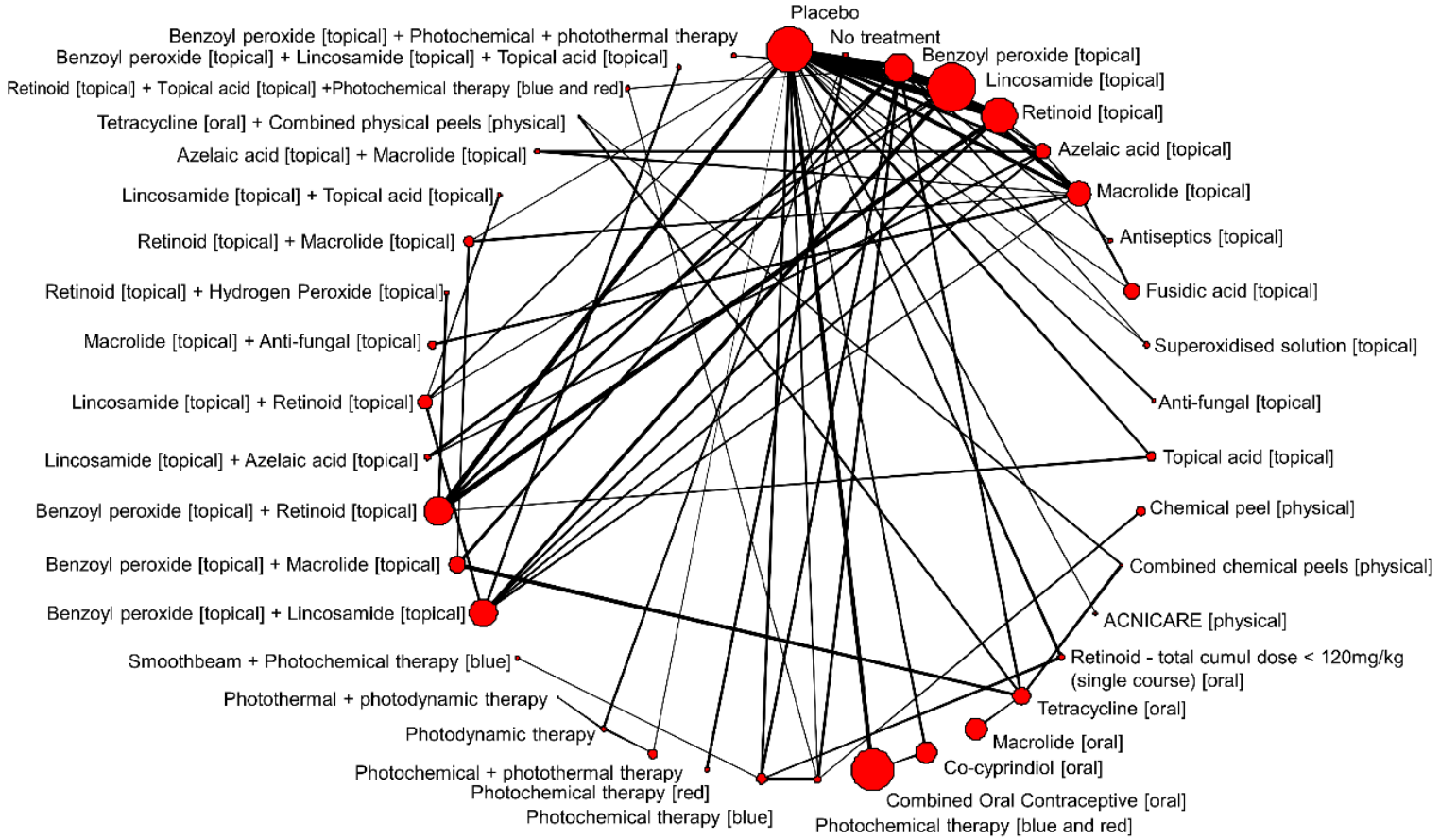


Figure 18: Network diagram of direct evidence between interventions included in efficacy analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular intervention

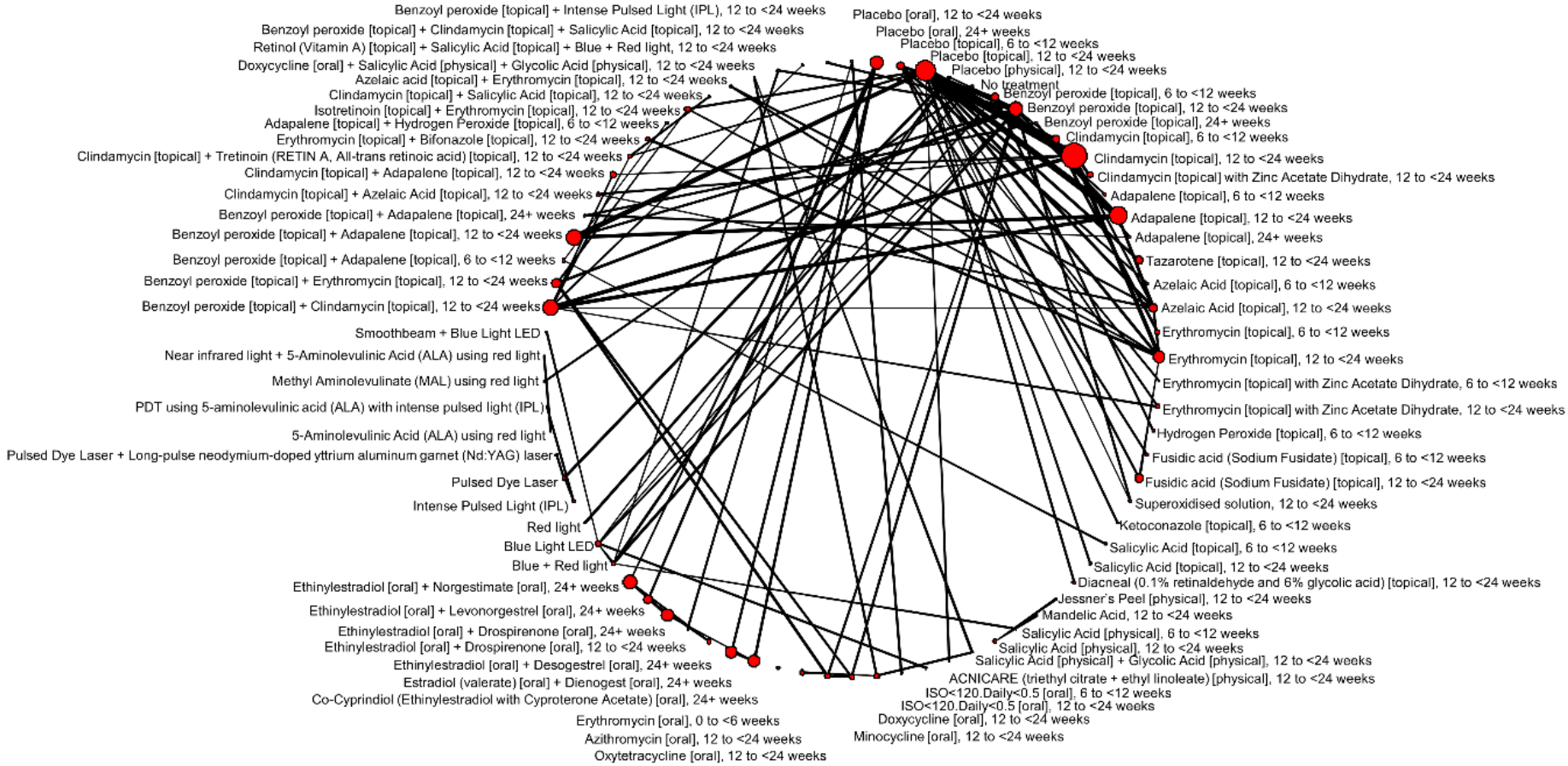


Table 33: Number of observations for each class, intervention and duration in efficacy analysis

Class	n	Treatment	n	Duration	n
Placebo	2698	Placebo [oral]	722	12 to <24 weeks	39
				24+ weeks	683
		Placebo [topical]	1945	6 to <12 weeks	231
				12 to <24 weeks	1714
		Placebo [physical]	31	12 to <24 weeks	31
No treatment	39	No treatment	39		39
Benzoyl peroxide [topical]	1109	Benzoyl peroxide [topical]	1109	6 to <12 weeks	246
				12 to <24 weeks	834
				24+ weeks	29
Lincosamide [topical]	3073	Clindamycin [topical]	2910	6 to <12 weeks	236
				12 to <24 weeks	2674
		Clindamycin [topical] with Zinc Acetate Dihydrate	163	12 to <24 weeks	163
Retinoid [topical]	1623	Adapalene [topical]	1377	6 to <12 weeks	30
				12 to <24 weeks	1315
				24+ weeks	32
		Tazarotene [topical]	246	12 to <24 weeks	246
Azelaic acid [topical]	301	Azelaic Acid [topical]	301	6 to <12 weeks	30
				12 to <24 weeks	271
Macrolide [topical]	765	Erythromycin [topical]	669	6 to <12 weeks	108
				12 to <24 weeks	561
		Erythromycin [topical] with Zinc Acetate Dihydrate	96	6 to <12 weeks	11
				12 to <24 weeks	85
Antiseptics [topical]	30	Hydrogen Peroxide [topical]	30	6 to <12 weeks	30
Fusidic acid [topical]	310	Fusidic acid (Sodium Fusidate) [topical]	310	6 to <12 weeks	36
				12 to <24 weeks	274
Superoxidised solution [topical]	39	Superoxidised solution	39	12 to <24 weeks	39

Class	n	Treatment	n	Duration	n
Anti-fungal [topical]	20	Ketoconazole [topical]	20	6 to <12 weeks	20
Topical acid [topical]	106	Salicylic Acid [topical]	64	6 to <12 weeks	31
				12 to <24 weeks	33
		Diacneal (0.1% retinaldehyde and 6% glycolic acid) [topical]	42	12 to <24 weeks	42
Chemical peel [physical]	101	Jessner's Peel [physical]	20	12 to <24 weeks	20
		Mandelic Acid	25	12 to <24 weeks	25
		Salicylic Acid [physical]	56	6 to <12 weeks	11
				12 to <24 weeks	45
Combined chemical peels [physical]	14	Salicylic Acid [physical] + Glycolic Acid [physical]	14	12 to <24 weeks	14
ACNICARE [physical]	20	ACNICARE (triethyl citrate + ethyl linoleate) [physical]	20	12 to <24 weeks	20
Retinoid - total cumul dose < 120mg/kg (single course) [oral]	54	Isotretinoin<120.Daily<0.5 [oral]	54	6 to <12 weeks	25
				12 to <24 weeks	29
Tetracycline [oral]	388	Doxycycline [oral]	127	12 to <24 weeks	127
		Minocycline [oral]	130	12 to <24 weeks	130
		Oxytetracycline [oral]	131	12 to <24 weeks	131
Macrolide [oral]	618	Azithromycin [oral]	109	12 to <24 weeks	109
		Erythromycin [oral]	34	0 to <6 weeks	34
Co-cyprindiol [oral]	584	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	584	24+ weeks	584
Combined Oral Contraceptive [oral]	2313	Estradiol (valerate) [oral] + Dienogest [oral]	530	24+ weeks	530
		Ethinylestradiol [oral] + Desogestrel [oral]	102	24+ weeks	102
		Ethinylestradiol [oral] + Drospirenone [oral]	626	12 to <24 weeks	11
				24+ weeks	615
		Ethinylestradiol [oral] + Levonorgestrel [oral]	303	24+ weeks	303
		Ethinylestradiol [oral] + Norgestimate [oral]	752	24+ weeks	752
Photochemical therapy [blue and red]	69	Blue + Red light	69		69
Photochemical therapy [blue]	138	Blue Light LED	138		138

Class	n	Treatment	n	Duration	n
Photochemical therapy [red]	28	Red light	28		28
Photochemical + photothermal therapy	107	Intense Pulsed Light (IPL)	27		27
		Pulsed Dye Laser	64		64
		Pulsed Dye Laser + Long-pulse neodymium-doped yttrium aluminum garnet (Nd:YAG) laser	16		16
Photodynamic therapy	36	5-Aminolevulinic Acid (ALA) using red light	9		9
		PDT using 5-aminolevulinic acid (ALA) with intense pulsed light (IPL)	15		15
		Methyl Aminolevulinate (MAL) using red light	12		12
Photothermal + photodynamic therapy	9	Near infrared light + 5-Aminolevulinic Acid (ALA) using red light	9		9
Smoothbeam + Photochemical therapy [blue]	24	Smoothbeam + Blue Light LED	24		24
Benzoyl peroxide [topical] + Lincosamide [topical]	992	Benzoyl peroxide [topical] + Clindamycin [topical]	992	12 to <24 weeks	992
Benzoyl peroxide [topical] + Macrolide [topical]	351	Benzoyl peroxide [topical] + Erythromycin [topical]	351	12 to <24 weeks	351
Benzoyl peroxide [topical] + Retinoid [topical]	1057	Benzoyl peroxide [topical] + Adapalene [topical]	1057	6 to <12 weeks	57
				12 to <24 weeks	968
				24+ weeks	32
Lincosamide [topical] + Azelaic acid [topical]	44	Clindamycin [topical] + Azelaic Acid [topical]	44	12 to <24 weeks	44
Lincosamide [topical] + Retinoid [topical]	276	Clindamycin [topical] + Adapalene [topical]	184	12 to <24 weeks	184
		Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	92	12 to <24 weeks	92
Macrolide [topical] + Anti-fungal [topical]	74	Erythromycin [topical] + Bifonazole [topical]	74	12 to <24 weeks	74
Retinoid [topical] + Hydrogen Peroxide [topical]	26	Adapalene [topical] + Hydrogen Peroxide [topical]	26	6 to <12 weeks	26
Retinoid [topical] + Macrolide [topical]	135	Isotretinoin [topical] + Erythromycin [topical]	135	12 to <24 weeks	135
Lincosamide [topical] + Topical acid [topical]	23	Clindamycin [topical] + Salicylic Acid [topical]	23	12 to <24 weeks	23
Azelaic acid [topical] + Macrolide [topical]	40	Azelaic acid [topical] + Erythromycin [topical]	40	12 to <24 weeks	40
Tetracycline [oral] + Combined physical peels [physical]	13	Doxycycline [oral] + Salicylic Acid [physical] + Glycolic Acid [physical]	13	12 to <24 weeks	13

Class	n	Treatment	n	Duration	n
Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red]	35	Retinol (Vitamin A) [topical] + Salicylic Acid [topical] + Blue + Red light	35	12 to <24 weeks	35
Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical]	24	Benzoyl peroxide [topical] + Clindamycin [topical] + Salicylic Acid [topical]	24	12 to <24 weeks	24
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	29	Benzoyl peroxide [topical] + Intense Pulsed Light (IPL)	29	12 to <24 weeks	29

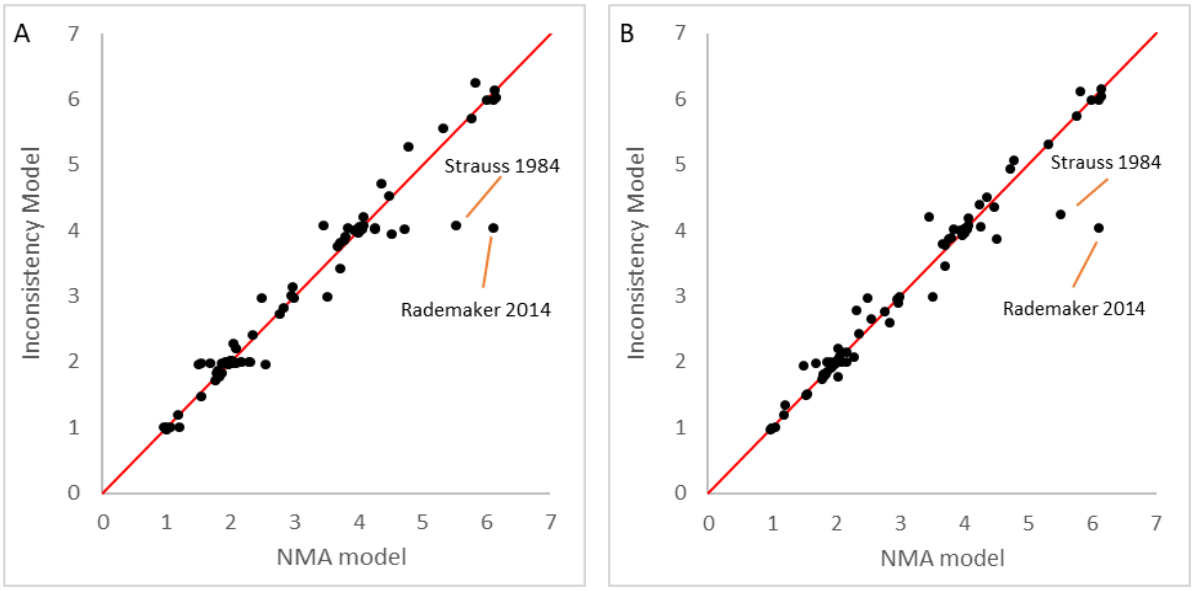
Table 34: Model fit statistics for efficacy. Only UK-licensed interventions included.

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]
FE, fixed class	---	984.4	2198.0
RE, fixed class	**9.88 (8.04, 12.25)**	**273.0**	**1540.0**
FE, random class (placebos coded the same)	---	719.4	1954.0
FE, random class (placebos coded separately)	---	712.5	1945.0
RE, random class (placebos coded the same)	9.23 (7.23, 11.76)	272.1	1540.0
RE, random class (placebos coded separately)	9.97 (8.38, 12.04)	273.7	inestimable
UME - RE, intervention level	8.25 (6.12, 11.39)	270.5	1550.0
UME - RE, class level	8.86 (7.00, 11.40)	271.5	1545.0

Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; RE, random study effects; SD, standard deviation; UME, unrelated mean effects
a Posterior mean residual deviance compared to 273 total data points
b Lower values of DIC preferred

Although there were no meaningful differences between the fit of the random effects consistency and inconsistency models, the between-study SD slightly decreased in the inconsistency models, suggesting some evidence of inconsistency (Table 34). The area below the line of equality in Figure 19 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in Rademaker 2014, which compared ISO<120.Daily<0.5 [oral], 12 to <24 weeks and Placebo [oral], 12 to < 24 weeks, and Strauss 1984, which compared Erythromycin [topical] with Zinc Acetate Dihydrate, 6 to <12 weeks and Placebo [topical], 6 to <12 weeks.

Figure 19: Deviance contributions for the random study, fixed class effects consistency and inconsistency models at (A) the intervention level and (B) the class level for efficacy.



Although there were no meaningful differences between the fit of the node split models and the consistency model (

Table 35), there were differences between the direct and indirect estimates of the following class comparisons (Figure 20):

- Azelaic acid [topical] vs. Placebo (6 vs. 1)
- Azelaic acid [topical] vs. Lincosamide [topical] (6 vs. 4)
- Retinoid - total cumul dose < 120mg/kg (single course) [oral] vs. Placebo (16 vs. 1)
- Photochemical therapy [blue] vs. Retinoid - total cumul dose < 120mg/kg (single course) [oral] (22 vs. 16)

A table of the direct, indirect, and NMA estimates for all pairwise relative effects between classes is available in supplement 6.

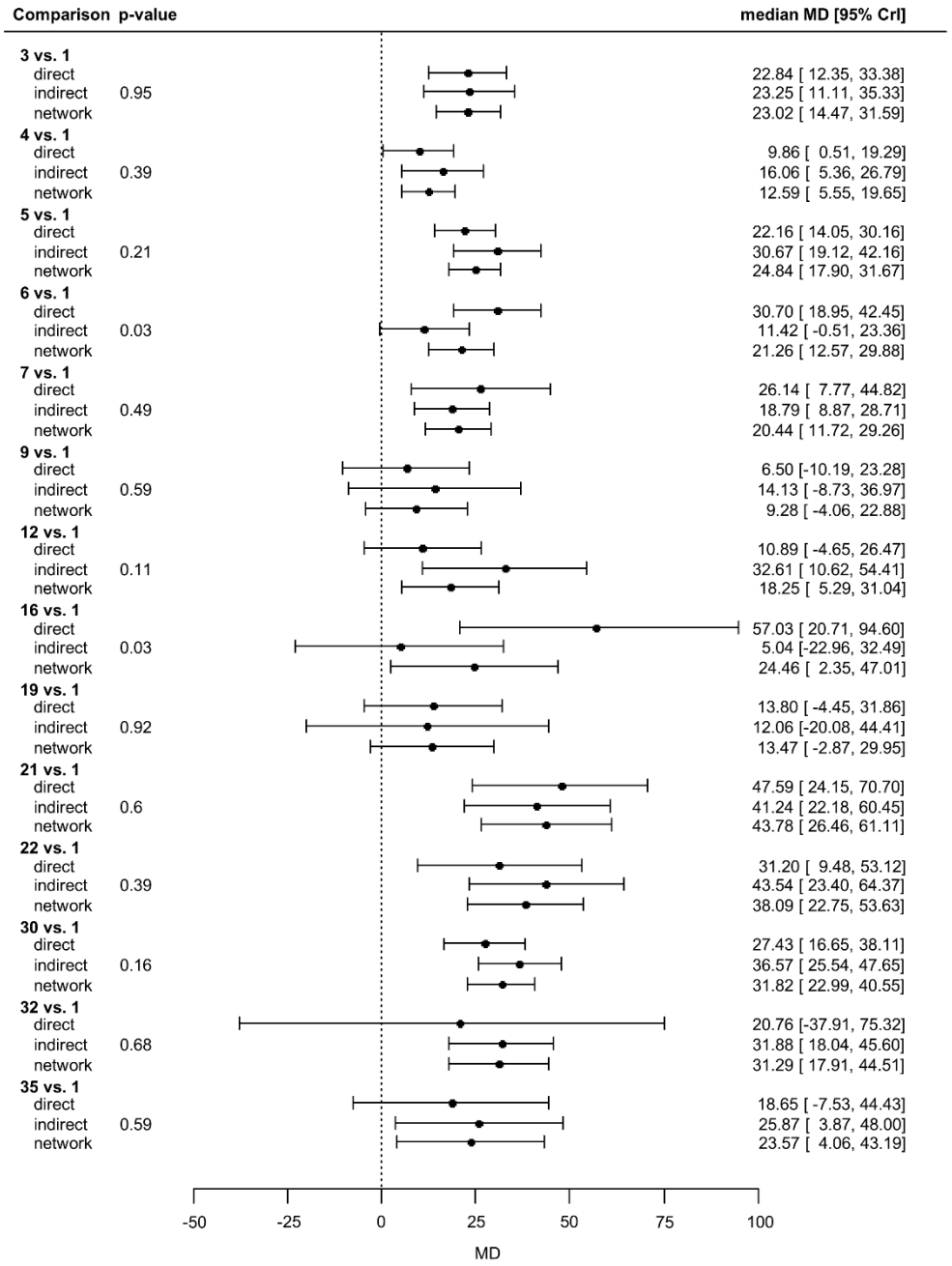
Table 35: Node split model fit statistics for efficacy

Node split model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]	p-value[c]
Benzoyl peroxide [topical] vs. Placebo (3 vs. 1)	9.95 (8.10, 12.37)	273.2	1682.0	0.95
Lincosamide [topical] vs. Placebo (4 vs. 1)	9.86 (8.02, 12.26)	273.1	1681.0	0.39
Retinoid [topical] vs. Placebo (5 vs. 1)	9.85 (8.03, 12.21)	272.3	1680.0	0.21
Azelaic acid [topical] vs. Placebo (6 vs. 1)	9.52 (7.73, 11.84)	273.0	1680.0	0.03
Macrolide [topical] vs. Placebo (7 vs. 1)	9.92 (8.08, 12.31)	273.0	1682.0	0.49
Fusidic acid [topical] vs. Placebo (9 vs. 1)	9.93 (8.07, 12.32)	273.1	1682.0	0.59
Topical acid [topical] vs. Placebo (12 vs. 1)	9.71 (7.88, 12.09)	273.1	1681.0	0.11
Retinoid - total cumul dose < 120mg/kg (single course) [oral] vs. Placebo (16 vs. 1)	9.69 (7.90, 12.00)	271.0	1679.0	0.03
Co-cyprindiol [oral] vs. Placebo (19 vs. 1)	9.94 (8.09, 12.33)	273.3	1682.0	0.92
Photochemical therapy [blue and red] vs. Placebo (21 vs. 1)	9.90 (8.04, 12.30)	273.5	1682.0	0.60
Photochemical therapy [blue] vs. Placebo (22 vs. 1)	9.94 (8.10, 12.33)	272.6	1681.0	0.39
Benzoyl peroxide [topical] + Retinoid [topical] vs. Placebo (30 vs. 1)	9.90 (8.08, 12.23)	271.3	1680.0	0.16
Lincosamide [topical] + Retinoid [topical] vs. Placebo (32 vs. 1)	9.90 (8.08, 12.31)	273.3	1683.0	0.68
Retinoid [topical] + Macrolide [topical] vs. Placebo (35 vs. 1)	9.93 (8.07, 12.34)	273.1	1682.0	0.59
Lincosamide [topical] vs. Benzoyl peroxide [topical] (4 vs. 3)	9.88 (8.03, 12.27)	273.3	1682.0	0.45
Retinoid [topical] vs. Benzoyl peroxide [topical] (5 vs. 3)	9.87 (8.00, 12.27)	273.4	1682.0	0.43
Photochemical therapy [blue] vs. Benzoyl peroxide [topical] (22 vs. 3)	9.86 (8.03, 12.25)	272.8	1681.0	0.28
Benzoyl peroxide [topical] + Macrolide [topical] vs. Benzoyl peroxide [topical] (29 vs. 3)	9.92 (8.08, 12.32)	273.2	1682.0	0.70
Benzoyl peroxide [topical] + Retinoid [topical] vs. Benzoyl peroxide [topical] (30 vs. 3)	9.94 (8.11, 12.34)	272.5	1681.0	0.42
Azelaic acid [topical] vs. Lincosamide [topical] (6 vs. 4)	9.47 (7.67, 11.80)	273.5	1681.0	0.03
Macrolide [topical] vs. Lincosamide [topical] (7 vs. 4)	9.83 (7.98, 12.25)	273.7	1682.0	0.41
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Lincosamide [topical] (28 vs. 4)	9.87 (8.03, 12.27)	272.9	1681.0	0.31
Lincosamide [topical] + Retinoid [topical] vs. Lincosamide [topical] (32 vs. 4)	9.98 (8.12, 12.40)	272.7	1681.0	0.76
Azelaic acid [topical] vs. Retinoid [topical] (6 vs. 5)	9.92 (8.08, 12.32)	273.0	1682.0	0.42
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Retinoid [topical] (28 vs. 5)	9.97 (8.11, 12.41)	273.0	1682.0	0.87
Benzoyl peroxide [topical] + Retinoid [topical] vs. Retinoid [topical] (30 vs. 5)	9.88 (8.02, 12.27)	272.9	1681.0	0.28
Macrolide [topical] vs. Azelaic acid [topical] (7 vs. 6)	9.82 (7.99, 12.21)	272.8	1681.0	0.18
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Azelaic acid [topical] (28 vs. 6)	9.70 (7.86, 12.07)	273.4	1681.0	0.12
Fusidic acid [topical] vs. Macrolide [topical] (9 vs. 7)	9.94 (8.08, 12.36)	273.0	1682.0	0.58

Node split model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]	p-value[c]
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Macrolide [topical] (28 vs. 7)	9.97 (8.10, 12.39)	273.0	1681.0	0.91
Retinoid [topical] + Macrolide [topical] vs. Macrolide [topical] (35 vs. 7)	9.92 (8.07, 12.35)	273.4	1682.0	0.72
Benzoyl peroxide [topical] + Retinoid [topical] vs. Topical acid [topical] (30 vs. 12)	9.69 (7.86, 12.07)	273.3	1681.0	0.10
Photochemical therapy [blue] vs. Retinoid - total cumul dose < 120mg/kg (single course) [oral] (22 vs. 16)	9.68 (7.91, 11.98)	271.2	1679.0	0.03
Photochemical therapy [blue] vs. Photochemical therapy [blue and red] (22 vs. 21)	9.94 (8.09, 12.30)	272.4	1681.0	0.41
Lincosamide [topical] + Retinoid [topical] vs. Benzoyl peroxide [topical] + Lincosamide [topical] (32 vs. 28)	9.98 (8.11, 12.38)	272.8	1681.0	0.95
Retinoid [topical] + Macrolide [topical] vs. Benzoyl peroxide [topical] + Macrolide [topical] (35 vs. 29)	9.91 (8.07, 12.31)	273.3	1682.0	0.75
NMA (no nodes split)[d]	**9.88 (8.05, 12.26)**	**272.9**	**1681.0**	

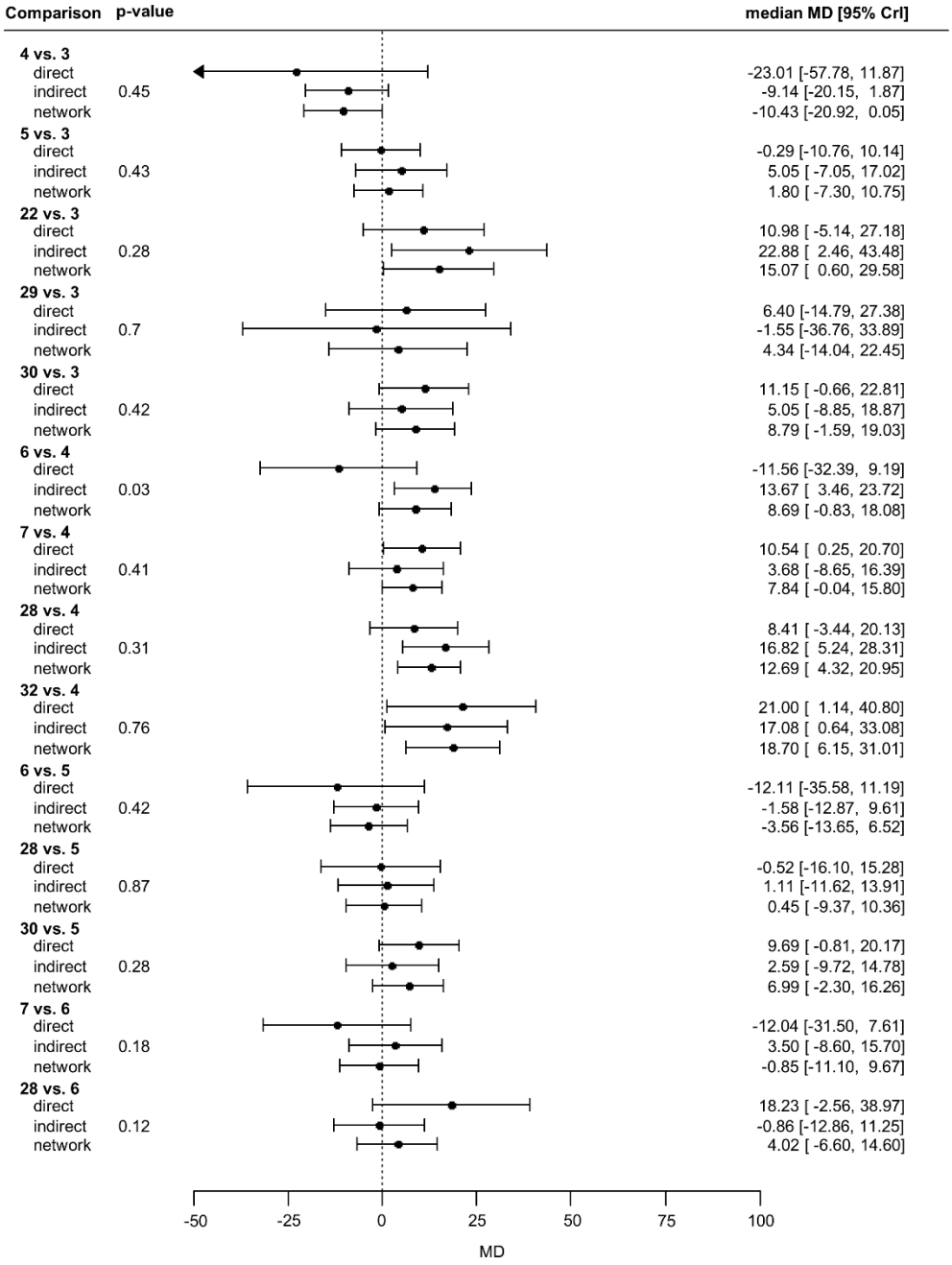
Abbreviations: CrI, credible interval; DIC, deviance information criteria; NMA, network meta-analysis; SD, standard deviation.
Values in red suggest evidence of inconsistency (either reduced between study heterogeneity following node-split testing, or p-value <0.05)
a Posterior mean residual deviance compared to 273 total data points
b Lower values of DIC preferred
c p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates
d Model fit statistics produced in R2OpenBUGS

Figure 20: Forest plot of direct, indirect and network meta-analysis estimates of class comparisons for efficacy (continued on next page)



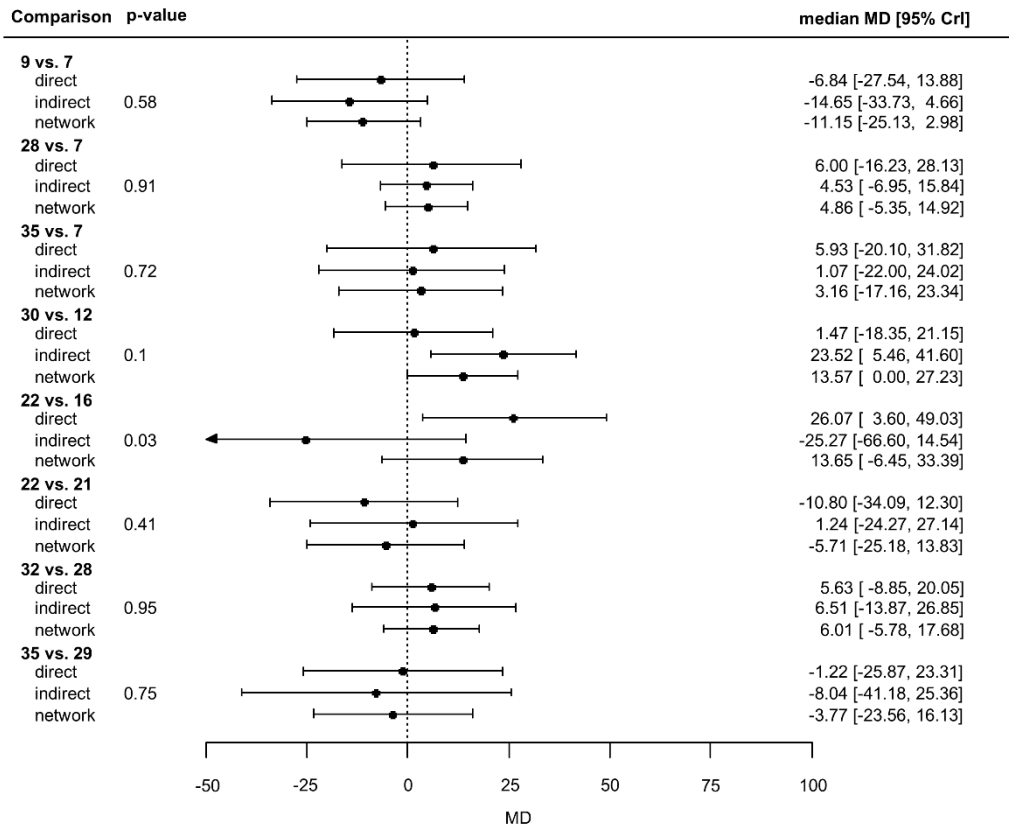
Class codes: 1 - Placebo, 2 - No treatment, 3 - Benzoyl peroxide [topical], 4 - Lincosamide [topical], 5 - Retinoid [topical], 6 - Azelaic acid [topical], 7 - Macrolide [topical], 8 - Antiseptics [topical], 9 - Fusidic acid [topical], 10 - Superoxidised solution [topical], 11 - Anti-fungal [topical], 12 - Topical acid [topical], 13 - Chemical peel [physical], 14 - Combined chemical peels [physical], 15 - ACNICARE [physical], 16 - Retinoid - total cumul dose < 120mg/kg (single course) [oral], 17 - Tetracycline [oral], 18 - Macrolide [oral], 19 - Co-cyprindiol [oral], 20 - Combined Oral Contraceptive [oral], 21 - Photochemical therapy [blue and red], 22 - Photochemical therapy [blue], 23 - Photochemical therapy [red], 24 - Photochemical + photothermal therapy, 25 - Photodynamic therapy, 26 - Photothermal + photodynamic therapy, 27 - Smoothbeam + Photochemical therapy [blue], 28 - Benzoyl peroxide [topical] + Lincosamide [topical], 29 - Benzoyl peroxide [topical] + Macrolide [topical], 30 - Benzoyl peroxide [topical] + Retinoid [topical], 31 - Lincosamide [topical] + Azelaic acid [topical], 32 - Lincosamide [topical] + Retinoid [topical], 33 - Macrolide [topical] + Anti-fungal [topical], 34 - Retinoid [topical] + Hydrogen Peroxide [topical], 35 - Retinoid [topical] + Macrolide [topical], 36 - Lincosamide [topical] + Topical acid [topical], 37 - Azelaic acid [topical] + Macrolide [topical], 38 - Tetracycline [oral] + Combined physical peels [physical], 39 - Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red], 40 - Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical], 41 - Benzoyl peroxide [topical] + Photochemical + photothermal therapy.

Continued from previous page and on next page



Class codes: 1 - Placebo, 2 - No treatment, 3 - Benzoyl peroxide [topical], 4 - Lincosamide [topical], 5 - Retinoid [topical], 6 - Azelaic acid [topical], 7 - Macrolide [topical], 8 - Antiseptics [topical], 9 - Fusidic acid [topical], 10 - Superoxidised solution [topical], 11 - Anti-fungal [topical], 12 - Topical acid [topical], 13 - Chemical peel [physical], 14 - Combined chemical peels [physical], 15 - ACNICARE [physical], 16 - Retinoid - total cumul dose < 120mg/kg (single course) [oral], 17 - Tetracycline [oral], 18 - Macrolide [oral], 19 - Co-cyprindiol [oral], 20 - Combined Oral Contraceptive [oral], 21 - Photochemical therapy [blue and red], 22 - Photochemical therapy [blue], 23 - Photochemical therapy [red], 24 - Photochemical + photothermal therapy, 25 - Photodynamic therapy, 26 - Photothermal + photodynamic therapy, 27 - Smoothbeam + Photochemical therapy [blue], 28 - Benzoyl peroxide [topical] + Lincosamide [topical], 29 - Benzoyl peroxide [topical] + Macrolide [topical], 30 - Benzoyl peroxide [topical] + Retinoid [topical], 31 - Lincosamide [topical] + Azelaic acid [topical], 32 - Lincosamide [topical] + Retinoid [topical], 33 - Macrolide [topical] + Anti-fungal [topical], 34 - Retinoid [topical] + Hydrogen Peroxide [topical], 35 - Retinoid [topical] + Macrolide [topical], 36 - Lincosamide [topical] + Topical acid [topical], 37 - Azelaic acid [topical] + Macrolide [topical], 38 - Tetracycline [oral] + Combined physical peels [physical], 39 - Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red], 40 - Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical], 41 - Benzoyl peroxide [topical] + Photochemical + photothermal therapy.

Continued from previous page



Class codes: 1 - Placebo, 2 - No treatment, 3 - Benzoyl peroxide [topical], 4 - Lincosamide [topical], 5 - Retinoid [topical], 6 - Azelaic acid [topical], 7 - Macrolide [topical], 8 - Antiseptics [topical], 9 - Fusidic acid [topical], 10 - Superoxidised solution [topical], 11 - Anti-fungal [topical], 12 - Topical acid [topical], 13 - Chemical peel [physical], 14 - Combined chemical peels [physical], 15 - ACNICARE [physical], 16 - Retinoid - total cumul dose < 120mg/kg (single course) [oral], 17 - Tetracycline [oral], 18 - Macrolide [oral], 19 - Co-cyprindiol [oral], 20 - Combined Oral Contraceptive [oral], 21 - Photochemical therapy [blue and red], 22 - Photochemical therapy [blue], 23 - Photochemical therapy [red], 24 - Photochemical + photothermal therapy, 25 - Photodynamic therapy, 26 - Photothermal + photodynamic therapy, 27 - Smoothbeam + Photochemical therapy [blue], 28 - Benzoyl peroxide [topical] + Lincosamide [topical], 29 - Benzoyl peroxide [topical] + Macrolide [topical], 30 - Benzoyl peroxide [topical] + Retinoid [topical], 31 - Lincosamide [topical] + Azelaic acid [topical], 32 - Lincosamide [topical] + Retinoid [topical], 33 - Macrolide [topical] + Anti-fungal [topical], 34 - Retinoid [topical] + Hydrogen Peroxide [topical], 35 - Retinoid [topical] + Macrolide [topical], 36 - Lincosamide [topical] + Topical acid [topical], 37 - Azelaic acid [topical] + Macrolide [topical], 38 - Tetracycline [oral] + Combined physical peels [physical], 39 - Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red], 40 - Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical], 41 - Benzoyl peroxide [topical] + Photochemical + photothermal therapy.

There was sufficient variation in the ratings of studies to fit bias models on two risk of bias domains:

- Domain 2: Deviation from interventions
- Domain 4: Outcome measurement (efficacy)

There was no evidence of bias arising from these domains as the 95% credible intervals of the posterior mean bias included zero (Table 36). However, there was evidence of small-study bias (Table 36).

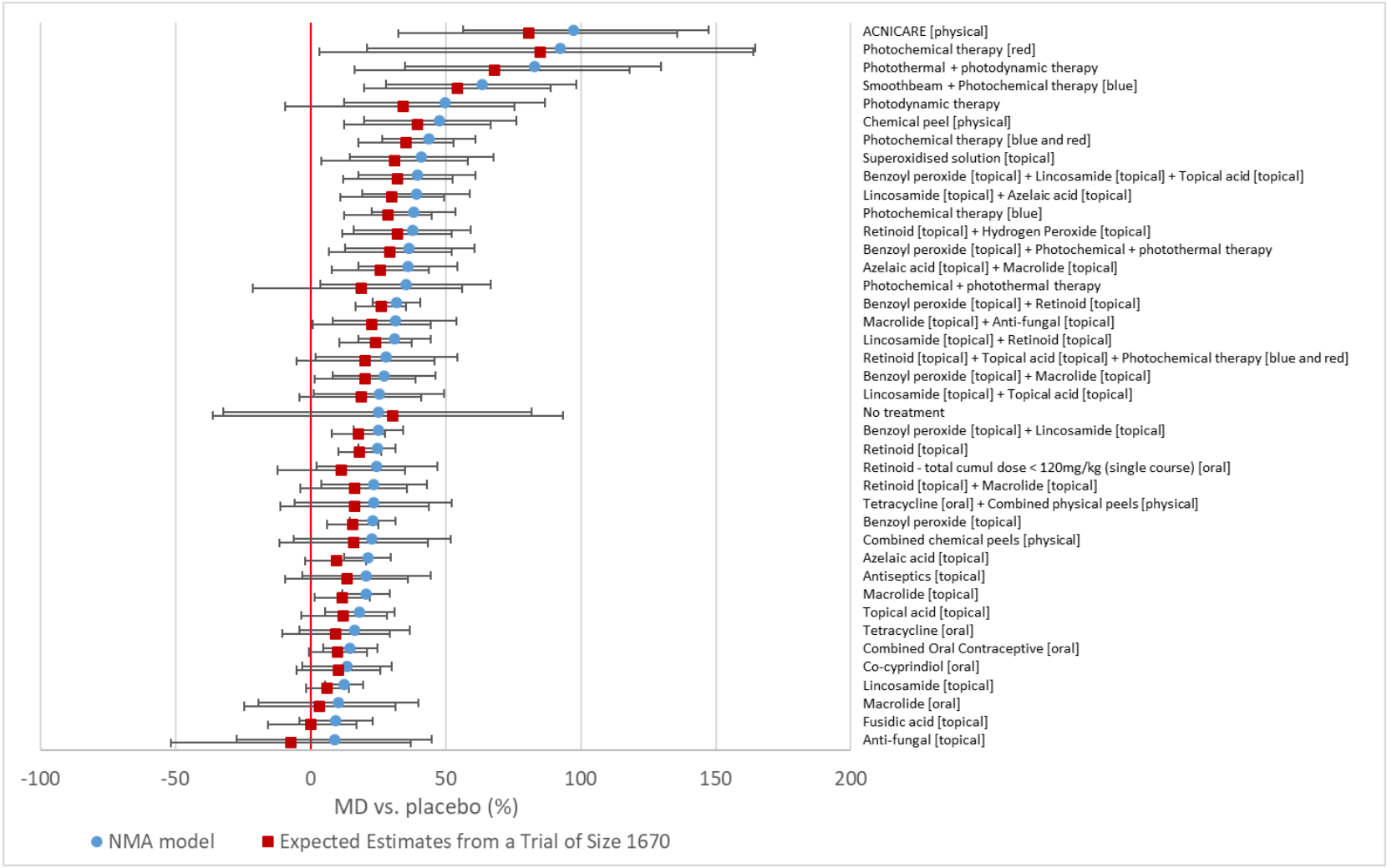
Figure 21 displays both the unadjusted and bias-adjusted relative effects of each class vs. placebo, where the bias-adjusted estimates are the expected estimates from an RCT of 1670 participants, the size of the largest RCT in the network.

Table 36: Bias model fit statistics for efficacy

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]	Bias	
				Posterior median (95% CrI)	Between Study SD (95% CrI)
NMA model: RE, fixed class	**9.88 (8.04, 12.25)**	**273.0**	**1540.0**	**---**	**---**
Bias model: Domain 2	9.60 (7.63, 12.09)	271.4	1539.0	7.53 (-3.17, 19.16)	6.06 (0.28, 15.63)
Bias model: Domain 4	9.79 (7.90, 12.23)	272.8	1540.0	2.44 (-6.95, 12.10)	5.51 (0.28, 16.14)
Bias model: Small study	8.89 (6.95, 11.28)	268.8	1536.0	123.1 (33.50, 216.50)	67.61 (4.81, 149.10)

Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; NMA, network meta-analysis; SD, standard deviation
Posterior median bias values in red suggest evidence of bias, as the 95% credible intervals do not include zero.
[a] *Posterior mean residual deviance compared to 273 total data points*
[b] *Lower values of DIC preferred*

Figure 21: Forest plot of unadjusted NMA estimates (blue circles) and bias-adjusted estimates which would be expected from a RCT of 1670 participants (red squares), efficacy analysis



The bias-adjusted results suggest the following interventions are more effective than Placebo, in decreasing order of effectiveness (Figure 21):

- ACNICARE [physical]
- Photochemical therapy [red]
- Photothermal + photodynamic therapy
- Smoothbeam + Photochemical therapy [blue]
- Chemical peel [physical]
- Photochemical therapy [blue and red]
- Superoxidised solution [topical]
- Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical]
- Lincosamide [topical] + Azelaic acid [topical]
- Photochemical therapy [blue]
- Retinoid [topical] + Hydrogen Peroxide [topical]
- Benzoyl peroxide [topical] + Photochemical + photothermal therapy
- Azelaic acid [topical] + Macrolide [topical]
- Benzoyl peroxide [topical] + Retinoid [topical]
- Macrolide [topical] + Anti-fungal [topical]
- Lincosamide [topical] + Retinoid [topical]
- Benzoyl peroxide [topical] + Macrolide [topical]
- Benzoyl peroxide [topical] + Lincosamide [topical]
- Retinoid [topical]
- Benzoyl peroxide [topical]
- Macrolide [topical]

No classes were less effective than Placebo (Figure 21).

ACNICARE [physical] is the highest ranked class for both females and males, with posterior mean ranks of 2.7 (95% CrI 1st to 10th) and 2.7 (95% CrI 1st to 10th), respectively (Table 37). The lowest ranked class is Placebo at 37.8 (95% CrI 33rd to 41st) for females and 35.9 (95% CrI 31st to 39th) for males (Table 37).

Table 37: Posterior mean rank and 95% credible intervals of classes for efficacy[a]

Class	Posterior Mean Rank (95% CrI)	
	Females	Males
ACNICARE [physical]	2.7 (1, 10)	2.7 (1, 10)
Photothermal + photodynamic therapy	4.3 (1, 22)	4.3 (1, 22)
Photochemical therapy [red]	4.3 (1, 35)	4.3 (1, 33)
Smoothbeam + Photochemical therapy [blue]	5.5 (1, 20)	5.5 (1, 20)
Chemical peel [physical]	9.2 (2, 28)	9.2 (2, 27)
Photochemical therapy [blue and red]	10.1 (4, 21)	10.0 (4, 21)
Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical]	12.1 (4, 28)	12.1 (4, 28)
Retinoid [topical] + Hydrogen Peroxide [topical]	12.3 (4, 29)	12.2 (4, 28)
Lincosamide [topical] + Azelaic acid [topical]	13.4 (4, 29)	13.3 (4, 29)
Superoxidised solution [topical]	13.9 (3, 35)	13.8 (3, 34)
Photodynamic therapy	14.0 (3, 39)	13.7 (3, 37)

Class	Posterior Mean Rank (95% CrI)	
	Females	Males
Photochemical therapy [blue]	14.1 (6, 27)	14.1 (6, 26)
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	14.4 (4, 33)	14.2 (4, 32)
Benzoyl peroxide [topical] + Retinoid [topical]	15.4 (8, 24)	15.4 (8, 24)
Azelaic acid [topical] + Macrolide [topical]	16.3 (6, 32)	16.2 (6, 31)
Lincosamide [topical] + Retinoid [topical]	17.2 (8, 29)	17.1 (8, 28)
No treatment	17.8 (2, 41)	17.3 (2, 39)
Macrolide [topical] + Anti-fungal [topical]	19.2 (5, 37)	18.9 (5, 35)
Benzoyl peroxide [topical] + Macrolide [topical]	21.0 (8, 35)	20.6 (8, 34)
Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red]	21.5 (6, 39)	21.0 (6, 38)
Lincosamide [topical] + Topical acid [topical]	22.6 (7, 39)	22.1 (7, 37)
Retinoid [topical]	22.7 (15, 31)	22.4 (15, 30)
Photochemical + photothermal therapy	23.0 (5, 41)	22.3 (5, 39)
Benzoyl peroxide [topical] + Lincosamide [topical]	23.1 (15, 32)	22.8 (15, 31)
Tetracycline [oral] + Combined physical peels [physical]	24.2 (6, 40)	23.5 (6, 38)
Combined chemical peels [physical]	24.5 (6, 40)	23.8 (6, 38)
Retinoid [topical] + Macrolide [topical]	24.7 (9, 39)	24.1 (9, 37)
Benzoyl peroxide [topical]	25.5 (18, 33)	25.0 (18, 32)
Antiseptics [topical]	26.9 (9, 40)	26.1 (9, 38)
Topical acid [topical]	28.3 (14, 39)	27.4 (13, 37)
Retinoid - total cumul dose < 120mg/kg (single course) [oral]	28.5 (10, 41)	27.6 (10, 39)
Macrolide [topical]	29.2 (20, 36)	28.3 (20, 35)
Co-cyprindiol [oral]	29.7 (14, 40)	not applicable
Combined Oral Contraceptive [oral]	30.4 (19, 38)	not applicable
Tetracycline [oral]	30.5 (15, 40)	29.5 (15, 38)
Azelaic acid [topical]	31.2 (22, 38)	30.1 (21, 37)
Macrolide [oral]	33.4 (13, 41)	32.0 (13, 39)
Lincosamide [topical]	34.0 (27, 39)	32.6 (26, 37)
Anti-fungal [topical]	35.4 (8, 41)	33.8 (8, 39)
Fusidic acid [topical]	36.7 (25, 41)	35.0 (25, 39)
Placebo	37.8 (33, 41)	35.9 (31, 39)

Abbreviations: CrI, credible interval
a Based on bias-adjusted relative effects expected from a trial of size 1670

Discontinuation for any Reason

After excluding trials with zero events in all arms, 85 trials of 40 classes of 76 interventions licensed in the UK were included for this outcome (Figure 22, Figure 23, Table 38). A continuity correction was applied to data in 10 studies containing at least one zero cell, to stabilize the results. The final results presented in this guideline are based on the fixed study effects, fixed class effects model, as the posterior residual deviance indicated good model fit, the DICs suggested fixed class models were preferred, and there were no meaningful differences between the DICs of this model and the random study, fixed class effects model (Table 39).

Figure 22: Network diagram of direct evidence between classes included in discontinuation for any reason analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular class

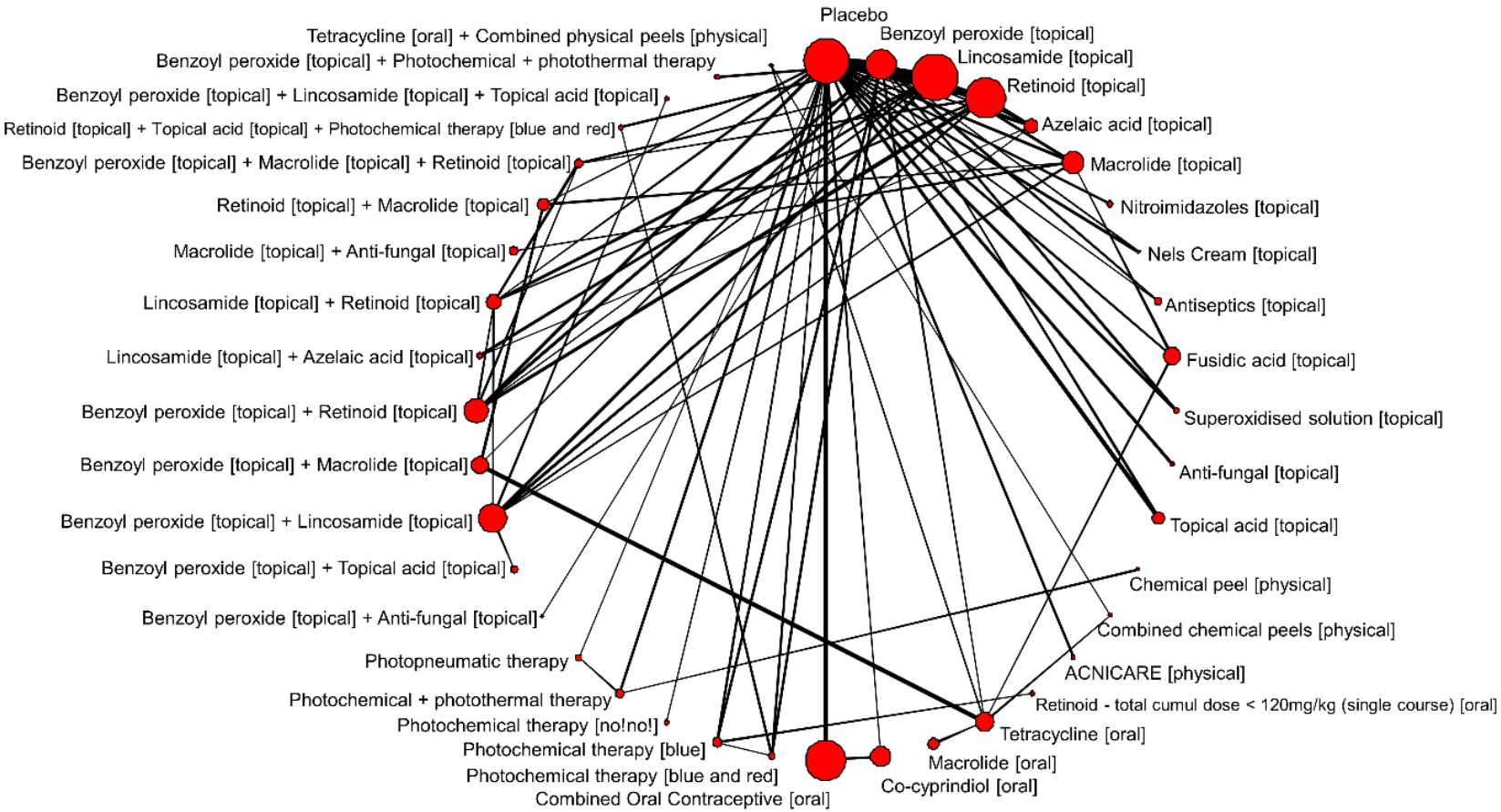


Figure 23: Network diagram of direct evidence between interventions included in discontinuation for any reason analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular intervention.

Table 38: Number of observations for each class, treatment and duration in discontinuation for any reason analysis

Class	n	Treatment	n	Duration	n
Placebo	2893	Placebo [oral]	570	24+ weeks	570
		Placebo [topical]	2256	0 to <6 weeks	60
				6 to <12 weeks	199
				12 to <24 weeks	1997
		Placebo [physical]	67	0 to <6 weeks	32
				12 to <24 weeks	35
Benzoyl peroxide [topical]	1270	Benzoyl peroxide [topical]	1270	6 to <12 weeks	220
				12 to <24 weeks	1015
				24+ weeks	35
Lincosamide [topical]	3073	Clindamycin [topical]	2910	6 to <12 weeks	183
				12 to <24 weeks	2727
		Clindamycin [topical] with Zinc Acetate Dihydrate	163	12 to <24 weeks	163
Retinoid [topical]	2290	Adapalene [topical]	1821	6 to <12 weeks	20
				12 to <24 weeks	1766
				24+ weeks	35
		Tazarotene [topical]	469	12 to <24 weeks	469
Azelaic acid [topical]	263	Azelaic Acid [topical]	263	6 to <12 weeks	25
				12 to <24 weeks	238
Macrolide [topical]	686	Erythromycin [topical]	599	6 to <12 weeks	61
				12 to <24 weeks	538
		Erythromycin [topical] with Zinc Acetate Dihydrate	87	6 to <12 weeks	12
				12 to <24 weeks	75
Nitroimidazoles [topical]	48	Metronidazole [topical]	48	12 to <24 weeks	48
Nels Cream [topical]	15	Nels Cream (chloroxylenol + zinc oxide) [topical]	15	6 to <12 weeks	15
Antiseptics [topical]	80	Chlorhexidine Gluconate/Digluconate [topical]	80	12 to <24 weeks	80
Fusidic acid [topical]	412	Fusidic acid (Sodium Fusidate) [topical]	412	6 to <12 weeks	135
				12 to <24 weeks	277

Class	n	Treatment	n	Duration	n
Superoxidised solution [topical]	39	Superoxidised solution	39	12 to <24 weeks	39
Anti-fungal [topical]	20	Ketoconazole [topical]	20	6 to <12 weeks	20
Topical acid [topical]	204	Glycolic Acid [topical]	59	12 to <24 weeks	59
		Salicylic Acid [topical]	35	12 to <24 weeks	35
		Nisal Cream (chloroxylenol + salicylic acid) [topical]	18	12 to <24 weeks	18
		Gluconolactone [topical]	50	12 to <24 weeks	50
		Diacneal (0.1% retinaldehyde and 6% glycolic acid)	42	12 to <24 weeks	42
Chemical peel [physical]	15	Trichloroaecetic Acid [physical]	15		15
Combined chemical peels [physical]	15	Salicylic Acid [physical] + Glycolic Acid [physical]	15	12 to <24 weeks	15
ACNICARE [physical]	20	ACNICARE (triethyl citrate + ethyl linoleate) [physical]	20	12 to <24 weeks	20
Retinoid - total cumul dose <120mg/kg (single course) [oral]	30	ISO<120.Daily<0.5 [oral]	30	6 to <12 weeks	30
Tetracycline [oral]	489	Doxycycline [oral]	135	12 to <24 weeks	135
		Minocycline [oral]	223	6 to <12 weeks	93
				12 to <24 weeks	130
		Oxytetracycline [oral]	131	12 to <24 weeks	131
Macrolide [oral]	160	Azithromycin [oral]	120	12 to <24 weeks	120
		Erythromycin [oral]	40	0 to <6 weeks	40
Co-cyprindiol [oral]	584	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	584	24+ weeks	584
Combined Oral Contraceptive [oral]	2305	Estradiol (valerate) [oral] + Dienogest [oral]	530	24+ weeks	530
		Ethinylestradiol [oral] + Desogestrel [oral]	118	24+ weeks	118
		Ethinylestradiol [oral] + Drospirenone [oral]	666	24+ weeks	666
		Ethinylestradiol [oral] + Levonorgestrel [oral]	191	24+ weeks	191
		Ethinylestradiol [oral] + Norgestimate [oral]	800	24+ weeks	800
Photochemical therapy [blue and red]	65	Blue + Red light	65	12 to <24 weeks	65
Photochemical therapy [blue]	127	Blue Light LED	127		127
Photochemical therapy [no!no!]	31	no!no! skin device	31		31

Class	n	Treatment	n	Duration	n
Photochemical + photothermal therapy	106	Intense Pulsed Light (IPL)	60		60
		Pulsed Dye Laser	46		46
Photopneumatic therapy	60	Intense Pulsed Light (IPL) + Vacuum	60		60
Benzoyl peroxide [topical] + Anti-fungal [topical]	13	Benzoyl peroxide [topical] + Butenifine [topical]	13	6 to <12 weeks	13
Benzoyl peroxide [topical] + Topical acid [topical]	69	Benzoyl peroxide [topical] + Salicylic Acid [topical]	69	6 to <12 weeks	69
Benzoyl peroxide [topical] + Lincosamide [topical]	1129	Benzoyl peroxide [topical] + Clindamycin [topical]	1129	6 to <12 weeks	70
				12 to <24 weeks	1059
Benzoyl peroxide [topical] + Macrolide [topical]	404	Benzoyl peroxide [topical] + Erythromycin [topical]	404	12 to <24 weeks	404
Benzoyl peroxide [topical] + Retinoid [topical]	834	Benzoyl peroxide [topical] + Adapalene [topical]	745	12 to <24 weeks	710
				24+ weeks	35
		Benzoyl peroxide [topical] + Tazarotene [topical]	89	12 to <24 weeks	89
Lincosamide [topical] + Azelaic acid [topical]	50	Clindamycin [topical] + Azelaic Acid [topical]	50	12 to <24 weeks	50
Lincosamide [topical] + Retinoid [topical]	315	Clindamycin [topical] + Adapalene [topical]	185	12 to <24 weeks	185
		Clindamycin [topical] + Tazarotene [topical]	87	12 to <24 weeks	87
		Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	43	12 to <24 weeks	43
Macrolide [topical] + Anti-fungal [topical]	101	Erythromycin [topical] + Bifonazole [topical]	101	12 to <24 weeks	101
Retinoid [topical] + Macrolide [topical]	194	Isotretinoin [topical] + Erythromycin [topical]	135	12 to <24 weeks	135
		Tretinoin (RETIN A, All-trans retinoic acid) [topical] + Erythromycin [topical]	59	12 to <24 weeks	59
Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical]	90	Benzoyl peroxide [topical] + Erythromycin [topical] + Tazarotene [topical]	90	12 to <24 weeks	90
Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red]	35	Retinol (Vitamin A) [topical] + Salicylic Acid [topical] + Blue + Red light	35	12 to <24 weeks	35
Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical]	25	Benzoyl peroxide [topical] + Clindamycin [topical] + Salicylic Acid [topical]	25	12 to <24 weeks	25
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	32	Benzoyl peroxide [topical] + Intense Pulsed Light (IPL)	32		32
Tetracycline [oral] + Combined physical peels [physical]	15	Doxycycline [oral] + Salicylic Acid [physical] + Glycolic Acid [physical]	15	12 to <24 weeks	15

Table 39: Model fit statistics for discontinuation for any reason

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]
FE, fixed class	**---**	**189.3**	**1023.19**
RE, fixed class	0.07 (0.00, 0.22)	187.0	1023.62
FE, random class (placebos coded the same)	---	187.8	1030.52
FE, random class (placebos coded separately)	---	188.5	1032.48
RE, random class (placebos coded the same)	0.07 (0.00, 0.23)	186.7	1032.26
RE, random class (placebos coded separately)	0.08 (0.00, 0.24)	186.4	1032.09
UME - FE, intervention level	---	207.5	1083.98
UME - FE, class level	---	195.9	1050.90

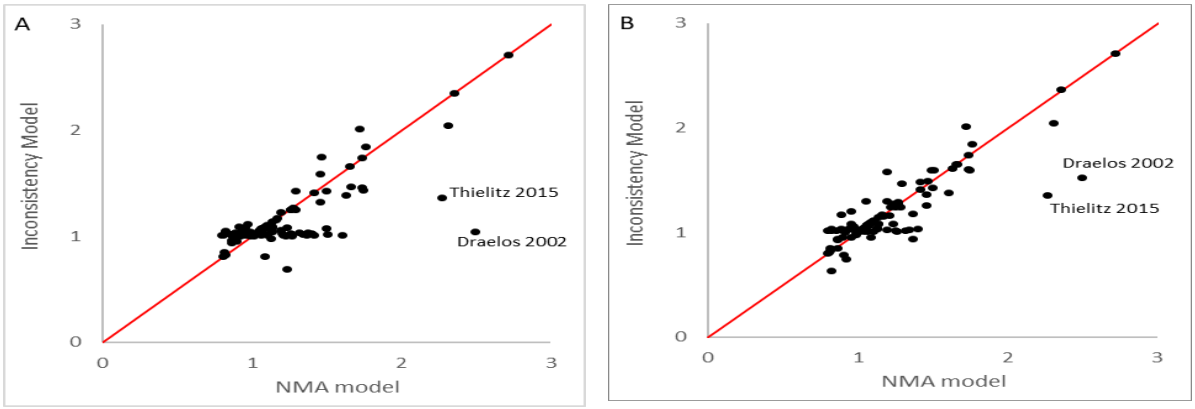
Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; RE, random study effects; SD, standard deviation; UME, unrelated mean effects

[a] *Posterior mean residual deviance compared to 202 total data points*

[b] *Lower values of DIC preferred*

There were no meaningful differences between the fit of the fixed effects consistency and inconsistency models (Table 39). Nevertheless, the area below the line of equality in Figure 24 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in Draelos 2002, a five-arm trial which compared Clindamycin [topical], Tazarotene [topical], Benzoyl peroxide [topical] + Tazarotene [topical], Clindamycin [topical] + Tazarotene [topical], and Benzoyl peroxide [topical] + Erythromycin [topical] + Tazarotene [topical], all with a duration of 12 to <24 weeks, and Thielitz 2015, a three-arm trial which compared Adapalene [topical], Azelaic Acid [topical], and another Azelaic Acid [topical], all with a duration of 12 to <24 weeks.

Figure 24: Deviance contributions for the fixed study, fixed class effects consistency and inconsistency models at (A) the intervention level and (B) the class level for discontinuation for any reason.



For most comparisons, there were no meaningful differences between the fit and DIC of the node split models and the consistency model, apart from Benzoyl peroxide [topical] + Macrolide [topical] vs. Tetracycline [oral] (30 vs. 18) and Lincosamide [topical] + Retinoid [topical] vs. Benzoyl peroxide [topical] + Retinoid [topical] (33 vs. 31) (Table 40). There were differences between the direct and indirect estimates of the latter class comparison (Table 40, Figure 25).

A table of the direct, indirect, and NMA estimates for all pairwise relative effects between classes is available in supplement 6.

Table 40: Node split model fit statistics for discontinuation for any reason

Node split model[a]	Posterior total residual deviance[b]	DIC[c]	p-value[d]
Benzoyl peroxide [topical] vs. Placebo (2 vs. 1)	188.9	1024.0	0.29
Lincosamide [topical] vs. Placebo (3 vs. 1)	189.9	1025.0	0.58
Retinoid [topical] vs. Placebo (4 vs. 1)	190.1	1025.0	0.73
Azelaic acid [topical] vs. Placebo (5 vs. 1)	188.6	1023.0	0.19
Macrolide [topical] vs. Placebo (6 vs. 1)	190.2	1025.0	0.78
Antiseptics [topical] vs. Placebo (9 vs. 1)	189.7	1024.0	0.35
Fusidic acid [topical] vs. Placebo (10 vs. 1)	190.1	1025.0	0.84
Topical acid [topical] vs. Placebo (13 vs. 1)	190.1	1025.0	0.43
Co-cyprindiol [oral] vs. Placebo (20 vs. 1)	190.3	1025.0	0.74
Photochemical therapy [blue and red] vs. Placebo (22 vs. 1)	188.3	1023.0	0.12
Photochemical therapy [blue] vs. Placebo (23 vs. 1)	190.1	1025.0	0.73
Benzoyl peroxide [topical] + Retinoid [topical] vs. Placebo (31 vs. 1)	190.3	1025.0	0.85

Node split model[a]	Posterior total residual deviance[b]	DIC[c]	p-value[d]
Lincosamide [topical] + Retinoid [topical] vs. Placebo (33 vs. 1)	189.6	1024.0	0.32
Retinoid [topical] + Macrolide [topical] vs. Placebo (35 vs. 1)	189.7	1025.0	0.46
Retinoid [topical] vs. Benzoyl peroxide [topical] (4 vs. 2)	189.8	1025.0	0.45
Azelaic acid [topical] vs. Benzoyl peroxide [topical] (5 vs. 2)	190.2	1025.0	0.54
Antiseptics [topical] vs. Benzoyl peroxide [topical] (9 vs. 2)	189.8	1025.0	0.34
Topical acid [topical] vs. Benzoyl peroxide [topical] (13 vs. 2)	190.2	1025.0	0.81
Tetracycline [oral] vs. Benzoyl peroxide [topical] (18 vs. 2)	189.1	1024.0	0.29
Benzoyl peroxide [topical] + Macrolide [topical] vs. Benzoyl peroxide [topical] (30 vs. 2)	189.6	1024.0	0.47
Benzoyl peroxide [topical] + Retinoid [topical] vs. Benzoyl peroxide [topical] (31 vs. 2)	189.8	1025.0	0.41
Retinoid [topical] vs. Lincosamide [topical] (4 vs. 3)	189.6	1024.0	0.45
Azelaic acid [topical] vs. Lincosamide [topical] (5 vs. 3)	189.6	1024.0	0.38
Macrolide [topical] vs. Lincosamide [topical] (6 vs. 3)	189.7	1025.0	0.44
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Lincosamide [topical] (29 vs. 3)	190.1	1025.0	0.70
Benzoyl peroxide [topical] + Retinoid [topical] vs. Lincosamide [topical] (31 vs. 3)	190.0	1025.0	0.62
Lincosamide [topical] + Retinoid [topical] vs. Lincosamide [topical] (33 vs. 3)	190.2	1025.0	0.71
Azelaic acid [topical] vs. Retinoid [topical] (5 vs. 4)	188.5	1023.0	0.17
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Retinoid [topical] (29 vs. 4)	188.7	1023.0	0.23
Benzoyl peroxide [topical] + Retinoid [topical] vs. Retinoid [topical] (31 vs. 4)	190.4	1025.0	0.78
Lincosamide [topical] + Retinoid [topical] vs. Retinoid [topical] (33 vs. 4)	189.7	1025.0	0.45
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Azelaic acid [topical] (29 vs. 5)	189.1	1024.0	0.26
Fusidic acid [topical] vs. Macrolide [topical] (10 vs. 6)	189.0	1024.0	0.25
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Macrolide [topical] (29 vs. 6)	189.8	1025.0	0.50
Retinoid [topical] + Macrolide [topical] vs. Macrolide [topical] (35 vs. 6)	190.1	1025.0	0.56
Tetracycline [oral] vs. Fusidic acid [topical] (18 vs. 10)	189.1	1024.0	0.28
Benzoyl peroxide [topical] + Macrolide [topical] vs. Tetracycline [oral] (30 vs. 18)	189.1	1019.0	0.43
Photochemical therapy [blue] vs. Photochemical therapy [blue and red] (23 vs. 22)	190.2	1025.0	0.74
Lincosamide [topical] + Retinoid [topical] vs. Benzoyl peroxide [topical] + Lincosamide [topical] (33 vs. 29)	190.3	1025.0	0.63
Retinoid [topical] + Macrolide [topical] vs. Benzoyl peroxide [topical] + Macrolide [topical] (35 vs. 30)	189.7	1025.0	0.46
Lincosamide [topical] + Retinoid [topical] vs. Benzoyl peroxide [topical] + Retinoid [topical] (33 vs. 31)	186.0	1021.0	0.03
NMA (no nodes split)	**189.3**	**1023.2**	

Abbreviations: CrI, credible interval; DIC, deviance information criteria; NMA, network meta-analysis; SD, standard deviation.

Values in red suggest evidence of inconsistency (either reduced posterior total residual deviance or DIC following node-split testing, or p-value <0.05)

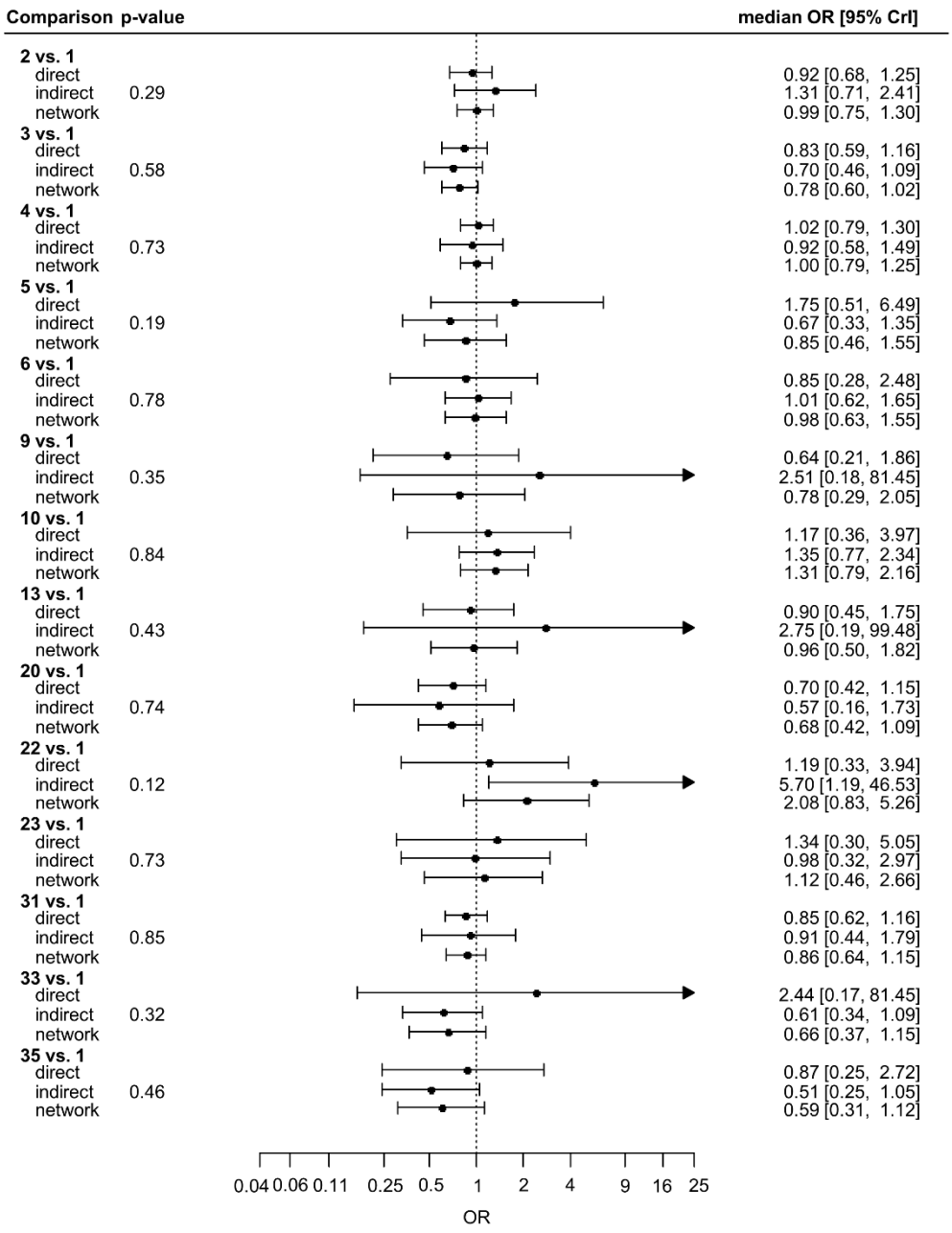
[a] *Continuity correction applied to studies containing zero cells*

[b] *Posterior mean residual deviance compared to 202 total data points*

[c] *Lower values of DIC preferred*

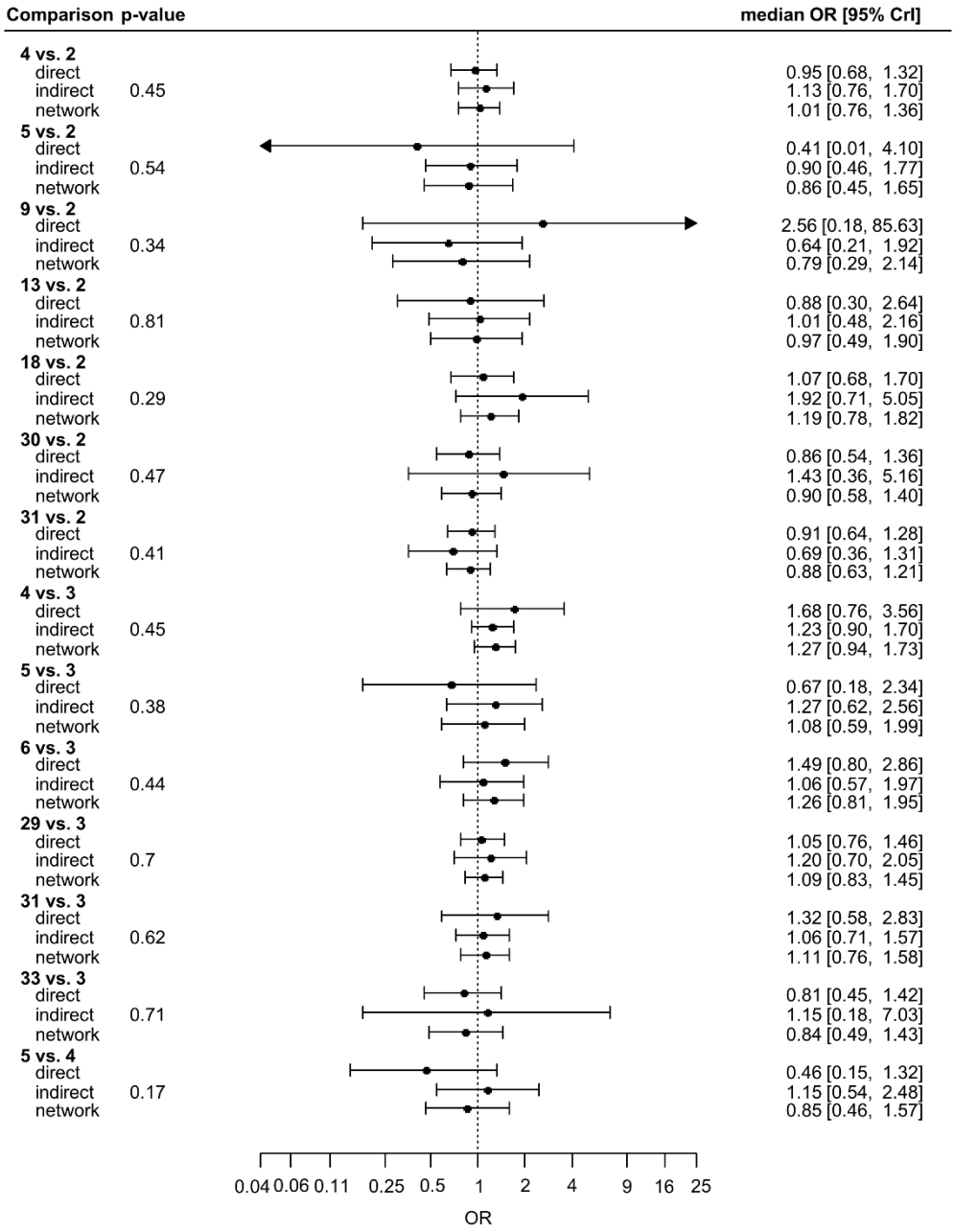
[d] *p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates*

Figure 25: Forest plot of direct, indirect and network meta-analysis estimates of class comparisons for discontinuation for any reason (continued on next page).



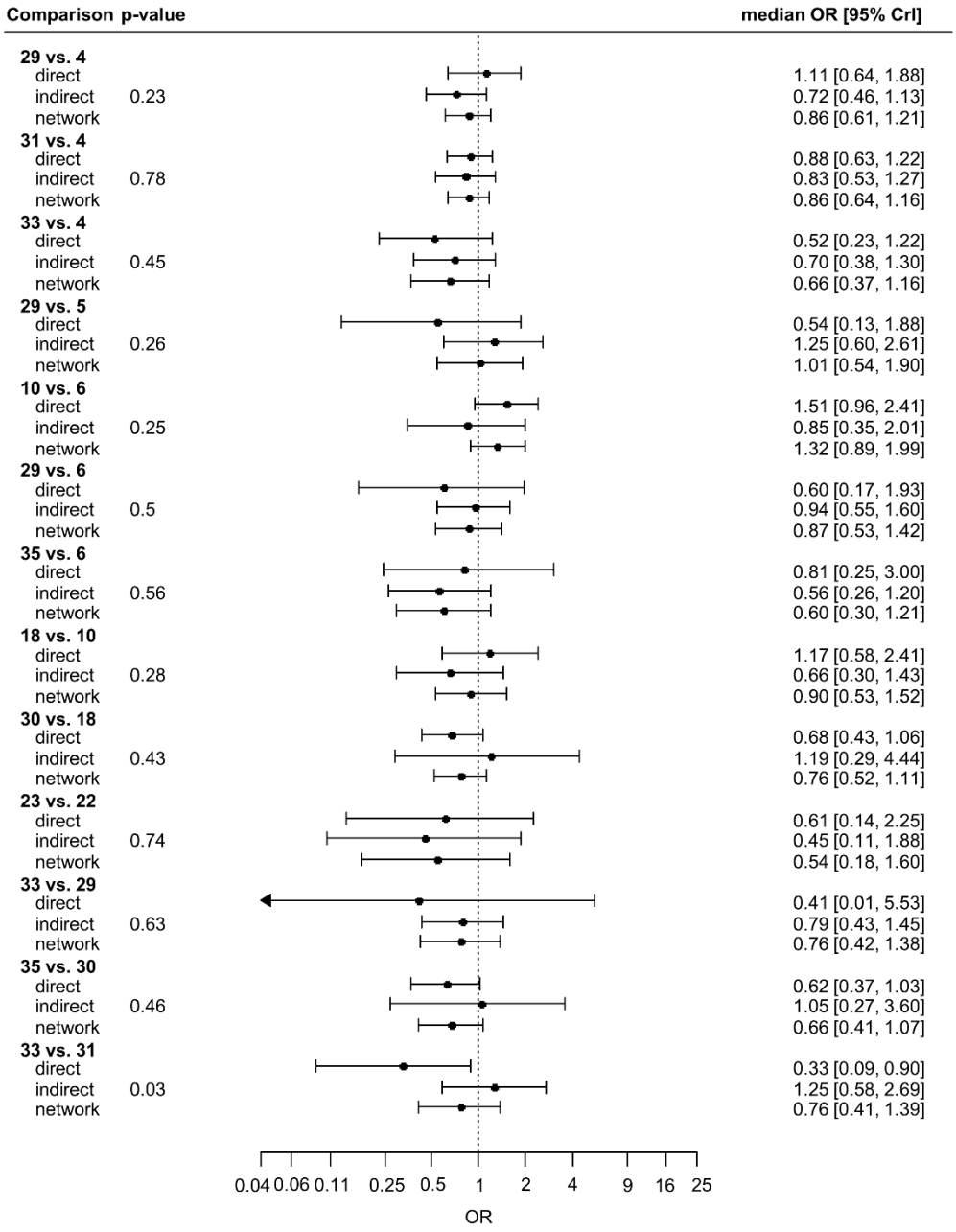
Class codes: 1 – Placebo, 2 - Benzoyl peroxide [topical], 3 - Lincosamide [topical], 4 - Retinoid [topical], 5 - Azelaic acid [topical], 6 - Macrolide [topical], 7 - Nitroimidazoles [topical], 8 - Nels Cream [topical], 9 - Antiseptics [topical], 10 - Fusidic acid [topical], 11 - Superoxidised solution [topical], 12 - Anti-fungal [topical], 13 - Topical acid [topical], 14 - Chemical peel [physical], 15 - Combined chemical peels [physical], 16 - ACNICARE [physical], 17 - Retinoid - total cumul dose < 120mg/kg (single course) [oral], 18 - Tetracycline [oral], 19 - Macrolide [oral], 20 - Co-cyprindiol [oral], 21 - Combined Oral Contraceptive [oral], 22 - Photochemical therapy [blue and red], 23 - Photochemical therapy [blue], 24 - Photochemical therapy [no!no!], 25 - Photochemical + photothermal therapy, 26 - Photopneumatic therapy, 27 - Benzoyl peroxide [topical] + Anti-fungal [topical], 28 - Benzoyl peroxide [topical] + Topical acid [topical], 29 - Benzoyl peroxide [topical] + Lincosamide [topical], 30 - Benzoyl peroxide [topical] + Macrolide [topical], 31 - Benzoyl peroxide [topical] + Retinoid [topical], 32 - Lincosamide [topical] + Azelaic acid [topical], 33 - Lincosamide [topical] + Retinoid [topical], 34 - Macrolide [topical] + Anti-fungal [topical], 35 - Retinoid [topical] + Macrolide [topical], 36 - Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical], 37 - Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red], 38 - Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical], 39 - Benzoyl peroxide [topical] + Photochemical + photothermal therapy, 40 - Tetracycline [oral] + Combined physical peels [physical].

Continued from previous page and on next page



Class codes: 1 – Placebo, 2 - Benzoyl peroxide [topical], 3 - Lincosamide [topical], 4 - Retinoid [topical], 5 - Azelaic acid [topical], 6 - Macrolide [topical], 7 - Nitroimidazoles [topical], 8 - Nels Cream [topical], 9 - Antiseptics [topical], 10 - Fusidic acid [topical], 11 - Superoxidised solution [topical], 12 - Anti-fungal [topical], 13 - Topical acid [topical], 14 - Chemical peel [physical], 15 - Combined chemical peels [physical], 16 - ACNICARE [physical], 17 - Retinoid - total cumul dose < 120mg/kg (single course) [oral], 18 - Tetracycline [oral], 19 - Macrolide [oral], 20 - Co-cyprindiol [oral], 21 - Combined Oral Contraceptive [oral], 22 - Photochemical therapy [blue and red], 23 - Photochemical therapy [blue], 24 - Photochemical therapy [no!no!], 25 - Photochemical + photothermal therapy, 26 - Photopneumatic therapy, 27 - Benzoyl peroxide [topical] + Anti-fungal [topical], 28 - Benzoyl peroxide [topical] + Topical acid [topical], 29 - Benzoyl peroxide [topical] + Lincosamide [topical], 30 - Benzoyl peroxide [topical] + Macrolide [topical], 31 - Benzoyl peroxide [topical] + Retinoid [topical], 32 - Lincosamide [topical] + Azelaic acid [topical], 33 - Lincosamide [topical] + Retinoid [topical], 34 - Macrolide [topical] + Anti-fungal [topical], 35 - Retinoid [topical] + Macrolide [topical], 36 - Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical], 37 - Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red], 38 - Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical], 39 - Benzoyl peroxide [topical] + Photochemical + photothermal therapy, 40 - Tetracycline [oral] + Combined physical peels [physical].

Continued from previous page



Class codes: 1 – Placebo, 2 - Benzoyl peroxide [topical], 3 - Lincosamide [topical], 4 - Retinoid [topical], 5 - Azelaic acid [topical], 6 - Macrolide [topical], 7 - Nitroimidazoles [topical], 8 - Nels Cream [topical], 9 - Antiseptics [topical], 10 - Fusidic acid [topical], 11 - Superoxidised solution [topical], 12 - Anti-fungal [topical], 13 - Topical acid [topical], 14 - Chemical peel [physical], 15 - Combined chemical peels [physical], 16 - ACNICARE [physical], 17 - Retinoid - total cumul dose < 120mg/kg (single course) [oral], 18 - Tetracycline [oral], 19 - Macrolide [oral], 20 - Co-cyprindiol [oral], 21 - Combined Oral Contraceptive [oral], 22 - Photochemical therapy [blue and red], 23 - Photochemical therapy [blue], 24 - Photochemical therapy [no!no!], 25 - Photochemical + photothermal therapy, 26 - Photopneumatic therapy, 27 - Benzoyl peroxide [topical] + Anti-fungal [topical], 28 - Benzoyl peroxide [topical] + Topical acid [topical], 29 - Benzoyl peroxide [topical] + Lincosamide [topical], 30 - Benzoyl peroxide [topical] + Macrolide [topical], 31 - Benzoyl peroxide [topical] + Retinoid [topical], 32 - Lincosamide [topical] + Azelaic acid [topical], 33 - Lincosamide [topical] + Retinoid [topical], 34 - Macrolide [topical] + Anti-fungal [topical], 35 - Retinoid [topical] + Macrolide [topical], 36 - Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical], 37 - Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red], 38 - Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical], 39 - Benzoyl peroxide [topical] + Photochemical + photothermal therapy, 40 - Tetracycline [oral] + Combined physical peels [physical].

There was sufficient variation in the ratings of studies to fit bias models on two risk of bias domains:

- Domain 1: Randomisation
- Domain 4: Outcome measurement (efficacy)

No evidence of bias arising from these domains was found, nor was study effect bias, as the 95% credible intervals of the posterior mean bias include zero (Table 41).

Evidence suggested that the Benzoyl peroxide [topical] + Photochemical + photothermal therapy class decreased the odds of discontinuation compared to Placebo. No other classes decreased or increased the odds of discontinuation compared to Placebo (supplement 6).

Chemical peel [physical] is the highest ranked class for both females and males, with posterior mean ranks of 4.3 (95% CrI 1st to 31st) and 4.1 (95% CrI 1st to 29th), respectively (Table 42). The lowest ranked class is Photochemical therapy [no!no!] at 36.5 (95% CrI 10th to 40th) for females and 34.6 (95% CrI 9th to 38th) for males (Table 42).

Table 41: Bias model fit statistics for discontinuation for any reason

Model	Posterior total residual deviance[a]	DIC[b]	Bias	
			Posterior median (95% CrI)	Between Study SD (95% CrI)
NMA model: FE, fixed class	**189.3**	**1023.19**	**---**	**---**
Bias model: Domain 1	188.8	1026.62	-0.06 (-0.41, 0.29)	0.11 (0.00, 0.34)
Bias model: Domain 4	189.1	1026.24	0.11 (-0.26, 0.51)	0.19 (0.01, 0.64)
Bias model: Small study	188.5	1026.23	2.62 (-2.69, 8.08)	1.39 (0.06, 4.54)

Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; NMA, network meta-analysis; SD, standard deviation

[a] *Posterior mean residual deviance compared to 202 total data points*

[b] *Lower values of DIC preferred*

Table 42: Posterior mean rank and 95% credible intervals of classes for discontinuation for any reason

Class	Posterior Mean Rank (95% CrI)	
	Females	Males
Chemical peel [physical]	4.3 (1, 31)	4.1 (1, 29)
Superoxidised solution [topical]	5.8 (1, 34)	5.7 (1, 32)
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	6.0 (1, 22)	5.9 (1, 20)
Anti-fungal [topical]	60. (1, 35)	5.8 (1, 33)
Combined chemical peels [physical]	9.4 (1, 36)	9.0 (1, 34)
Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical]	10.1 (3, 28)	9.8 (3, 26)
Photopneumatic therapy	12 (4, 30)	11.6 (4, 28)
Retinoid [topical] + Macrolide [topical]	12.1 (5, 26)	11.6 (5, 24)
Lincosamide [topical] + Retinoid [topical]	13.8 (6, 28)	13.2 (6, 27)
Photochemical + photothermal therapy	14.2 (5, 31)	13.6 (5, 29)
Co-cyprindiol [oral]	14.4 (6, 28)	not applicable
Lincosamide [topical]	16.7 (10, 25)	15.8 (10, 23)
Benzoyl peroxide [topical] + Topical acid [topical]	17.0 (3, 36)	16.2 (3, 34)
ACNICARE [physical]	17.3 (3, 38)	16.4 (3, 36)

Class	Posterior Mean Rank (95% CrI)	
	Females	Males
Tetracycline [oral] + Combined physical peels [physical]	17.6 (2, 38)	16.7 (2, 36)
Antiseptics [topical]	18.3 (5, 35)	17.4 (5, 33)
Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red]	18.8 (3, 37)	17.9 (3, 35)
Lincosamide [topical] + Azelaic acid [topical]	18.9 (4, 36)	17.9 (4, 34)
Benzoyl peroxide [topical] + Lincosamide [topical]	19.5 (11, 29)	18.4 (11, 28)
Benzoyl peroxide [topical] + Retinoid [topical]	19.5 (11, 29)	18.4 (11, 27)
Azelaic acid [topical]	19.6 (8, 33)	18.5 (7, 31)
Benzoyl peroxide [topical] + Macrolide [topical]	20.6 (10, 32)	19.4 (10, 30)
Combined Oral Contraceptive [oral]	22.3 (13, 32)	not applicable
Topical acid [topical]	22.4 (8, 35)	21.1 (8, 33)
Macrolide [topical]	23.2 (12, 32)	21.8 (11, 31)
Benzoyl peroxide [topical]	23.7 (15, 31)	22.2 (15, 29)
Retinoid [topical]	24.2 (16, 31)	22.7 (15, 30)
Placebo	24.4 (18, 31)	22.8 (16, 29)
Photochemical therapy [blue]	25.2 (8, 36)	23.7 (8, 34)
Tetracycline [oral]	27.7 (16, 35)	25.9 (15, 33)
Macrolide [topical] + Anti-fungal [topical]	28.3 (11, 37)	26.6 (11, 35)
Nels Cream [topical]	28.7 (4, 39)	27.1 (4, 37)
Fusidic acid [topical]	29.6 (18, 36)	27.8 (17, 34)
Nitroimidazoles [topical]	30.1 (4, 40)	28.5 (4, 38)
Benzoyl peroxide [topical] + Anti-fungal [topical]	30.2 (4, 40)	28.6 (4, 38)
Retinoid - total cumul dose < 120mg/kg (single course) [oral]	31.0 (6, 40)	29.3 (6, 38)
Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical]	31.9 (3, 40)	30.3 (3, 38)
Photochemical therapy [blue and red]	33.7 (19, 39)	31.7 (18, 37)
Macrolide [oral]	35.2 (21, 40)	33.3 (20, 38)
Photochemical therapy [no!no!]	36.5 (10, 40)	34.6 (9, 38)

[a] *Abbreviations: CrI, credible interval*

Discontinuation due to Side Effects

After excluding trials with zero events in all arms, 48 trials of 47 interventions and 23 classes were included for this outcome (Figure 26, Figure 27, Table 43). A continuity correction was applied to data in 22 studies containing at least one zero cell to stabilize the results. The final results presented in this guideline are based on the fixed study effects, fixed class effects model, as the posterior residual deviance indicated adequate model fit, the smaller posterior residual deviances of the more complex models suggested overfitting, and there were no meaningful differences between the DICs (Table 44).

Figure 26: Network diagram of direct evidence between classes included in discontinuation due to side effects analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular class.

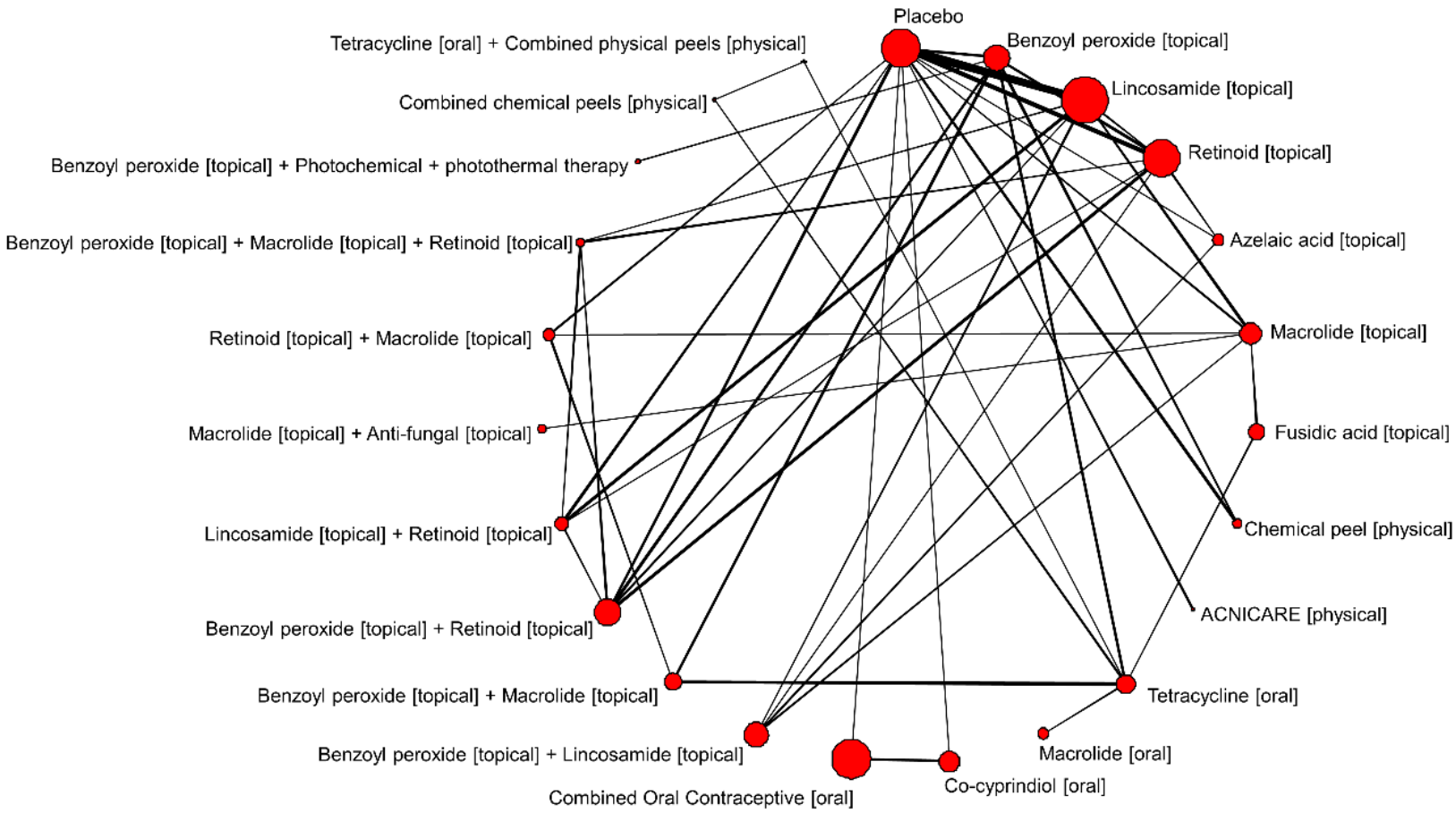


Figure 27: Network diagram of direct evidence between interventions included in discontinuation due to side effects analysis. The width of the lines is proportional to the number of studies making the comparisons, while the size of the nodes is proportional to the number of observations on a particular intervention.

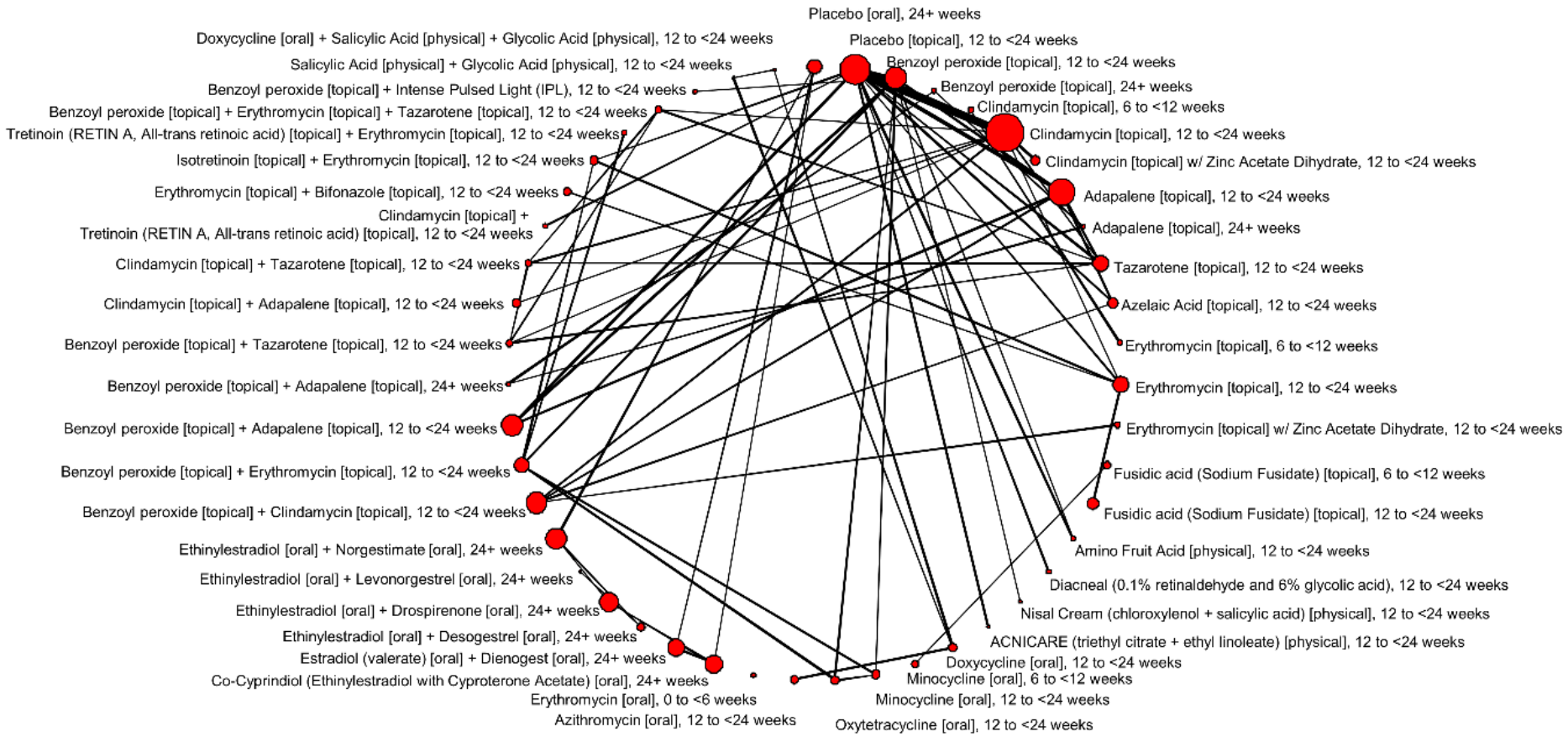


Table 43: Number of observations for each class, treatment and duration in discontinuation due to side effects analysis

Class	n	Treatment	n	Duration	N
Placebo	2024	Placebo [oral]	380	24+ weeks	380

Class	n	Treatment	n	Duration	N
		Placebo [topical]	1644	12 to <24 weeks	1644
Benzoyl peroxide [topical]	912	Benzoyl peroxide [topical]	912	12 to <24 weeks	877
				24+ weeks	35
Lincosamide [topical]	2916	Clindamycin [topical]	2753	6 to <12 weeks	59
				12 to <24 weeks	2694
		Clindamycin [topical] with Zinc Acetate Dihydrate	163	12 to <24 weeks	163
Retinoid [topical]	1840	Adapalene [topical]	1371	12 to <24 weeks	1336
				24+ weeks	35
		Tazarotene [topical]	469	12 to <24 weeks	469
Azelaic acid [topical]	188	Azelaic Acid [topical]	188	12 to <24 weeks	188
Macrolide [topical]	619	Erythromycin [topical]	544	6 to <12 weeks	61
				12 to <24 weeks	483
		Erythromycin [topical] with Zinc Acetate Dihydrate	75	12 to <24 weeks	75
Fusidic acid [topical]	344	Fusidic acid (Sodium Fusidate) [topical]	344	6 to <12 weeks	95
				12 to <24 weeks	249
Topical acid [topical]	110	Gluconolactone [topical]	50	12 to <24 weeks	50
		Diacneal (0.1% retinaldehyde and 6% glycolic acid) [topical]	42	12 to <24 weeks	42
		Nisal Cream (chloroxylenol + salicylic acid) [topical]	18	12 to <24 weeks	18
ACNICARE [physical]	20	ACNICARE (triethyl citrate + ethyl linoleate) [physical]	20	12 to <24 weeks	20
Tetracycline [oral]	489	Doxycycline [oral]	135	12 to <24 weeks	135
		Minocycline [oral]	223	6 to <12 weeks	93
				12 to <24 weeks	130
		Oxytetracycline [oral]	131	12 to <24 weeks	131
Macrolide [oral]	160	Azithromycin [oral]	120	12 to <24 weeks	120
		Erythromycin [oral]	40	0 to <6 weeks	40
Co-cyprindiol [oral]	584	Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral]	584	24+ weeks	584
Combined Oral Contraceptive [oral]	2115	Estradiol (valerate) [oral] + Dienogest [oral]	530	24+ weeks	530

Class	n	Treatment	n	Duration	N
		Ethinylestradiol [oral] + Desogestrel [oral]	118	24+ weeks	118
		Ethinylestradiol [oral] + Drospirenone [oral]	650	24+ weeks	650
		Ethinylestradiol [oral] + Levonorgestrel [oral]	17	24+ weeks	17
		Ethinylestradiol [oral] + Norgestimate [oral]	800	24+ weeks	800
Benzoyl peroxide [topical] + Lincosamide [topical]	829	Benzoyl peroxide [topical] + Clindamycin [topical]	829	12 to <24 weeks	829
Benzoyl peroxide [topical] + Macrolide [topical]	404	Benzoyl peroxide [topical] + Erythromycin [topical]	404	12 to <24 weeks	404
Benzoyl peroxide [topical] + Retinoid [topical]	957	Benzoyl peroxide [topical] + Adapalene [topical]	868	12 to <24 weeks	833
				24+ weeks	35
		Benzoyl peroxide [topical] + Tazarotene [topical]	89	12 to <24 weeks	89
Lincosamide [topical] + Retinoid [topical]	255	Clindamycin [topical] + Adapalene [topical]	125	12 to <24 weeks	125
		Clindamycin [topical] + Tazarotene [topical]	87	12 to <24 weeks	87
		Clindamycin [topical] + Tretinoin (RETIN A, All-trans retinoic acid) [topical]	43	12 to <24 weeks	43
Macrolide [topical] + Anti-fungal [topical]	101	Erythromycin [topical] + Bifonazole [topical]	101	12 to <24 weeks	101
Retinoid [topical] + Macrolide [topical]	194	Isotretinoin [topical] + Erythromycin [topical]	135	12 to <24 weeks	135
		Tretinoin (RETIN A, All-trans retinoic acid) [topical] + Erythromycin [topical]	59	12 to <24 weeks	59
Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical]	90	Benzoyl peroxide [topical] + Erythromycin [topical] + Tazarotene [topical]	90	12 to <24 weeks	90
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	32	Benzoyl peroxide [topical] + Intense Pulsed Light (IPL)	32	12 to <24 weeks	32
Combined chemical peels [physical]	15	Salicylic Acid [physical] + Glycolic Acid [physical]	15	12 to <24 weeks	15
Tetracycline [oral] + Combined physical peels [physical]	15	Doxycycline [oral] + Salicylic Acid [physical] + Glycolic Acid [physical]	15	12 to <24 weeks	15

1 **Table 44: Model fit statistics for discontinuation due to side effects**

Model	Between Study Heterogeneity - SD (95% CrI)	Posterior total residual deviance[a]	DIC[b]
FE, fixed class	**---**	**125.3**	**500.612**

RE, fixed class	0.37 (0.03, 0.83)	117.1	500.054
FE, random class (placebos coded the same)	---	118.8	501.961
FE, random class (placebos coded separately)	---	118.7	501.968
RE, random class (placebos coded the same)	0.30 (0.02, 0.79)	115.2	502.678
RE, random class (placebos coded separately)	0.32 (0.02, 0.80)	115.0	502.715
UME - FE, intervention level	---	122.8	520.408
UME - FE, class level	---	118.8	505.968

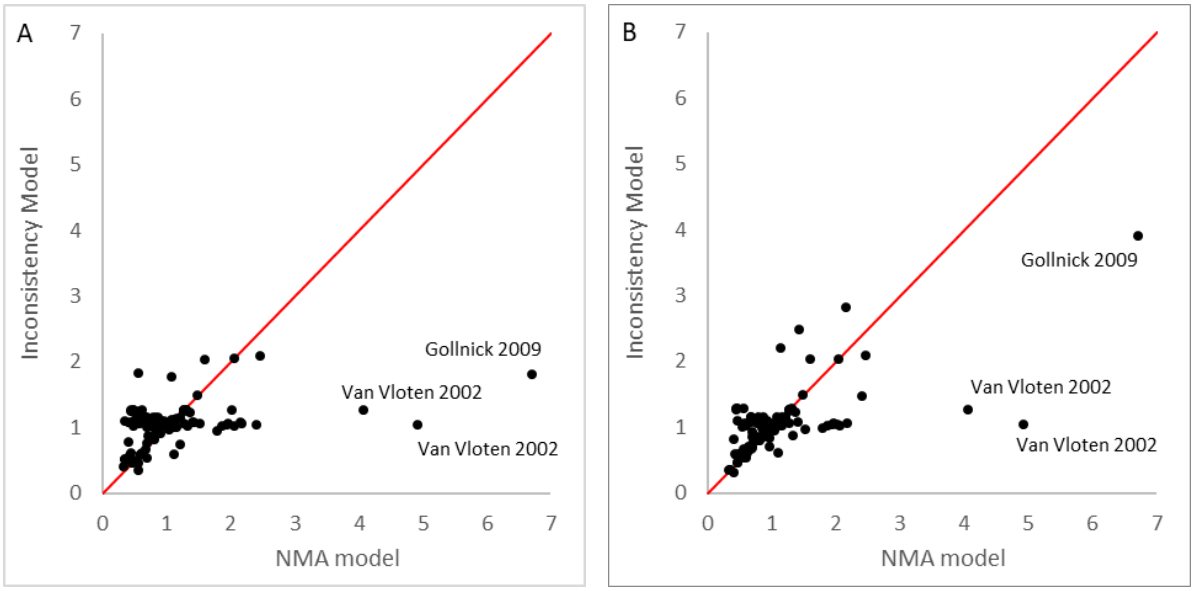
Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; RE, random study effects; SD, standard deviation; UME, unrelated mean effects

[a] *Posterior mean residual deviance compared to 123 total data points*

[b] *Lower values of DIC preferred*

There were no meaningful differences between the fit of the fixed effects consistency and inconsistency models (Table 44). Nevertheless, the area below the line of equality in Figure 28 highlights where the inconsistency model better predicted data points, and there were notable improvements in the prediction of data in Gollnick 2009, a four-arm trial which compared Placebo [topical], Benzoyl peroxide [topical], Adapalene [topical], and Benzoyl peroxide [topical] + Adapalene [topical], all with a duration of 12 to <24 weeks, and Van Vloten 2002, a two-arm trial which compared Co-Cyprindiol (Ethinylestradiol with Cyproterone Acetate) [oral] and Ethinylestradiol [oral] + Drospirenone [oral], all with a duration of 24+ weeks.

Figure 28: Deviance contributions for the fixed study, fixed class effects consistency and inconsistency models at (A) the intervention level and (B) the class level for discontinuation due to side effects.



For most comparisons, there were no meaningful differences between the fit and/or DIC of the node split models and the consistency model. There were some differences for the following class comparisons (Table 45):

- Co-cyprindiol [oral] vs. Placebo (12 vs. 1)
- Retinoid [topical] vs. Benzoyl peroxide [topical] (4 vs. 2)
- Benzoyl peroxide [topical] + Retinoid [topical] vs. Lincosamide [topical] (16 vs. 3)
- Benzoyl peroxide [topical] + Macrolide [topical] vs. Tetracycline [oral] (15 vs. 10)

In addition to the first three listed class comparisons, there were differences between the direct and indirect estimates of the following class comparisons (Table 45, Figure 29):

- Tetracycline [oral] vs. Benzoyl peroxide [topical] (10 vs. 2)
- Fusidic acid [topical] vs. Macrolide [topical] (7 vs. 6)
- Tetracycline [oral] vs. Fusidic acid [topical] (10 vs. 7)

A table of the direct, indirect, and NMA estimates for all pairwise relative effects between classes is available in supplement 6.

Table 45: Node split model fit statistics for discontinuation due to side effects

Node split model[a]	Posterior total residual deviance[b]	DIC[c]	p-value[d]
Benzoyl peroxide [topical] vs. Placebo (2 vs. 1)	126.3	502.6	0.82
Lincosamide [topical] vs. Placebo (3 vs. 1)	126.1	502.5	0.68
Retinoid [topical] vs. Placebo (4 vs. 1)	123.6	500.0	0.09
Azelaic acid [topical] vs. Placebo (5 vs. 1)	125.9	502.3	0.46
Macrolide [topical] vs. Placebo (6 vs. 1)	126.3	502.4	0.45
Topical [acid] vs. Placebo (8 vs. 1)	126.2	502.4	0.72
Co-cyprindiol [oral] vs. Placebo (12 vs. 1)	116.1	492.1	0.00
Benzoyl peroxide [topical] + Retinoid [topical] vs. Placebo (16 vs. 1)	123.3	499.6	0.08
Lincosamide [topical] + Retinoid [topical] vs. Placebo (17 vs. 1)	126.4	502.5	0.53
Retinoid [topical] + Macrolide [topical] vs. Placebo (19 vs. 1)	125.4	501.6	0.27
Retinoid [topical] vs. Benzoyl peroxide [topical] (4 vs. 2)	114.3	490.6	0.00
Topical [acid] vs. Benzoyl peroxide [topical] (8 vs. 2)	126.5	502.5	0.59
Tetracycline [oral] vs. Benzoyl peroxide [topical] (10 vs. 2)	122.8	499.1	0.04
Benzoyl peroxide [topical] + Macrolide [topical] vs. Benzoyl peroxide [topical] (15 vs. 2)	125.4	501.6	0.27
Benzoyl peroxide [topical] + Retinoid [topical] vs. Benzoyl peroxide [topical] (16 vs. 2)	126	502.3	0.63
Retinoid [topical] vs. Lincosamide [topical] (4 vs. 3)	123.1	499.5	0.07
Macrolide [topical] vs. Lincosamide [topical] (6 vs. 3)	124.2	500.5	0.14
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Lincosamide [topical] (14 vs. 3)	125.4	501.7	0.29
Benzoyl peroxide [topical] + Retinoid [topical] vs. Lincosamide [topical] (16 vs. 3)	122.2	498.6	0.04
Lincosamide [topical] + Retinoid [topical] vs. Lincosamide [topical] (17 vs. 3)	126.4	502.6	0.53
Azelaic acid [topical] vs. Retinoid [topical] (5 vs. 4)	126.3	502.6	0.79
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Retinoid [topical] (14 vs. 4)	124.9	501.1	0.18
Benzoyl peroxide [topical] + Retinoid [topical] vs. Retinoid [topical] (16 vs. 4)	122.8	499.2	0.06
Lincosamide [topical] + Retinoid [topical] vs. Retinoid [topical] (17 vs. 4)	123.1	499.4	0.07
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Azelaic acid [topical] (14 vs. 5)	126.1	502.2	0.39
Fusidic acid [topical] vs. Macrolide [topical] (7 vs. 6)	122.9	499.2	0.04
Benzoyl peroxide [topical] + Lincosamide [topical] vs. Macrolide [topical] (14 vs. 6)	126.2	502.3	0.61
Retinoid [topical] + Macrolide [topical] vs. Macrolide [topical] (19 vs. 6)	126.3	502.5	0.46
Tetracycline [oral] vs. Fusidic acid [topical] (10 vs. 7)	122.8	499.0	0.04
Benzoyl peroxide [topical] + Macrolide [topical] vs. Tetracycline [oral] (15 vs. 10)[e]	124.8	497.2	0.30
Retinoid [topical] + Macrolide [topical] vs. Benzoyl peroxide [topical] + Macrolide [topical] (19 vs. 15)	125.5	501.8	0.26
Lincosamide [topical] + Retinoid [topical] vs. Benzoyl peroxide [topical] + Retinoid [topical] (17 vs. 16)	126.5	502.8	0.99
NMA (no nodes split)	125.3	500.6	

Abbreviations: CrI, credible interval; DIC, deviance information criteria; NMA, network meta-analysis; SD, standard deviation

Values in red suggest evidence of inconsistency (either reduced posterior total residual deviance or DIC following node-split testing, or p-value <0.05)

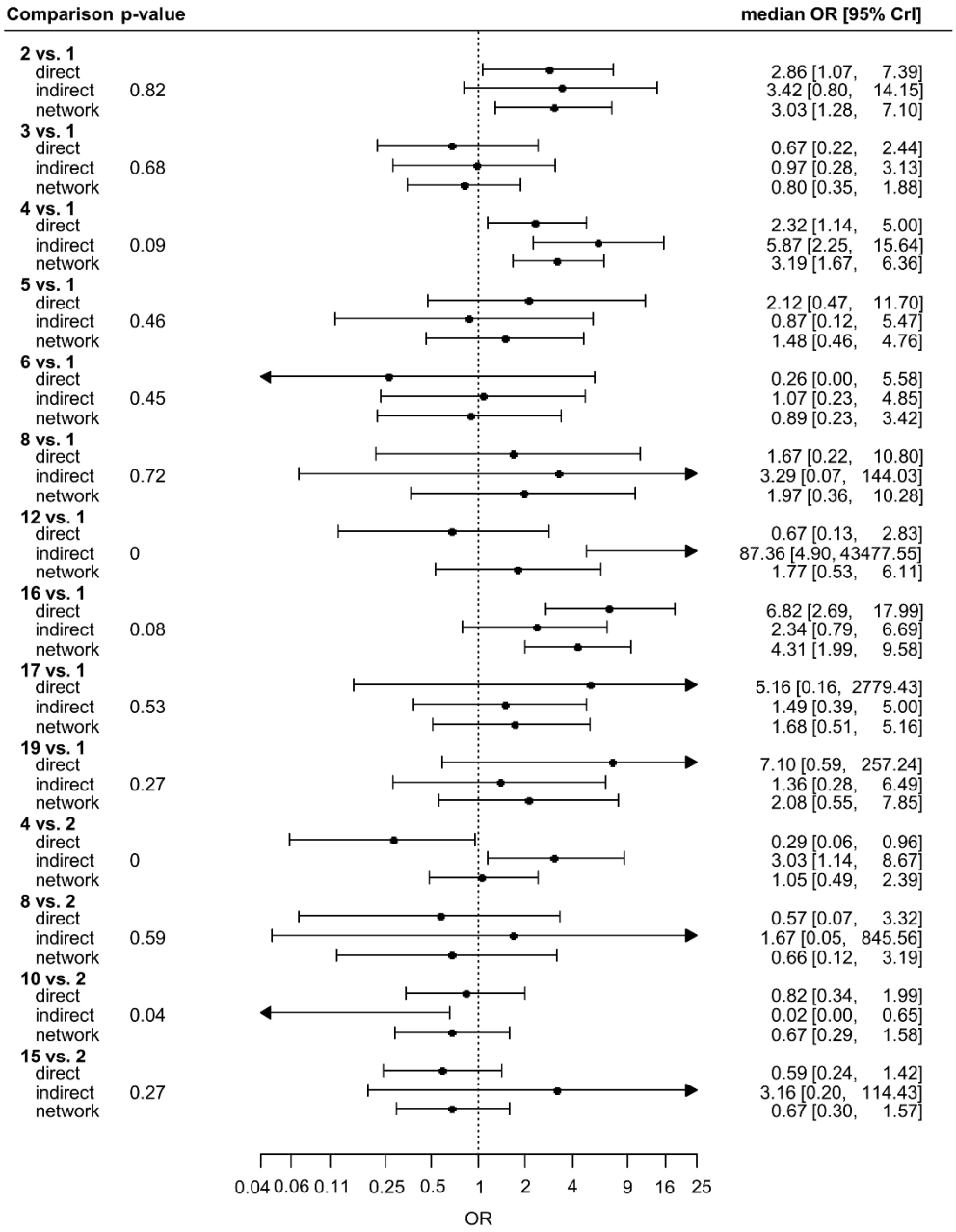
[a] *Continuity correction applied to studies containing zero cells*

[b] *Posterior mean residual deviance compared to 123 total data points*

[c] *Lower values of DIC preferred*

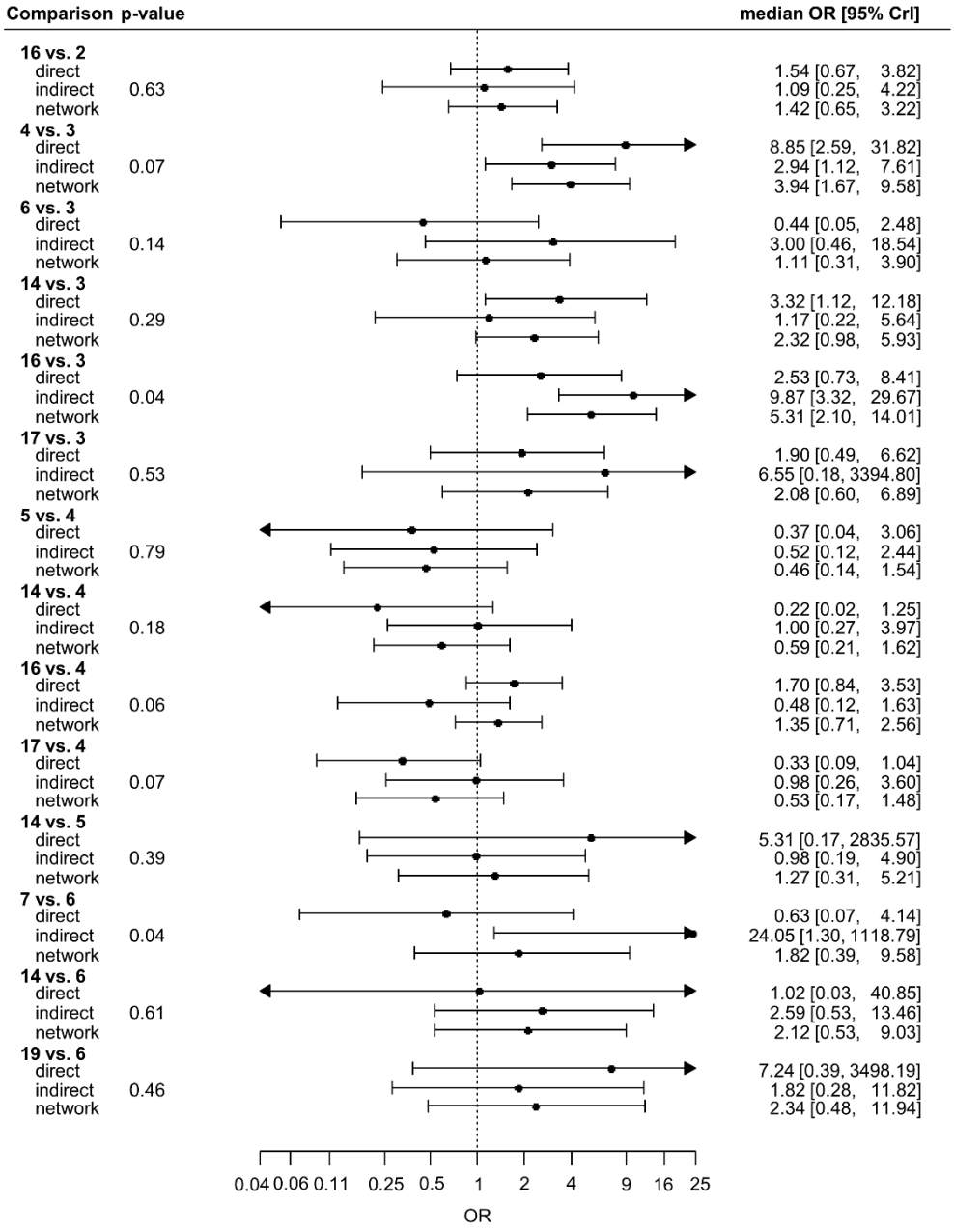
[d] *p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates*
[e] *One multi-arm trial made this comparison twice, so one of the repeated interventions was randomly removed to approximate direct and indirect estimates.*

Figure 29: Forest plot of direct, indirect and network meta-analysis estimates of class comparisons for discontinuation due to side effects. Continued on next page.



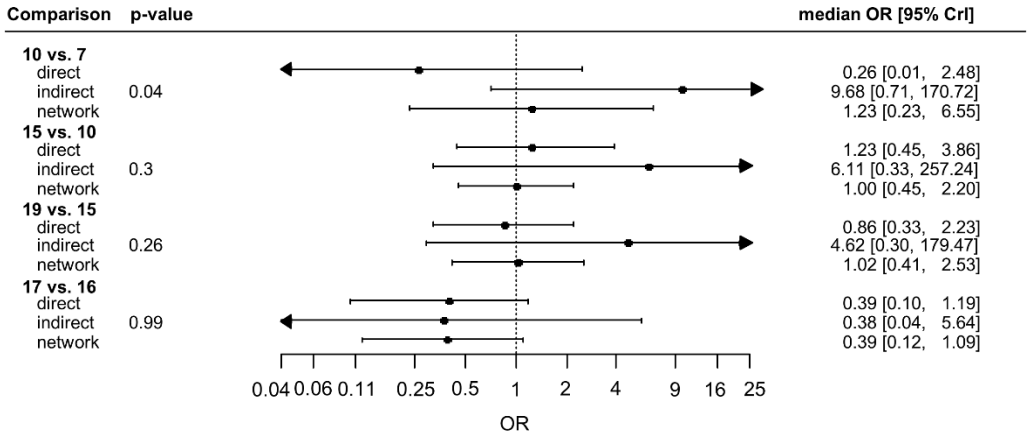
Class codes: 1 – Placebo, 2 - Benzoyl peroxide [topical], 3 - Lincosamide [topical], 4 - Retinoid [topical], 5 - Azelaic acid [topical], 6 - Macrolide [topical], 7 - Fusidic acid [topical], 8 - Topical [acid], 9 - ACNICARE [physical], 10 - Tetracycline [oral], 11 - Macrolide [oral], 12 - Co-cyprindiol [oral], 13 - Combined Oral Contraceptive [oral], 14 - Benzoyl peroxide [topical] + Lincosamide [topical], 15 - Benzoyl peroxide [topical] + Macrolide [topical], 16 - Benzoyl peroxide [topical] + Retinoid [topical], 17 - Lincosamide [topical] + Retinoid [topical], 18 - Macrolide [topical] + Anti-fungal [topical], 19 - Retinoid [topical] + Macrolide [topical], 20 - Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical], 21 - Benzoyl peroxide [topical] + Photochemical + photothermal therapy, 22 - Combined chemical peels [physical], 23 - Tetracycline [oral] + Combined physical peels [physical].

Continued from previous page and on next page



Class codes: 1 – Placebo, 2 - Benzoyl peroxide [topical], 3 - Lincosamide [topical], 4 - Retinoid [topical], 5 - Azelaic acid [topical], 6 - Macrolide [topical], 7 - Fusidic acid [topical], 8 - Topical [acid], 9 - ACNICARE [physical], 10 - Tetracycline [oral], 11 - Macrolide [oral], 12 - Co-cyprindiol [oral], 13 - Combined Oral Contraceptive [oral], 14 - Benzoyl peroxide [topical] + Lincosamide [topical], 15 - Benzoyl peroxide [topical] + Macrolide [topical], 16 - Benzoyl peroxide [topical] + Retinoid [topical], 17 - Lincosamide [topical] + Retinoid [topical], 18 - Macrolide [topical] + Anti-fungal [topical], 19 - Retinoid [topical] + Macrolide [topical], 20 - Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical], 21 - Benzoyl peroxide [topical] + Photochemical + photothermal therapy, 22 - Combined chemical peels [physical], 23 - Tetracycline [oral] + Combined physical peels [physical].

Continued from previous page



Class codes: 1 – Placebo, 2 - Benzoyl peroxide [topical], 3 - Lincosamide [topical], 4 - Retinoid [topical], 5 - Azelaic acid [topical], 6 - Macrolide [topical], 7 - Fusidic acid [topical], 8 - Topical [acid], 9 - ACNICARE [physical], 10 - Tetracycline [oral], 11 - Macrolide [oral], 12 - Co-cyprindiol [oral], 13 - Combined Oral Contraceptive [oral], 14 - Benzoyl peroxide [topical] + Lincosamide [topical], 15 - Benzoyl peroxide [topical] + Macrolide [topical], 16 - Benzoyl peroxide [topical] + Retinoid [topical], 17 - Lincosamide [topical] + Retinoid [topical], 18 - Macrolide [topical] + Anti-fungal [topical], 19 - Retinoid [topical] + Macrolide [topical], 20 - Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical], 21 - Benzoyl peroxide [topical] + Photochemical + photothermal therapy, 22 - Combined chemical peels [physical], 23 - Tetracycline [oral] + Combined physical peels [physical].

There was sufficient variation in the ratings of studies to fit bias models on one risk of bias domains:

- Domain 4: Outcome measurement (efficacy)

Although there was a meaningful reduction in the posterior mean residual deviance of the model exploring this domain, the 95% credible intervals of the posterior mean bias included zero (Table 46). Similarly, there was no evidence of small study effect bias, as the 95% credible intervals of the posterior mean bias included zero (Table 46).

There was evidence that the Benzoyl peroxide [topical], Retinoid [topical], and Benzoyl peroxide [topical] + Retinoid [topical] classes increased the odds of discontinuation due to side effects compared to Placebo. No other classes decreased or increased the odds of discontinuation compared to Placebo (supplement 6).

Table 46: Bias model fit statistics for discontinuation due to side effects

Model	Posterior total residual deviance[a]	DIC[b]	Bias	
			Posterior median (95% CrI)	Between Study SD (95% CrI)
NMA model: FE, fixed class	**125.3**	**500.612**	**---**	**---**
Bias model: Domain 4	120.8	501.349	0.54 (-0.92, 1.98)	0.98 (0.05, 3.21)
Bias model: Small study	122.7	501.466	15.72 (-2.77, 35.59)	4.55 (0.24, 17.38)

Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed study effects; NMA, network meta-analysis; SD, standard deviation

[a] *Posterior mean residual deviance compared to 123 total data points*

[b] *Lower values of DIC preferred*

Lincosamide [topical] is the highest ranked class for both females and males, with posterior mean ranks of 4.0 (95% CrI 1st to 10th) and 3.8 (95% CrI 1st to 9th), respectively (Table 47). The lowest ranked class is Macrolide [oral] at 20.1 (95% CrI 4th to 23rd) for females and 18.3 (95% CrI 4th to 21st) for males (Table 47).

Table 47: Posterior mean rank and 95% credible intervals of classes for discontinuation due to side effects

Class	Posterior Mean Rank (95% CrI)	
	Females	Males
Lincosamide [topical]	4.0 (1, 10)	3.8 (1, 9)
Placebo	5.2 (1, 11)	5.0 (1, 10)
Macrolide [topical]	5.2 (1, 15)	4.8 (1, 14)
Azelaic acid [topical]	8.9 (1, 20)	8.2 (1, 18)
Lincosamide [topical] + Retinoid [topical]	9.9 (2, 19)	9.0 (2, 17)
Fusidic acid [topical]	10.0 (1, 21)	9.1 (1, 19)
Benzoyl peroxide [topical] + Photochemical + photothermal therapy	10.0 (1, 22)	9.1 (1, 20)
Co-cyprindiol [oral]	10.5 (1, 21)	not applicable
Benzoyl peroxide [topical] + Lincosamide [topical]	11.0 (3, 20)	10.0 (3, 18)
Topical [acid]	11.4 (1, 22)	10.3 (1, 20)
Combined chemical peels [physical]	11.4 (1, 23)	10.4 (1, 21)
Tetracycline [oral]	11.5 (4, 19)	10.4 (3, 17)
Benzoyl peroxide [topical] + Macrolide [topical]	11.5 (4, 19)	10.5 (3, 17)
Combined Oral Contraceptive [oral]	11.7 (3, 20)	not applicable
Retinoid [topical] + Macrolide [topical]	11.8 (2, 21)	10.7 (2, 19)
Benzoyl peroxide [topical] + Macrolide [topical] + Retinoid [topical]	11.8 (2, 21)	10.7 (2, 19)
Benzoyl peroxide [topical]	15.5 (9, 20)	14.0 (8, 19)
ACNICARE [physical]	15.6 (1, 23)	14.2 (1, 21)
Retinoid [topical]	16.0 (10, 21)	14.4 (9, 19)
Macrolide [topical] + Anti-fungal [topical]	16.5 (2, 23)	15.0 (2, 21)
Tetracycline [oral] + Combined physical peels [physical]	18.2 (2, 23)	16.5 (2, 21)
Benzoyl peroxide [topical] + Retinoid [topical]	18.3 (12, 22)	16.6 (11, 20)
Macrolide [oral]	20.1 (4, 23)	18.3 (4, 21)

Abbreviations: CrI, credible interval

References

Altman, D.G., & Bland, J.M. (2011) How to obtain the confidence interval from a P value. BMJ, 343, d2090.

Brooks, S.P., & Gelman, A. (1998) General methods for monitoring convergence of iterative simulations. Journal of Computational and Graphical Statistics, 7(4), 434-455.

Caldwell, D.M., A.E. Ades, Higgins, J.P.T. (2005) Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ, 331, 897-900.

Casella, G., & Berger, R.L. (2002) Statistical Inference. Thomson Learning.

Dias, S., et al. (2010a) Checking Consistency in Mixed Treatment Comparison Meta-analysis. Statistics In Medicine, 29, 932-944.

Dias, S., et al. (2010b) Estimation and adjustment of bias in randomised evidence by using Mixed Treatment Comparison Meta-analysis. Journal of the Royal Statistical Society (A), 173(3), 613-629.

Dias, S., et al. (2011a) NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials, in Technical Support Document.

Dias, S., et al. (2011b) NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials, in Technical Support Document.

Dias, S., et al. (2013a) Evidence Synthesis for Decision Making 2: A generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical Decision Making, 33, 607-617.

Dias, S., et al. (2013b) Evidence Synthesis for Decision Making 4: Inconsistency in networks of evidence based on randomized controlled trials. Medical Decision Making, 33, 641-656.

Dias, S., et al. (2018) Network meta-analysis for decision making. Statistics in Practice. 2018, Hoboken, NJ: Wiley.

Gelman, A., & Rubin, D.B. (1992) Inferences from iterative simulation using multiple sequences. Statistical Science, 7, 457-472.

Lu, G., & Ades, A. (2004) Combination of direct and indirect evidence in mixed treatment comparisons. Statistics In Medicine, 23, 3105-3124.

Lunn, D.J., et al. (2000) WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing, 10, 325-337.

Lunn, D., et al. (2013) The BUGS book. Boca Raton, FL: CRC Press.

Moreno, S.G., et al. (2009a) Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study. BMC Medical Research Methodology, 9(2).

Moreno, S.G., et al. (2009b) Novel methods to deal with publication biases: secondary analysis of antidepressant trials in the FDA trial registry database and related journal publications. BMJ, 339, b2981.

Spiegelhalter, D.J., et al. (2002) Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society (B), 64(4), 583-616.

Sturtz, S., Ligges, U., Gelman, A. (2005) R2WinBUGS: A package for running WinBUGS from R. Journal of Statistical Software, 12(3), 1-16 (http://www.jstatsoft.org/v12/i03).

Sweeting, M.J., Sutton, A.J., Lambert, P.C. (2004) What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Statistics In Medicine, 23, 1351-1375.

van Valkenhoef, G., et al. (2016) Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Research Synthesis Methods, 7, 80-93.

Welton, N.J., et al. (2009) Models for potentially biased evidence in meta-analysis using empirically based priors. Journal of the Royal Statistical Society (A), 172(1), 119-136.

Wiebe, N., et al. (2006) A systematic review identifies a lack of standardization in methods for handling missing variance data. J Clin Epidemiol, 59(4), 342-53.

Appendix N – Threshold analysis report from the NICE Guidelines Technical Support Unit (TSU)

Threshold analysis report for review question: For people with mild to moderate acne vulgaris what are the most effective treatment options?

Prepared by: NICE Guidelines TSU, Bristol (Nicky J. Welton, Caitlin Daly, David Phillippo)

Introduction

The TSU was invited to explore the application of the threshold analysis method (Phillippo 2018 & 2019) in the Acne vulgaris guideline for treatments for people with mild to moderate acne, and to apply the method where relevant. Threshold analysis can be used to assess the robustness of recommendations made to potential limitations in the evidence, when the recommendations are based on a Network Meta-Analysis (NMA). Such limitations arise because the observed estimates differ from the true effects of interest, for example due to study biases, sampling variation, or issues of relevance. Threshold analysis quantifies precisely how much the evidence could change before the recommendation changes, and what the revised recommendation would be.

Requirements for use of the method are that there is a clear decision rule that is used to base the recommendations on the NMA results. For example: choose the treatment class with the highest estimated reduction in percentage change from baseline total lesion counts. Currently the methods are only available to be used on one outcome at a time.

The TSU attended the Acne Guideline Committee meetings on 20th July and 7th Aug 2020, where they observed the discussion of the clinical and economic evidence and drafting of preliminary recommendations. In this report, we begin by summarising the draft preliminary recommendations made by the committee, prior to discussion of the threshold analyses at the meeting on the 2nd Sept 2020. We then discuss the links between the draft preliminary recommendations and the NMA results to identify decision rules that could be used in the threshold method. For those draft preliminary recommendations where a decision rule could be identified, we perform the threshold analysis and present the results. We end with a brief summary of our findings.

Draft Preliminary Recommendations Following the Guideline Committee Meeting on 20th July and 7th August 2020

The relevant parts of the draft preliminary recommendations (prior to the threshold analysis) for treatments for people with mild to moderate acne that are informed by the NMA are as follows:

Topical treatments (with or without an oral antibiotic)

1.5.2 For mild, moderate or severe acne offer one of the following treatments, taking account of the person preferences [indication in brackets]:

- a fixed combination of a topical retinoid with topical clindamycin [mild to moderate and moderate to severe acne]
- a fixed combination of topical benzoyl peroxide and topical adapalene [mild to moderate and moderate to severe acne]
- a fixed combination of topical benzoyl peroxide with topical clindamycin [during pregnancy]

1.5.5 Do not use topical or oral antibiotics as monotherapy, or a combination of topical and oral antibiotics only.

Oral isotretinoin treatment

There was no recommendation on oral isotretinoin for people with mild-to-moderate acne, according to the draft recommendation below:

1.5.11 Consider oral isotretinoin, prescribed in a hospital dermatology setting, for people aged 12 or older who have:

- nodulo-cystic or conglobate acne
- acne vulgaris with a severe inflammatory component (acne fulminans without systemic symptoms)
- acne of at least moderate severity causing psychological distress or adding to a mental health condition
- moderate to severe acne which has not responded to prior treatment with a systemic antibacterial (as in recommendation 1.5.2).

Physical treatments

There was no recommendation on physical treatments for people with mild to moderate acne.

Threshold Analysis

Decision Rule Linking Recommendations to NMA Results: mild to moderate acne

The committee considered the topical and oral treatments separately to the physical treatments. The committee opted not to recommend physical treatments (light therapies and chemical peels), a number of which appeared to rank in a high position in terms of clinical and cost-effectiveness, because they had a more limited evidence base and the clinical experience with these treatments is very limited within the NHS context. We therefore focus on the topical and oral treatments in the threshold analysis.

Further restrictions on the treatments for consideration were made by the committee. Treatments with fewer than 50 observations each (in total across study arms) were excluded. Antibiotic monotherapies were excluded due to concerns about antibiotic resistance. The committee decided not to make a recommendation for the combination of topical benzoyl peroxide and topical macrolide, because this treatment is not available as a fixed combination and therefore it would be impractical for people with acne vulgaris to apply as two separate formulations, but also impractical and potentially costly for pharmacists to prepare as a single formulation on an individual basis. The committee considered the oral retinoid classes unsuitable for people with mild to moderate acne according to MHRA and BNF advice due to having a higher risk of serious side effects. These classes were therefore excluded from recommendations. Finally, the committee decided not to make a recommendation for the combination of topical macrolide and anti-fungal, because available data on its efficacy were based on a small number of people tested [N=74] and it is not commonly used in the treatment of acne, and therefore the committee had no relevant clinical experience. The remaining treatment classes are displayed in Table 48, and the NMA results for the mild-to-moderate population for these classes relative to placebo are shown in Figure 30. The committee preferred the NMA results that were adjusted for small study effects, and it is these results that are displayed in Figure 30.

For people with mild to moderate acne, the recommendations for first line treatment are from the following classes:

- a fixed combination of a topical retinoid with topical clindamycin. Class: retinoid (topical) + lincosamide (topical)
- a fixed combination of topical benzoyl peroxide and topical adapalene. Class: benzoyl peroxide (topical) + retinoid (topical)

These recommendations link to the NMA results in Figure 30 directly, as these classes had the highest mean difference in efficacy.

To assess the robustness of the decision to the NMA evidence, we therefore conducted a threshold analysis based on the classes listed in Table 48, with a decision rule to recommend the top 2 classes within this set. If the top 2 treatment classes change, this implies that one of the non-recommended treatment classes would be recommended in place of one of the currently recommended treatment classes. This allows us to assess how robust this recommendation is to changes in the evidence.

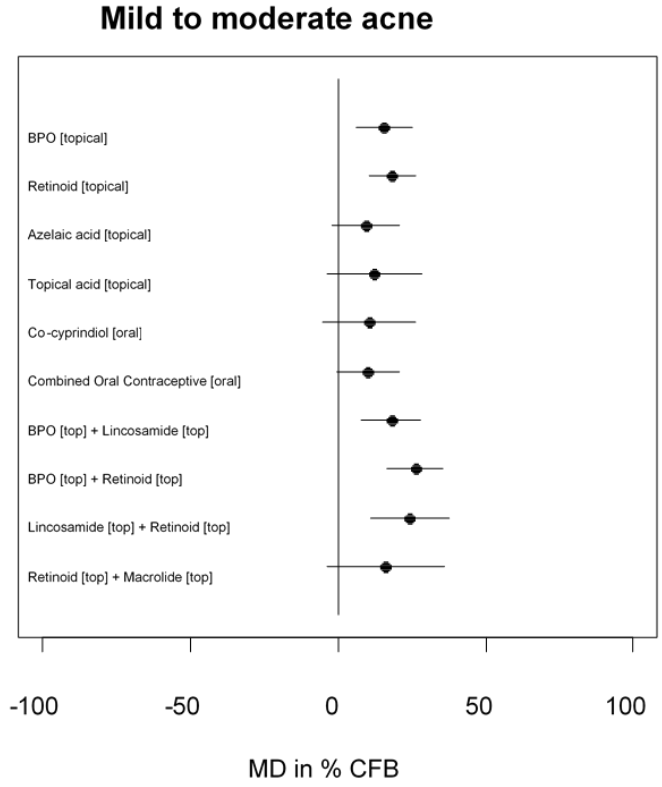
Table 48: NMA of efficacy of treatments for people with mild to moderate acne: treatment classes, number of observations to each class, whether included in the decision for topical and oral treatments, and reason for exclusion if not

NMA Code	Treatment Class	Number of observations to treatment class	Included?	Reason for exclusion
1	Placebo	2698	Yes	
3	Benzoyl peroxide [topical]	1109	Yes	
5	Retinoid [topical]	1623	Yes	
6	Azelaic acid [topical]	301	Yes	
12	Topical acid [topical]	106	Yes	
19	Co-cyprindiol [oral]	584	Yes	
20	Combined Oral Contraceptive [oral]	2313	Yes	
28	Benzoyl peroxide [topical] + Lincosamide [topical]	992	Yes	
30	Benzoyl peroxide [topical] + Retinoid [topical]	1057	Yes	
32	Lincosamide [topical] + Retinoid [topical]	276	Yes	
35	Retinoid [topical] + Macrolide [topical]	135	Yes	
16	Retinoid - total cumul dose < 120mg/kg (single course) [oral]	54	No	MHRA and BNF advice due to having a higher risk of serious side effects
29	Benzoyl peroxide [topical] + Macrolide [topical]	351	No	No fixed combination available
7	Macrolide [topical]	765	No	antibiotic monotherapy
9	Fusidic acid [topical]	310	No	antibiotic monotherapy
2	No treatment	39	No	small sample
4	Lincosamide [topical]	3073	No	antibiotic monotherapy
8	Antiseptics [topical]	30	No	small sample
10	Superoxidised solution [topical]	39	No	small sample
11	Anti-fungal [topical]	20	No	small sample
13	Chemical peel [physical]	101	No	physical therapy
14	Combined chemical peels [physical]	14	No	physical therapy and small sample
15	ACNICARE [physical]	20	No	small sample

NMA Code	Treatment Class	Number of observations to treatment class	Included?	Reason for exclusion
17	Tetracycline [oral]	388	No	antibiotic monotherapy
18	Macrolide [oral]	618	No	antibiotic monotherapy
21	Photochemical therapy [blue and red]	69	No	physical therapy
22	Photochemical therapy [blue]	138	No	physical therapy
23	Photochemical therapy [red]	28	No	physical therapy and small sample
24	Photochemical + photothermal therapy	107	No	physical therapy
25	Photodynamic therapy	36	No	physical therapy and small sample
26	Photothermal + photodynamic therapy	9	No	physical therapy and small sample
27	Smoothbeam + Photochemical therapy [blue]	24	No	physical therapy and small sample
31	Lincosamide [topical] + Azelaic acid [topical]	44	No	small sample
33	Macrolide [topical] + Anti-fungal [topical]	74	No	small sample and lack of clinical experience
34	Retinoid [topical] + Hydrogen Peroxide [topical]	26	No	small sample
36	Lincosamide [topical] + Topical acid [topical]	23	No	small sample
37	Azelaic acid [topical] + Macrolide [topical]	40	No	small sample
38	Tetracycline [oral] + Combined physical peels [physical]	13	No	physical therapy and small sample
39	Retinoid [topical] + Topical acid [topical] + Photochemical therapy [blue and red]	35	No	physical therapy and small sample
40	Benzoyl peroxide [topical] + Lincosamide [topical] + Topical acid [topical]	24	No	small sample
41	Benzoyl peroxide [topical] + Photochemical + photothermal therapy	29	No	physical therapy and small sample

1

Figure 30: People with mild to moderate acne: Forest plot of bias-adjusted estimates of efficacy for treatment classes under consideration for the topical / oral recommendations.



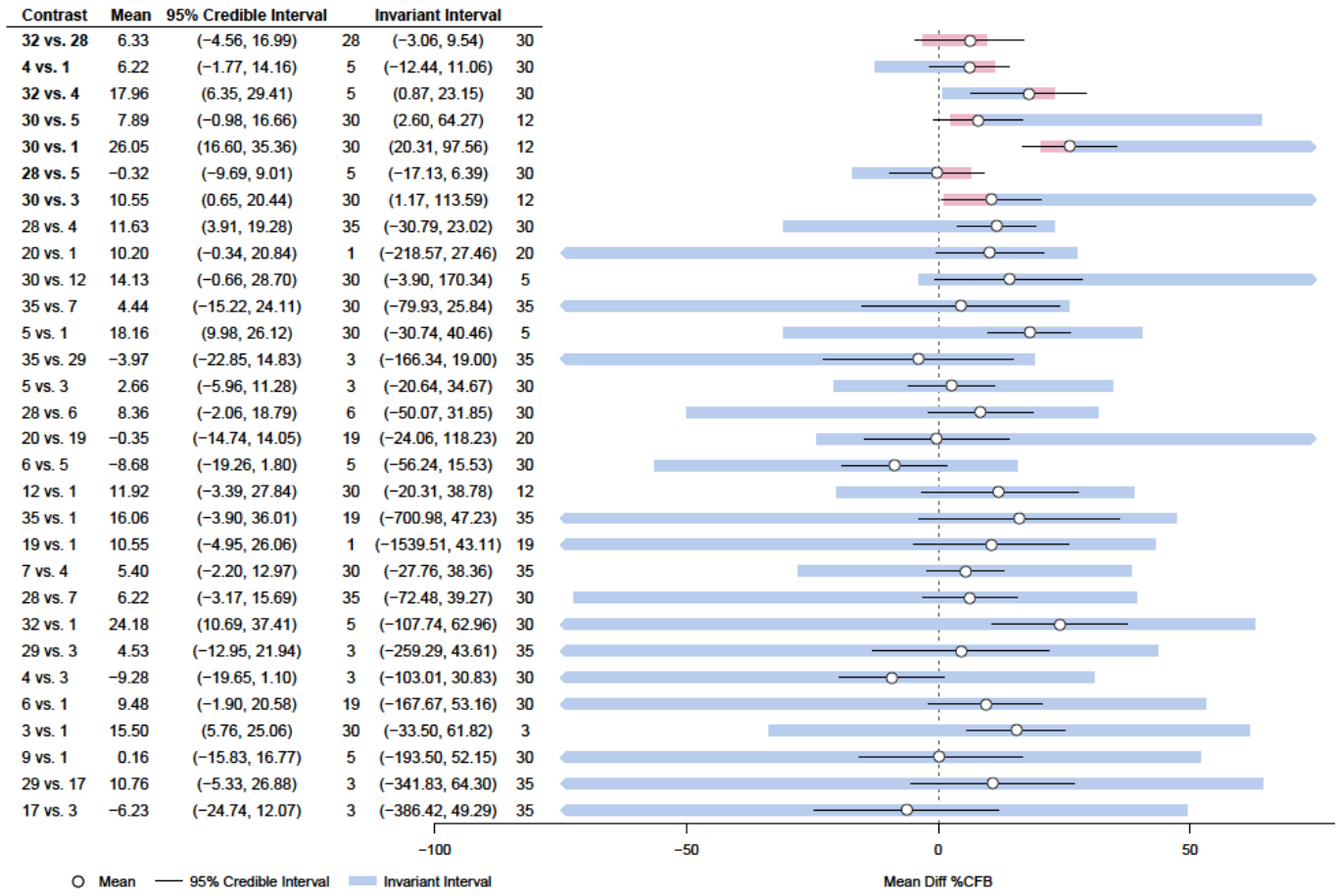
Threshold Analysis Results

The results from the threshold analysis for topical and oral treatment classes for people with mild to moderate acne are displayed in Figure 31, which shows, for each pair of treatments ("contrast") where we have evidence, the range of values for which the evidence from that contrast could change without changing the draft provisional recommendations. Figure 31 also shows the treatment class the recommendation would switch to and highlights in pink where the recommendations change for contrast estimates that are within their credibility limits (ie within sampling error). The recommendations are for 2 treatment classes (codes 30 and 32), and so the decision will only change if the treatment class that the decision switches to is not already recommended. The decision is fairly robust to changes in the evidence. If the evidence on the contrast 32 vs 28 (Lincosamide [topical] + Retinoid [topical] vs Benzoyl peroxide [topical] + Lincosamide [topical]) was smaller than -3.06 (near the bottom of the credible interval), then class Benzoyl peroxide [topical] + Lincosamide [topical] would enter the top 2 treatment classes.

Conclusions

For the mild-to-moderate population the draft provisional recommendations are fairly robust to changes in the evidence. The evidence on Lincosamide [topical] + Retinoid [topical] vs Benzoyl peroxide [topical] + Lincosamide [topical] would have to be close to the lower credible interval for the class Benzoyl peroxide [topical] + Lincosamide [topical] to enter the top 2 treatment classes.

Figure 31: Threshold analysis results by contrast for topical and oral treatment classes for people with mild to moderate acne, by intervention contrast, sorted by increasing threshold magnitude.



The optimal decision rule is to recommend treatment classes {30, 32}. The study/contrast estimate (labelled "Mean") and credible intervals are shown by the black lines. The blue shaded areas show the invariant interval where the optimal set of recommended interventions does not change, and the intervention that would enter the recommended intervention set is indicated by the figures either side of the invariant interval, and the decision only changes if this is not in the set {30, 32}. The pink area indicates where the recommendations changes within the credible limits of the current estimates. NT = No Threshold, no change to the evidence in this direction could lead to a new decision. Treatment class codes are as defined in Table 48.

References

Phillippo DM, Dias S, Ades AE, Didelez V, Welton NJ (2018). *Sensitivity of treatment recommendations to bias in network meta-analysis*. JRSSA, 181:843-867. https://doi.org/10.1111/rssa.12341

Phillippo DM, Dias S, Welton NJ, Caldwell DM, Taske N, Ades AE (2019). *Confidence in recommendations based on Network Meta-Analysis: threshold analysis as an alternative to GRADE NMA in guideline development.* Annals of Internal Medicine, 170: 538-546.