ClinicalEvidence

Acne vulgaris

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ABSTRACT

INTRODUCTION: Acne vulgaris affects over 80% of teenagers, and persists beyond the age of 25 years in 3% of men and 12% of women. Typical lesions of acne include comedones, inflammatory papules, and pustules. Nodules and cysts occur in more severe acne and can cause scarring and psychological distress. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of topical and oral treatments in people with acne vulgaris? We searched: Medline, Embase, The Cochrane Library and other important databases up to June 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 67 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: topical treatments (adapalene, azelaic acid, benzoyl peroxide, clindamycin, erythromycin (alone or plus zinc), isotretinoin, tetracycline, tretinoin), and oral treatments (doxycycline, isotretinoin, lymecycline, minocycline, oxytetracycline, tetracycline).

QUESTIONS

INTERVENTIONS

Key points

- Acne vulgaris affects over 80% of teenagers, and persists beyond the age of 25 years in 3% of men and 12% of women.

  Typical lesions of acne include comedones, inflammatory papules, and pustules. Nodules and cysts occur in more severe acne, and can cause scarring and psychological distress.

- Topical benzoyl peroxide should be considered as first-line treatment in mild acne.

  Topical benzoyl peroxide and topical azelaic acid reduce inflammatory and non-inflammatory lesions compared with placebo, but can cause itching, burning, stinging, and redness of the skin.

- Topical antibiotics such as clindamycin and erythromycin (alone or with zinc) reduce inflammatory lesions compared with placebo, but have not been shown to reduce non-inflammatory lesions. Tetracycline may reduce overall acne severity.

  Antimicrobial resistance can develop with use of topical or oral antibiotics, and their efficacy may decrease over time.

  Tetracyclines may cause skin discoloration, and should be avoided in pregnant or breastfeeding women.

Topical preparations of tretinoin, adapalene, and isotretinoin may reduce inflammatory and non-inflammatory lesions, but can also cause redness, burning, dryness, and soreness of the skin.

- Oral antibiotics (doxycycline, erythromycin, lymecycline, minocycline, oxytetracycline, and tetracycline) are considered useful for people with more severe acne, although we don't know for sure whether they are effective.

  Oral antibiotics can cause adverse effects such as contraceptive failure.

  Minocycline has been associated with an increased risk of systemic lupus erythematosus, and of liver disorders.

  Oral isotretinoin has been associated with skin problems, change in liver function, teratogenesis, and psychiatric disorders.

DEFINITION

Acne vulgaris is a common inflammatory pilosebaceous disease characterised by comedones, papules, pustules, inflamed nodules, superficial pus-filled cysts, and (in extreme cases) canalising and deep, inflamed, sometimes purulent sacs. [1] Lesions are most common on the face, but the neck, chest, upper back, and shoulders may also be affected. Acne can cause scarring and considerable psychological distress. [2] It is classified as mild, moderate, or severe. [1] **Mild acne** is defined as non-inflammatory lesions (comedones), a few inflammatory (papulopustular) lesions, or both. **Moderate acne** is defined as more inflammatory lesions, occasional nodules, or both, and mild scarring. **Severe acne** is defined as widespread inflammatory lesions, nodules, or both, and scarring, moderate acne that has not settled with 6 months of treatment, or acne of any "severity" with serious psychological upset. This review does not cover acne rosacea, acne secondary to industrial occupations, and treatment of acne in people under 13 years of age.

INCIDENCE/ PREVALENCE

Acne is the most common skin disease of adolescence, affecting over 80% of teenagers (aged 13–18 years) at some point. [3] Estimates of prevalence vary depending on study populations and the method of assessment used. Prevalence of acne in a community sample of 14- to 16-year-olds in the UK has been recorded as 50%. [4] In a sample of adolescents from schools in New Zealand, acne was present in 91% of males and 79% of females, and in a similar population in Portugal the prevalence was 82%. [5] [6] It has been estimated that up to 30% of teenagers have acne of sufficient severity to require medical treatment. [7] Acne was the presenting complaint in 3.1% of people aged 13–25 years attending primary care in a UK population. [8] Overall incidence is similar in both men and women, and peaks at 17 years of age. [7] The number of adults with acne, including people over 25 years, is increasing; the reasons for this increase are uncertain. [9]

AETIOLOGY/ RISK FACTORS

The exact cause of acne is unknown. Four factors contribute to the development of acne: increased sebum secretion rate, abnormal follicular differentiation causing obstruction of the pilosebaceous duct, bacteriology of the pilosebaceous duct, and inflammation. [10] The anaerobic bacterium *Propionibacterium acnes* plays an important role in the pathogenesis of acne. Androgen secretion is the major trigger for adolescent acne. [11]

PROGNOSIS

In 3% of men (95% CI 1.2% to 4.8%) and 12% of women (95% CI 9% to 15%), facial acne persists after the age of 25 years, [12] and in a few people (1% of men and 5% of women) acne persists into their 40s. [9]

AIMS OF INTERVENTION

To reduce the number of non-inflammatory and inflammatory lesions and scarring, with minimal adverse effects of treatment.

OUTCOMES

Number of non-inflammatory lesions (comedones); number of inflammatory lesions (papules, pustules, and nodules); severity scores and scales; patient perception of improvement; quality of life; psychological distress; adverse effects of treatment. Commonly used severity scores and scales include: Leeds Acne Grading Technique, which involves counting and categorising lesions into inflammatory and non-inflammatory; [13] Cook's acne grading scale method, which uses photographs to document severity of acne and grades severity from 0 (least severe) to 8 (most severe); [14] and the Pillsbury Scale, which classifies acne from 1 (mildest) to 4 (severe). [15]

METHODS

BMJ Clinical Evidence search and appraisal June 2007. The following databases were used to identify studies for this review: Medline 1966 to June 2007, Embase 1980 to June 2007, and The Cochrane Library 2007, Issue 2. Additional searches were carried out using the websites: NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE guidance. Abstracts of the studies retrieved were assessed independently by two information specialists using predetermined criteria to identify relevant studies. Design criteria included: systematic reviews and RCTs, in any language, that were at least single blind, containing more than 20 individuals, and with a follow-up of more than 80%. There was no minimum length of follow-up. We excluded individual RCTs described as "open", "open label", or non-blinded. However, if open-label RCTs were

included in systematic reviews, we have included these, and have stated that they were open-label studies where this was reported by the review. The review by Lehmann et al [16] included both randomised and non-randomised controlled trials, and did not state in all cases whether trials were randomised. We have focused on reporting results for RCTs only and, where necessary, have analysed original papers to ascertain whether trials were randomised. None of the reviews we identified were able to perform a meta-analysis owing to heterogeneity among the trials identified. We have described the results of each RCT identified by the reviews and, where we found numerous RCTs on an intervention, we have tabulated results. We compared all listed oral treatments versus each other and included all RCTs of sufficient quality that we retrieved. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 32).

QUESTION What are the effects of topical treatments in people with acne vulgaris?

OPTION BENZOYL PEROXIDE (TOPICAL)

Symptom severity
Compared with placebo Topical benzoyl peroxide may be more effective at reducing the total lesion count or the number of inflammatory and non-inflammatory lesions at 4–12 weeks in people with moderate acne (low-quality evidence).

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Topical benzoyl peroxide versus placebo:
We found two systematic reviews comparing topical benzoyl peroxide acid versus placebo (vehicle) (see table 1, p 23). [16] [17] The first review (search date 1999, 5 RCTs, [18] [19] [20] [21] [22] 875 people with mild to moderate acne) did not perform a meta-analysis owing to heterogeneity among the trials in methods of outcome assessment. [16] The second review (search date 2004), [17] which had more stringent inclusion criteria than the earlier review, included one RCT, [19] which was also identified by the earlier review. Four of the identified RCTs, primarily in people with moderate acne, found that topical benzoyl peroxide significantly reduced either total lesion count or the number of inflammatory and non-inflammatory lesions at 4–12 weeks compared with vehicle. [18] [19] [21] [22] A fifth RCT found more limited evidence from within-group comparisons that benzoyl peroxide reduced total lesion count and the number of inflammatory and non-inflammatory lesions from baseline at 12 weeks. [20] None of the RCTs assessed patient perception of improvement.

Harms:

Topical benzoyl peroxide versus placebo:
One of the RCTs found that benzoyl peroxide 5% significantly increased the proportion of people who had adverse effects compared with vehicle, including dryness, scaling, burning, tingling, and redness; [20] a second RCT found that more people using benzoyl peroxide 5% had peeling compared with vehicle (see table 1, p 23). [19] A third RCT found that benzoyl peroxide 5% was associated with erythema, dryness, soreness, and burning; [21] another RCT found that benzoyl peroxide 20% and vehicle were associated with similar rates of local adverse effects, including redness and peeling. [22] One of the RCTs gave no quantitative information about adverse effects. [18]

Comment:

Clinical guide:
Benzoyl peroxide is indicated as an effective first-line treatment for mild acne. It has both anti-microbial and anti-comedonal properties, it also has an anti-inflammatory effect. It is recommended to start with a lower strength and increase gradually. Reducing frequency of application or temporarily discontinuing treatment helps with irritation.

OPTION CLINDAMYCIN (TOPICAL)

Symptom severity
Compared with placebo/vehicle Topical clindamycin may be more effective at reducing the number of inflammatory lesions at 8–12 weeks in people with mild to severe acne (very low-quality evidence).

Patient perception of improvement
Compared with placebo/vehicle Topical clindamycin may be more effective at increasing the proportion of people with mild to severe acne who rate their acne as markedly improved or improved (very low-quality evidence).

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Topical clindamycin versus placebo:
We found two systematic reviews. [16] [17] The first review (search date 1999, 7 RCTs, [19] [23] [24] [25] [26] [27] [28] 1502 people with mild to severe acne) compared topical clindamycin 1%

(phosphate or hydrochloride) one to four times daily versus placebo or vehicle for 8–12 weeks (see table 2, p 24). [16] The review did not perform a meta-analysis owing to heterogeneity among the trials in comparisons and outcomes assessed. The second systematic review (search date 2004), which had more stringent inclusion criteria, identified two RCTs, [19] [27] both of which were included by the earlier review. Three of the RCTs identified by the first systematic review found inconclusive evidence about the effects of clindamycin compared with placebo on non-inflammatory lesions; [19] [25] [28] the other RCTs did not assess non-inflammatory lesions. [23] [24] [26] [27] Four RCTs found that clindamycin significantly reduced the number of inflammatory lesions compared with placebo, [19] [24] [26] [27] and a fifth found no significant difference in the number of inflammatory lesions. [25] A sixth RCT found that clindamycin significantly reduced the number of pustules, but not papules. [28] The seventh RCT did not compare clindamycin versus placebo directly, although within-group comparisons found that clindamycin significantly reduced the number of inflammatory lesions from baseline. [23] Three RCTs found that clindamycin increased the proportion of people who perceived that their acne was “markedly improved” or “improved”; in two of these RCTs the difference between groups was significant, [26] [27] whereas the third RCT did not conduct between-group comparisons. [23]

Harms:

Topical clindamycin versus placebo:
Five of the RCTs identified by the first review found that clindamycin was associated with diarrhoea and burning in a small proportion of people, although none of these studies performed significance tests (see table 2, p 24). [23] [24] [26] [27] [28] The sixth RCT found no significant difference in adverse effects between clindamycin and placebo. [19] The seventh RCT gave no information on adverse effects. [25]

Comment:

Studies of development of bacterial resistance to antibiotics suggest that topical application of antibiotics in acne may result in antibiotic resistance to *Propionibacterium acnes*. [7] [29] One systematic review (search date 2003) analysed the efficacy of topical antibiotics in clinical trials (randomised and non-randomised) conducted between 1966 and 2003 using linear regression. [30] It found no significant change in the efficacy of 12 weeks' treatment with topical clindamycin 1.0–1.2% for inflammatory or non-inflammatory lesion count over this period (inflammatory lesions: 8 studies, change in efficacy [regression coefficient]: +0.2%/year, P = 0.7; non-inflammatory lesions: 7 studies, change in efficacy: –0.3%/year, P = 0.7). [30]

Clinical guide:
Topical antibiotics or topical retinoids are indicated as treatments for mild acne that does not respond to benzoyl peroxide. Within the antibiotic class, there is more evidence of benefit with topical clindamycin or erythromycin than with erythromycin plus zinc or tetracycline. A conjoint analysis study of patient preference for different topical antibiotic characteristics found that acne patients preferred a gel formulation that could be applied with the fingers once daily and stored at room temperature for up to 18 months. [31]

OPTION ERYTHROMYCIN (TOPICAL)

Symptom severity
Compared with placebo Topical erythromycin may be more effective at reducing inflammatory lesions at 8–12 weeks in people with mild to severe acne (low-quality evidence).

Patient perception of improvement
Compared with placebo We don’t know whether topical erythromycin is more effective at increasing the proportion of people with mild to moderate acne who perceive their acne as improved at 12 weeks (very low-quality evidence).

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Topical erythromycin versus placebo:
We found two systematic reviews. [16] [17] The first review (search date 1999, 8 RCTs, [32] [33] [34] [35] [36] [37] [38] [39] 347 people with mild to moderate acne, 555 people with moderate to severe acne) compared topical erythromycin 1–2% versus vehicle for 4–12 weeks (see table 3, p 26). [16] The review did not perform a meta-analysis owing to heterogeneity among the trials in outcomes assessed. The second systematic review (search date 2004), [17] which had more stringent inclusion criteria, included three RCTs, all of which were identified by the earlier review. [33] [35] [36] Five RCTs identified by the first review found that erythromycin significantly reduced the number of inflammatory lesions at 8–12 weeks compared with vehicle. [33] [34] [35] [36] [37] The sixth RCT found that, in most people, erythromycin was more effective than vehicle at reducing the number of inflammatory lesions at 4–8 weeks, but it did not assess the significance of the difference between treatments. [38] The seventh RCT found no significant difference in the proportion of people who had a greater than 50% reduction in the number of inflammatory lesions at 12 weeks. [39] The eighth RCT did not report direct comparisons of erythromycin alone versus placebo; it re-

ported changes from baseline within the erythromycin and the placebo groups. [32] Few of the RCTs assessed effects on non-inflammatory lesions, and those that did found inconclusive results. One RCT found that a similar proportion of people using erythromycin compared with vehicle perceived that their acne had improved from baseline at 12 weeks; [32] the other RCTs did not assess patient perception of improvement.

Harms:

Topical erythromycin versus placebo:
The RCTs identified by the reviews found no significant difference in adverse effects between topical erythromycin and placebo or vehicle (see table 3, p 26). [16]

Comment:

Studies of development of bacterial resistance to antibiotics suggest that topical application of antibiotics in acne may result in antibiotic resistance in *Propionibacterium acnes*. [7] [29] One systematic review (search date 2003) analysed the efficacy of topical antibiotics in clinical trials (randomised and non-randomised) conducted between 1966–2003 using linear regression. [30] It found that the efficacy of 12 weeks' treatment with topical erythromycin 1.5–2% for inflammatory and non-inflammatory lesion count decreased significantly over this period (inflammatory lesions, 8 studies, change in efficacy [regression coefficient]: –2.1%/year, P = 0.001; non-inflammatory lesions, 6 studies, change in efficacy: –2.0%/year, P = 0.001).

Clinical guide:
Topical antibiotics or topical retinoids are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the antibiotic class, there is more evidence of benefit with topical erythromycin or clindamycin than with erythromycin plus zinc or tetracycline. However, there is some evidence that topical erythromycin may be less effective now than in the past, owing to increasing *P acnes* resistance.

OPTION TRETINOIN (TOPICAL)

Symptom severity
Compared with placebo Topical tretinoin may be more effective at 8–12 weeks at reducing the number of inflammatory and non-inflammatory lesions in people with mild to severe acne (low-quality evidence).

Patient perception of improvement
Compared with placebo We don't know whether topical tretinoin is more effective at increasing patient perception of improvement in people with mild to moderate acne (very low-quality evidence).

Note
Topical tretinoin has been associated with erythema, peeling, burning, and pruritus. Topical retinoids are not recommended in women of childbearing age not taking adequate contraceptive precautions, or during pregnancy.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Topical tretinoin versus placebo:
We found one systematic review [16] (search date 1999, 5 RCTs, [40] [41] [42] [43] [44] 802 people with mild to moderate acne, 257 people with moderate to severe acne) comparing topical tretinoin 0.02%, 0.025%, or 0.05% versus vehicle twice daily for 8–12 weeks (see table 4, p 28). The review did not perform a meta-analysis because of heterogeneity among the RCTs in methods of outcome assessment. [16] Four RCTs found that topical tretinoin 0.025 to 0.05% significantly reduced the number of inflammatory and non-inflammatory lesions at 8–12 weeks compared with vehicle. [40] [41] [43] [44] The fifth RCT did not assess lesion count, but found that tretinoin 0.025% increased patient perception of improvement compared with vehicle (significance of difference between groups not assessed). [42] The other RCTs did not assess patient perception of improvement. [40] [41] [43] [44]

Harms:

Topical tretinoin versus placebo:
The RCTs found that topical tretinoin 0.02%, 0.025%, or 0.05% significantly increased erythema, peeling, burning, and pruritus compared with vehicle (see table 4, p 28).

Birth defects:
We found no RCTs assessing the risk of birth defects in women using topical retinoids. One non-systematic review found that oral retinoids were teratogenic in case reports and case series in humans, and in experimental studies in animals. [45] In the absence of data regarding the risk of birth defects, it is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

Comment:

Two of the RCTs used weak methods of assessing outcomes (see table 4, p 28). [40] [42]

Clinical guide:
Topical retinoids or topical antibiotics are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the retinoid class, there is more evidence of benefit with topical tretinoin than with isotretinoin or adapalene. It is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

OPTION ADAPALENE (TOPICAL)

Symptom severity
Compared with placebo Topical adapalene is more effective at reducing the number of non-inflammatory and inflammatory lesions at 12 weeks in people with mild to moderate acne, and at maintaining improvement of lesions at 16 weeks in people who have responded to previous treatment with oral doxycycline with or without adapalene gel (moderate-quality evidence).

Note
Topical retinoids are not recommended in women of childbearing age not taking adequate contraceptive precautions, or during pregnancy.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Topical adapalene versus placebo:
We found one systematic review (search date 2004; 1 RCT) [17] and two subsequent RCTs. [46] [47] The RCT identified by the systematic review compared adapalene 0.1% daily versus placebo (vehicle). [48] It found that adapalene significantly reduced total lesion count at 12 weeks compared with vehicle (237 people with moderate acne; mean reduction in total lesion count: 40% with adapalene *v* 20% with vehicle; P less than 0.01). It also found that, compared with vehicle, adapalene significantly reduced the number of non-inflammatory lesions (mean reduction: 38% with adapalene *v* 20% with vehicle; P less than 0.01) and the number of inflammatory lesions (mean reduction: 35% with adapalene *v* 19% with vehicle; P less than 0.01). The RCT assessed quality of life at 12 weeks through a patient questionnaire that evaluated self-perception, social and emotional status, and acne symptoms, and found similar scores in both groups (no further data reported). The first subsequent RCT compared adapalene gel 0.1% daily versus placebo as maintenance treatment in people with severe acne vulgaris who had experienced at least 50% improvement in total lesion count after 12 weeks' treatment with oral doxycycline plus adapalene 0.1% gel or oral doxycycline plus placebo (vehicle). [46] It found that adapalene 0.1% significantly improved maintenance of at least 50% of the improvement in total lesion count compared with placebo at 16 weeks (253 people; AR for maintenance of 50% of improvement: 75% with adapalene *v* 54% with placebo; P less than 0.001; absolute numbers not reported). It also found that, at 16 weeks, adapalene significantly reduced lesion counts compared with placebo (absolute data reported graphically; significance for adapalene *v* placebo: total lesions P = 0.005, inflammatory lesions P = 0.01, non-inflammatory lesions P = 0.02). [46] Adapalene significantly increased participant satisfaction with maintenance treatment compared with placebo (details of satisfaction scale not reported; proportion reporting being “satisfied” or “very satisfied”: 76% with adapalene *v* 65% with placebo; P = 0.01; absolute numbers not reported).The second subsequent RCT (653 people with mild to moderate acne vulgaris) compared adapalene gel 0.3% or 0.1% daily versus placebo. [47] It found that, compared with placebo, adapalene 0.1% significantly reduced the total number of lesions (mean reduction: 48% with adapalene 0.1% *v* 36% with vehicle; P less than 0.001, no absolute figures reported), number of non-inflammatory lesions (mean reduction: 43% with adapalene 0.1% *v* 29% with vehicle; P less than 0.001, no absolute figures reported) and the number of inflammatory lesions (mean reduction: 58% with adapalene 0.1% *v* 47% with vehicle; P less than 0.001, no absolute figures reported) at 12 weeks. It also found that adapalene 0.1% significantly increased success rate as assessed by the Investigators Global Assessment (clear or almost clear) compared with vehicle (17% success rate with adapalene 0.1% *v* 10% success rate with vehicle; P = 0.02, no absolute figures reported). Adapalene 0.3% is not available in the UK.

Harms:

Topical adapalene versus placebo:
The RCT identified by systematic review found that adapalene significantly increased erythema, dryness, scaling, stinging/burning, and pruritus compared with vehicle (P less than 0.01), with the highest incidence at 2 weeks. By 12 weeks of follow-up, no significant difference in adverse effects was found between the groups. Two people taking adapalene withdrew, one because of adverse effects. The first subsequent RCT found similar rates of mild adverse events (erythema, scaling, dryness, stinging, burning) with adapalene and placebo (25% with adapalene *v* 23% with placebo; significance not reported). [46] The second subsequent RCT found low rates of mild adverse effects (dry skin and skin discomfort) with adapalene and placebo (12% with adapalene 0.1% *v* 5% with placebo; significance not reported). [47]

Birth defects:
We found no RCTs assessing the risk of birth defects in women using topical retinoids. One non-systematic review found that oral retinoids were teratogenic in case reports and case series in humans, and in experimental studies in animals. [45] In the absence of data regarding the risk of birth defects, it is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

Comment: **Clinical guide:**
Topical retinoids or topical antibiotics are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the retinoid class, there is more evidence of benefit with topical tretinoin than with isotretinoin or adapalene. It is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

OPTION AZELAIC ACID (TOPICAL)

Symptom severity
Compared with placebo Topical azelaic acid may be more effective at 8–12 weeks at reducing the number of comedones and inflammatory lesions in people with moderate acne (low-quality evidence).

Adverse effects
Topical azelaic acid has been associated with itching, stinging, burning, and erythema.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits: **Topical azelaic acid versus placebo:**
We found two systematic reviews, which compared topical azelaic acid 20% versus placebo. [16] [17] The first review (search date 1999) [16] identified two RCTs. [49] [50] The second review (search date 2004), [17] which had more stringent inclusion criteria than the earlier review, included one RCT [50] also identified by the earlier review. The RCT identified by both reviews found that, compared with placebo (vehicle), azelaic acid significantly reduced the number of comedones and inflammatory lesions (92 people with moderate acne; % reduction in comedones: 56% with azelaic acid *v* 0% with placebo; P = 0.05 [reported as significant]; % reduction in inflammatory lesions: 72% with azelaic acid *v* 47% with vehicle; P = 0.05 [reported as significant]). It also found that azelaic acid significantly increased the proportion of people who had a physician rating of response to treatment of "excellent" or "good" after 12 weeks of treatment compared with placebo (reduction in total lesion count by 75–100% rated as "excellent" and 50–75% as "good"; AR for "excellent/good" rating: 28/43 [65%] with azelaic acid *v* 18/49 [37%] with vehicle; P = 0.05 [reported as significant]). [50] These results should be treated with caution because the RCT did not perform an intention-to-treat analysis, and 13% of people did not complete the trial. [50] The RCT did not assess patient perception of improvement. The second RCT identified by the first review found that, compared with placebo, azelaic acid significantly reduced the number of inflammatory lesions and of non-inflammatory lesions after 8 weeks' treatment (40 people, severity of acne unclear; % reduction in inflammatory lesions: 50% with azelaic acid *v* 12% with placebo; P = 0.001; % reduction in non-inflammatory lesions: 50% with azelaic acid *v* 25% with placebo; P = 0.027). [49] These results should be treated with caution because it is unclear whether people taking azelaic acid and placebo had comparable duration and severity of acne. [49] The RCT did not assess patient perception of improvement.

Harms: **Topical azelaic acid versus placebo:**
The RCT identified by both reviews found that a higher proportion of people using azelaic acid than placebo (vehicle) had burning (4/43 [9%] with azelaic acid *v* 1/49 [2%] with vehicle), itching (2/43 [5%] with azelaic acid *v* 0/49 [0%] with vehicle), and erythema (2/43 [5%] with azelaic acid *v* 1/49 [2%] with vehicle; P values not reported for any outcome). [50] The second RCT (40 people) found that two people taking azelaic acid (10%) had itching and stinging compared with one person taking placebo (5%). [49] One non-systematic review of RCTs and uncontrolled studies found that 0–5% of people taking azelaic acid had scaling, 5–23% had burning, and 13–29% had itching. [51]

Comment: **Clinical guide:**
Azelaic acid is a similar type of treatment to benzoyl peroxide, but there is less evidence of benefit for azelaic acid than for benzoyl peroxide. It can also cause irritation which is helped by reducing the frequency of application or temporarily discontinuing treatment.

OPTION ERYTHROMYCIN PLUS ZINC (TOPICAL)

Symptom severity

Compared with placebo Topical erythromycin plus zinc may be more effective at reducing inflammatory and non-inflammatory lesions and at reducing overall acne severity at 10–12 weeks (low-quality evidence).

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Topical erythromycin plus zinc versus placebo:
We found one systematic review (search date 1999, 2 RCTs, 222 people with mild to severe acne), which compared topical erythromycin 4% plus zinc acetate 1.2% versus placebo. [16] The review did not perform a meta-analysis because of heterogeneity among the trials in outcomes assessed. [16] The first RCT compared four interventions for 10 weeks: erythromycin 4% plus zinc acetate 1.2% gel twice daily plus oral placebo; erythromycin 4% plus zinc octoate 1.2% liquid twice daily plus oral placebo; oral tetracycline 250 mg twice daily plus topical vehicle; and topical vehicle plus oral placebo. [52] It found that erythromycin plus zinc (liquid or gel) significantly reduced overall acne severity at 10 weeks compared with topical vehicle plus oral placebo (149 men, severity of acne unclear; reduction in severity measured by Cook's acne grading scale: 46% with topical erythromycin plus zinc liquid *v* 7% with topical vehicle plus oral placebo, P less than 0.001; reduction in severity: 33% with topical erythromycin plus zinc gel *v* 7% with topical vehicle plus oral placebo, P less than 0.01). It also found that erythromycin plus zinc significantly reduced papules compared with placebo (reduction in papules measured by Cook's acne grading scale: 58% with topical erythromycin plus zinc liquid *v* 25% with topical vehicle plus oral placebo, P less than 0.001; reduction in papules: 45% with topical erythromycin plus zinc gel *v* 25% with topical vehicle plus oral placebo, P less than 0.05). It found no significant difference in pustules between treatments (reported as non-significant, no further data reported). [52] The RCT did not assess patient perception of improvement. The second RCT compared topical erythromycin 4% plus zinc acetate 1.2% twice daily versus vehicle. [53] It found that topical erythromycin plus zinc acetate significantly reduced both non-inflammatory and inflammatory lesions at 12 weeks compared with vehicle (73 women with Cook's acne grade score 3 or more in non-inflammatory lesions: 61% with topical erythromycin plus zinc acetate *v* 48% with vehicle, P less than 0.01; reduction in inflammatory lesions: 73% with topical erythromycin plus zinc acetate *v* 46% with vehicle, P less than 0.01). [53] The RCT did not assess patient perception of improvement.

Harms:

Topical erythromycin plus zinc versus placebo:
One person in the first RCT withdrew from the trial because of irritation with topical erythromycin plus zinc acetate liquid plus oral placebo. [52] The second RCT reported that no one withdrew from the trial owing to irritation or other adverse effects of treatment; it gave no further information on adverse effects. [53]

Comment:

Studies of development of bacterial resistance to antibiotics suggest that topical application of antibiotics in acne may result in antibiotic resistance in *Propionibacterium acnes*. [7] [29] One systematic review (search date 2003) has found evidence that the efficacy of topical erythromycin 1.5–2% has decreased over the period 1966–2003, which may be as a result of increasing bacterial resistance (see comment on topical erythromycin, p 4). [30]

Clinical guide:
Topical antibiotics or topical retinoids are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the antibiotic class, there is more evidence of benefit with topical clindamycin or erythromycin than with erythromycin plus zinc or tetracycline. However, there is some evidence that topical erythromycin may be less effective now than in the past, owing to increasing *P acnes* resistance. Erythromycin plus zinc is available as a formulated combination topical solution.

OPTION ISOTRETINOIN (TOPICAL)

Symptom severity
Compared with placebo Topical isotretinoin may be more effective at reducing the number of inflammatory and non-inflammatory lesions at 12 weeks in people with mild to moderate acne (low-quality evidence).

Patient perception of improvement
Compared with placebo We don't know whether topical isotretinoin is more effective at increasing the proportion of people who perceive their acne as improved at 12 weeks (very low-quality evidence).

Note
Topical isotretinoin has been associated with severe erythema, dryness, soreness, and burning. Topical retinoids are not recommended in women of childbearing age who taking adequate contraceptive precautions, or during pregnancy.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Topical isotretinoin versus placebo:

We found one systematic review [16] (search date 1999, 3 RCTs, [21] [54] [55] 472 people with mild to moderate acne) and one subsequent RCT (160 people with mild to moderate acne) [32] comparing isotretinoin versus placebo (vehicle). The review did not perform a meta-analysis because of heterogeneity among the trials in methods of outcome assessment. [16] The first RCT identified by the review found that isotretinoin significantly reduced the number of inflammatory lesions (313 people with moderate acne; mean reduction: 55% with isotretinoin *v* 25% with vehicle), the number of non-inflammatory lesions (46% with isotretinoin *v* 14% with vehicle), and severity scores (measured by Cook's acne grading scale method [14] : 40% with isotretinoin *v* 20% with vehicle; differences reported as significant for all outcomes, CI not reported) compared with vehicle. [54] The RCT did not assess patient perception of improvement. The second RCT identified by the review compared three interventions: isotretinoin, benzoyl peroxide, and vehicle. [21] It found that, at 12 weeks, isotretinoin significantly reduced the number of inflammatory lesions (77 people with mild to moderate acne; mean change: –33% with isotretinoin *v* +9% with vehicle; P = 0.01), the number of non-inflammatory lesions (mean change: –47% with isotretinoin *v* +6% with vehicle; P = 0.01), and severity scores compared with vehicle (measured using the Leeds score where 0 = no acne and 10 = severest acne; mean score: 0 with isotretinoin *v* 1 with vehicle; P less than 0.05). [21] The RCT did not assess patient perception of improvement. The third RCT identified by the review did not assess the effects of isotretinoin on the number of inflammatory or non-inflammatory lesions. [55] It assessed effects on comedones and papules but did not compare isotretinoin versus vehicle directly; rather, it assessed within-group differences from baseline in each group. It found that isotretinoin 0.05% or 0.1% significantly reduced the number of whiteheads or papules from baseline at 12 weeks (82 people with mild to moderate acne; mean change in whiteheads from baseline with isotretinoin 0.05%: –9.6, P less than 0.01; mean change in papules with isotretinoin 0.05%: –7.6, P less than 0.01; mean change in whiteheads from baseline with isotretinoin 0.1%: –9.4, P less than 0.01; mean change in papules with isotretinoin 0.1%: –13.3, P less than 0.01; mean change in whiteheads with placebo from baseline: –2.6, reported as not significant; mean change in papules with placebo: –7.3, P less than 0.01). [55] The RCT did not assess patient perception of improvement. The subsequent RCT compared isotretinoin 0.05% alone, erythromycin 2% alone, isotretinoin plus erythromycin, or vehicle for 12 weeks' treatment. [32] The RCT did not report direct comparisons of isotretinoin alone versus vehicle; it reported changes from baseline within the isotretinoin alone and the vehicle groups. It found a significant reduction in total lesion count from baseline at 12 weeks with isotretinoin, but not with vehicle (160 people with mild to moderate acne; mean change in total lesion count: –21.52%, 95% CI –32.44% to –10.60% with isotretinoin *v* –10.82%, 95% CI –24.29% to +2.65% with vehicle). It also found significant reductions in the number of non-inflammatory and inflammatory lesions from baseline to 12 weeks with isotretinoin, but not with vehicle (mean change in non-inflammatory lesion count: –18.49, 95% CI –35.5 to –1.63 with isotretinoin *v* –7.07, 95% CI –28.31 to +14.16 with vehicle; mean change in inflammatory lesion count: –15.66, 95% CI –27.71 to –3.62 with isotretinoin *v* –9.58, 95% CI –24.51 to +5.36 with vehicle). [32] However, the RCT found that a similar proportion of people using isotretinoin compared with vehicle perceived that their acne had improved from baseline at 12 weeks (66% with isotretinoin *v* 53% with vehicle; P value not reported).

Harms:

Topical isotretinoin versus placebo:

The first RCT identified by the review found that more people using isotretinoin had peeling or erythema compared with vehicle cream (peeling: 71% with isotretinoin *v* 51% with vehicle; erythema: 76% with isotretinoin *v* 62% with vehicle). [54] The second RCT identified by the review found that isotretinoin was associated with severe erythema (2 people), dryness (3 people), redness (10 people), soreness (4 people), and burning (4 people). One person taking isotretinoin withdrew because of erythema. [21] The third RCT identified by the review found that isotretinoin (0.05% and 0.1%) significantly increased peeling at 12 weeks compared with vehicle (P less than 0.01, no further data reported). [55] The subsequent RCT found no significant difference among treatments in “overall tolerance” over 12 weeks (reported as non-significant, P value not reported). [32] This RCT is likely to have been underpowered to detect a clinically important difference in adverse effects among treatments.

Birth defects:

In the absence of data regarding the risk of birth defects, it is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

Comment:

Clinical guide:

Topical retinoids or topical antibiotics are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the retinoid class, there is more evidence of benefit with topical tretinoin than with isotretinoin or adapalene. It is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

OPTION TETRACYCLINE (TOPICAL)

Symptom severity
Compared with placebo Topical tetracycline may be more effective at reducing severity of acne at 12–16 weeks in people with mild to moderate acne (very low-quality evidence).

Patient perception of improvement
Compared with placebo Topical tetracycline may be no more effective at increasing the proportion of people who consider their condition better than before treatment (low-quality evidence).

Note
Topical tetracycline has been associated with skin discoloration.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Topical tetracycline versus placebo:
We found one systematic review (search date 1999, 4 RCTs, 355 people with moderate to severe acne). [16] The review did not perform a meta-analysis because of heterogeneity among the trials in outcomes assessed. The first RCT identified by the review compared three interventions for 13 weeks: topical tetracycline 0.5% plus oral placebo, oral tetracycline 250 mg twice daily plus topical placebo, and topical plus oral placebo. [56] It found that topical tetracycline significantly reduced acne severity at 12 weeks compared with placebo (75 people; mean reduction in severity measured by Cook's acne grading scale [14] : 1.43 with topical tetracycline *v* 0.62 with placebo; P less than 0.05). The results of the RCT should be interpreted with caution, as it did not perform an intention-to-treat analysis of results, and 11/75 (15%) people withdrew from the trial. [56] The RCT did not assess patient perception of improvement. The second RCT identified by the review also compared three interventions: topical tetracycline plus oral placebo, topical vehicle plus oral tetracycline, and topical vehicle plus oral placebo. [57] It found that more people taking topical tetracycline had reduced acne severity compared with people taking placebo (60 male adolescents; AR for improvement of at least 1 on a scale from 0 [least improvement] to 8 [most improvement]: 14/19 [74%] with topical tetracycline *v* 6/17 [35%] with placebo). The RCT did not assess the significance of the difference among groups, and did not assess patient perception of improvement. [57] The third RCT identified by the review compared three interventions for 12 weeks: topical tetracycline 0.22% plus oral placebo, oral tetracycline plus topical vehicle, and topical vehicle plus oral placebo. [58] It found that topical tetracycline significantly reduced acne severity at 7, 10, and 12 weeks compared with placebo (135 people aged 18–25 years with mild to moderate acne, Cook's acne grades 0–8, P less than 0.05; absolute results presented graphically). The RCT did not assess patient perception of improvement. [58] The fourth RCT compared topical tetracycline 2.2% versus placebo for 16 weeks. [59] All participants took oral tetracycline for 8 weeks before beginning treatment with topical tetracycline or placebo. The RCT found that topical tetracycline significantly increased the proportion of people who had improved acne at 16 weeks (85 people with mild to moderate acne; proportion with improvement measured on a scale from 0 to 8: 29/31 [94%] with topical tetracycline *v* 13/23 [57%] with placebo; P = 0.035). It is unclear how the authors dichotomised results to calculate the proportion of people who had improved acne severity. The RCT found that a similar proportion of people taking topical tetracycline compared with placebo "considered that their condition was better than before treatment" (25/31 [81%] with topical tetracycline *v* 18/24 [75%] with placebo; P value not reported).

Harms:

Topical tetracycline versus placebo:
Three of the RCTs identified by the review found that some people using topical tetracycline had skin discoloration. [56] [58] [59] In one RCT, the difference between groups was significant (proportion with skin discoloration: 17/43 [40%] with tetracycline *v* 4/42 [10%] with placebo; P less than 0.005). [59] One RCT gave no information on adverse effects. [57]

Comment:

Studies of development of bacterial resistance to antibiotics suggest that topical application of antibiotics in acne may result in antibiotic resistance in *Propionibacterium acnes*. [7] [29]

Clinical guide:
Topical antibiotics or topical retinoids are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the antibiotic class, there is more evidence of benefit with topical clindamycin or erythromycin than with erythromycin plus zinc, or with tetracycline.

QUESTION What are the effects of oral treatments in people with acne vulgaris?

OPTION ERYTHROMYCIN (ORAL)

Symptom severity
Compared with oral doxycycline We don't know whether oral erythromycin is more effective at reducing the number of papules and pustules at 6 weeks in people with moderate acne (low-quality evidence).

Compared with oral tetracycline We don't know whether oral erythromycin is more effective at improving inflammation scores at 6 months, or at reducing the number of pustules, papules, or open or closed comedones at 12 weeks in people with moderate to severe acne (low-quality evidence).

Patient perception of improvement
Compared with oral tetracycline Oral erythromycin and oral tetracycline are equally effective at increasing the proportion of people with moderate to severe acne who perceive their acne as markedly improved or improved at 12 weeks (moderate-quality evidence).

Note
We found no direct information about whether oral erythromycin is better than no active treatment in people with acne. Oral erythromycin may cause contraceptive failure during the initial weeks of treatment.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Oral erythromycin versus placebo:
We found two systematic reviews (search date 2004) [17] and (no search date given) [60] which identified no RCTs comparing oral erythromycin versus placebo. We found no subsequent RCTs.

Oral erythromycin versus oral doxycycline:
We found one RCT (56 people with moderate acne) comparing oral doxycycline (100 mg daily for 2 weeks, then on alternate days for 4 weeks) versus oral erythromycin (500 mg twice daily for 2 weeks, then 250 mg twice daily for 4 weeks). [61] Before treatment, people taking doxycycline had a mean of 38 inflammatory lesions, and people taking erythromycin had a mean of 46 inflammatory lesions (significance not reported). The RCT found no significant difference in the number of papules and pustules after 6 weeks between doxycycline and erythromycin (mean number per person: 16 with doxycycline *v* 15 with erythromycin; P greater than 0.1). The RCT did not assess patient perception of improvement.

Oral erythromycin versus oral tetracycline:
We found two systematic reviews. [16] [17] The first review (search date 1999) [16] identified three RCTs [62] [63] [64] (300 people), which compared oral erythromycin versus oral tetracycline in people with mild, moderate, or severe acne. The second review (search date 2004), [17] which had more stringent inclusion criteria, included one RCT identified by the first review. [63] The first RCT included in the first review found no significant difference in cure or total inflammation scores between erythromycin 200–400 mg daily and tetracycline 250–400 mg daily for 6 months (60 people with moderate to severe acne; proportion symptom free: 9/21 [43%] with erythromycin *v* 7/21 [33%] with tetracycline; inflammation score on face: 1 in both groups; reported as non-significant, P value not reported). [62] The RCT did not assess patient perception of improvement. The second RCT compared erythromycin (333 mg three times daily for 4 weeks, then once daily for 8 weeks) versus tetracycline (500 mg twice daily for 4 weeks, then once daily for 8 weeks). [63] It found no significant difference between erythromycin and tetracycline at 12 weeks in the number of pustules, papules, open comedones, or closed comedones (200 people with moderate to severe acne; % change, pustules: –73% with erythromycin *v* –65% with tetracycline; papules: –60% with erythromycin *v* –62% with tetracycline; open comedones: –26% with erythromycin *v* –31% with tetracycline; closed comedones: –17% with erythromycin *v* –36% with tetracycline; P value reported as non-significant for all outcomes, CI not reported). It also found no significant difference between erythromycin and tetracycline in the proportion of people who perceived that their acne had improved (proportion who reported acne as "markedly improved" or "improved": 77% with erythromycin *v* 89% with tetracycline; difference reported as non-significant, P value and CI not reported). The third RCT compared erythromycin 250 mg twice daily versus tetracycline 250 mg twice daily for 16 weeks. [64] It did not compare the two treatments directly, but found that fewer people in the erythromycin group than in the tetracycline group had a "good" or "very good" response as assessed by their physician (40 people with mild, moderate, or severe acne; AR for "good" or "very good" response: 65% with erythromycin *v* 90% with tetracycline). It did not assess patient perception of improvement.

Harms:

Oral erythromycin versus placebo:
We found no RCTs.

Oral erythromycin versus oral doxycycline:
The RCT reported no withdrawals due to adverse effects, but gave no further information. [61]

Oral erythromycin versus oral tetracycline:
The RCTs found that oral erythromycin and oral tetracycline were associated with similar rates of adverse effects, mostly gastrointestinal. In the first RCT, one person in each treatment group discontinued treatment in the first week because of diarrhoea, and 14% of people in the trial had adverse effects, mostly gastrointestinal. [62] In the second RCT, 12 people taking erythromycin and seven taking tetracycline had adverse effects, again mostly gastrointestinal. [63] One person taking oral tetracycline developed a pseudotumour cerebri, but later recovered. [63] In the third RCT, one person taking erythromycin had nausea and vomiting, and one person taking tetracycline had mild diarrhoea, one had nausea, and one had pruritus. [64] Both oral erythromycin and oral tetracycline may cause contraceptive failure during the initial weeks of treatment.

Comment:

Propionibacterium acnes are becoming increasingly resistant to systemic antibiotics. One systematic review (search date 1998, 12 studies) found an increase in the prevalence of *P acnes* resistance from 20% in 1978 to 62% in 1996. [65] Resistance to systemic antibiotics varied, but was most commonly reported in people taking erythromycin, clindamycin, tetracycline, doxycycline, and trimethoprim. Resistance to minocycline was rare.

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and can be supplemented by non-antibiotic topical treatment (e.g. benzoyl peroxide) if needed. There is evidence that erythromycin is effective, but there are some concerns about bacterial resistance. Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION DOXYCYCLINE (ORAL)

Symptom severity
Compared with placebo We don't know whether oral doxycyline is more effective at reducing the number of inflammatory lesions at 4 weeks in people with mild acne (very low-quality evidence).

Compared with oral erythromycin We don't know whether oral doxycycline is more effective at reducing the number of papules and pustules at 6 weeks in people with moderate acne (low-quality evidence).

Compared with oral minocycline We don't know whether oral doxycline is more effective at increasing the proportion of people with mild to moderate or inflammatory acne with at least 50% reduction in inflammatory lesions, and in total lesion count (very low-quality evidence).

Compared with oral oxytetracycline We don't know whether oral doxycycline is more effective at reducing the number of lesions at 8 weeks in people with moderate to severe acne (low-quality evidence).

Note
Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. They may cause contraceptive failure during the initial weeks of treatment.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Oral doxycycline versus placebo:
We found two systematic reviews. [16] [17] [60] The first review (search date 1999) [16] identified one crossover RCT (62 people with mild acne), which compared oral doxycycline 100 mg daily versus placebo for 8 weeks. [66] The RCT did not report direct comparisons of oral doxycycline with placebo, but reported changes from baseline within the doxycycline and the placebo groups. Comparing changes from baseline within the oral doxycycline group before crossover, it found that oral doxycycline significantly reduced the number of inflammatory lesions from baseline at 4 weeks compared with placebo (% change from baseline: –36% with doxycycline, P = 0.001; +12% with placebo, change reported as non-significant, P value and CI not reported). It found no significant difference in the number of comedones and cysts from baseline within the doxycycline group. The RCT had major losses to follow-up (no further data reported). It did not assess patient perception of improvement.

Oral doxycycline versus oral erythromycin:
See benefits of oral erythromycin, p 12 .

Oral doxycycline versus oral minocycline:
See benefits of oral minocycline, p 14 .

Oral doxycycline versus oral oxytetracycline:
We found one double blind crossover RCT comparing oral doxycycline (100 mg daily for 8 weeks) versus oral oxytetracycline (250 mg three times daily for 4 weeks then once daily for 4 weeks). [67] Before crossover, it found no significant difference in mean number of lesions between oral doxycycline and oxytetracycline (28 people with moderate to severe acne; mean number per person at 8 weeks: 62 with doxycycline *v* 32 with oxytetracycline; reported as non-significant, P value not reported). The RCT did not assess patient perception of improvement.

Harms:

Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. [68] [69] They may cause contraceptive failure during the initial weeks of treatment.

Oral doxycycline versus placebo:
The RCT identified by the review found no adverse effects in people taking doxycycline or placebo, but may have been underpowered to detect adverse effects. [66]

Oral doxycycline versus oral erythromycin:
The RCT (56 people) comparing doxycycline with erythromycin reported that no one withdrew from treatment because of adverse effects after 6 weeks with either treatment. [61]

Oral doxycycline versus minocycline:
See harms of oral minocycline, p 14 .

Oral doxycycline versus oral oxytetracycline:
The RCT reported no “significant adverse effects”. [67]

Comment:

See comment on oral erythromycin regarding antibiotic resistance, p 11 .

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and can be supplemented by non-antibiotic topical treatment (e.g. benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) offer benefits, but have differing adverse-effect profiles that need to be considered in treatment decisions. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION LYMECYCLINE (ORAL)

Symptom severity
Compared with oral minocycline Oral lymecycline and oral minocycline seem equally effective at 12 weeks at increasing the proportion of people with 50% or greater reduction in inflammatory or non-inflammatory lesions (moderate-quality evidence).

Patient perception of improvement
Compared with oral minocycline Oral lymecycline and oral minocycline seem equally effective at 12 weeks at increasing the proportion of people who perceive an overall improvement in their acne (moderate-quality evidence).

Note
We found no direct information about whether oral lymecycline is more effective than no active treatment in people with acne vulgaris.

Note
Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. They may cause contraceptive failure during the initial weeks of treatment.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Oral lymecycline versus placebo:
We found one systematic review (search date 1999), which identified no RCTs comparing oral lymecycline versus placebo. [16] We found no subsequent RCTs.

Oral lymecycline versus oral minocycline:
See benefits of oral minocycline, p 14 .

Harms:

Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. [68] [69] They may cause contraceptive failure during the initial weeks of treatment.

Oral lymecycline versus placebo:
We found no RCTs.

Oral lymecycline versus oral minocycline:
See harms of oral minocycline, p 14 .

Comment: See comment on oral erythromycin regarding antibiotic resistance, p 11 .

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and may be supplemented by non-antibiotic topical treatment (e.g. benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) are beneficial, but have different adverse-effect profiles that need to be considered in treatment decisions. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION MINOCYCLINE (ORAL)

Symptom severity
Compared with placebo We don't know whether oral minocycline is more effective at reducing the number of inflammatory lesions and total number of lesions at 12 weeks (low-quality evidence).

Compared with oral doxycycline We don't know whether oral minocycline is more effective at increasing the proportion of people with mild to moderate or inflammatory acne with 50% or greater reduction in inflammatory lesions, and at decreasing total lesion count (very low-quality evidence).

Compared with oral lymecycline Oral minocycline and oral lymecycline seem equally effective at 12 weeks at increasing the proportion of people with 50% or greater reduction in inflammatory or non-inflammatory lesions (moderate-quality evidence).

Compared with oral oxytetracyline We don't know whether oral minocycline is more effective at increasing the proportion of people who report moderate improvement, or whose acne improves by at least two grades on the Cook's acne grading severity scale at 12–24 weeks (very low-quality evidence).

Compared with oral tetracycline We don't know whether oral minocycline is more effective at improving overall acne severity assessed on a variety of scales (including the Samuelson Lesion and Pillsbury Scale), or at increasing the proportion of people who report an overall improvement or rate response as satisfactory in people with moderate to severe acne (very low-quality evidence).

Patient perception of improvement
Compared with placebo We don't know whether oral minocycline is more effective at improving patient perception of overall efficacy (very low-quality evidence).

Compared with oral lymecycline Oral minocycline and oral lymecycline seem equally effective at 12 weeks at increasing the proportion of people who perceive an overall improvement in their acne (moderate-quality evidence).

Note
Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. They may also cause contraceptive failure during the initial weeks of treatment.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Oral minocycline versus placebo:
We found one systematic review (search date 2002), which identified one crossover RCT comparing oral minocycline versus placebo for 5 weeks. [70] The RCT did not compare minocycline versus placebo directly, but assessed within-group differences from baseline in each group. Before crossover, it found that minocycline significantly reduced total lesion score from baseline (P less than 0.05), whereas placebo did not (no further data reported). It found no significant change in patient perception of overall efficacy of minocycline compared with baseline (43 people; perceived efficacy measured on a 10 cm visual analogue scale: WMD –1.25, 95% CI –7.22 to +4.72). The RCT was of insufficient duration to adequately assess the effects of minocycline. The review did not report on results post-crossover because there was no washout period before crossover, which could have affected results in the placebo group. [70] We found one subsequent RCT (924 people with moderate or severe facial acne) comparing extended-release minocycline (1 mg/kg daily) versus placebo. [71] The RCT found that, compared with placebo, extended-release minocyline significantly reduced the number of inflammatory lesions (reduction from baseline to day 84: 46%

with extended-release minocycline *v* 32% with placebo, P less than 0.001; absolute figures not reported) and total number of lesions (reduction from baseline to day 84: 33% with extended-release minocycline *v* 22 %, P less than 0.001; absolute figures not reported) at 12 weeks.

Oral minocycline versus oral doxycycline:
We found one systematic review (search date 2002, 5 RCTs, 419 people with mild to moderate or inflammatory acne) comparing oral minocycline versus oral doxycycline. [70] The review did not perform a meta-analysis because of heterogeneity among the trials in methods, outcomes assessed, and drug doses. All of the RCTs found no significant difference in outcomes between minocycline and doxycycline. Outcomes assessed included proportion of people with at least a 50% reduction in inflammatory lesions, total lesion count, patient perception of improvement, and overall efficacy. The review found problems with the methods used in all of the RCTs: three were open label, and the two double blind RCTs reported insufficient information to allow calculation of effect sizes.

Oral minocycline versus oral lymecycline:
We found one systematic review (search date 2002), which identified one multicentre RCT comparing oral minocycline versus oral lymecycline. [70] It found no significant difference between minocycline and lymecycline in the proportion of people with at least a 50% reduction in inflammatory or non-inflammatory lesions at 12 weeks (144 people with at least 20 inflammatory lesions on the face; AR for at least 50% reduction in inflammatory lesions: 46/73 [63%] with minocycline *v* 41/71 [58%] with lymecycline, RR 1.09, 95% CI 0.84 to 1.42; AR for at least 50% reduction in non-inflammatory lesions: 22/73 [30%] with minocycline *v* 33/71 [46%] with lymecycline, RR 0.65, 95% CI 0.42 to 1.00). The RCT also found no significant difference between minocycline and lymecycline in the proportion of people who perceived that there had been “overall improvement” in their acne (59/71 [83%] with minocycline *v* 55/65 [85%] with lymecycline; RR 0.98, 95% CI 0.91 to 1.24).

Oral minocycline versus oral oxytetracycline:
We found one systematic review (search date 2002), which identified one open-label RCT comparing oral minocycline versus oral oxytetracycline, [70] and one subsequent RCT. [72] The RCT identified by the review found that minocycline significantly increased the proportion of people whose acne had improved by at least two grades on the Cook's acne grading severity scale over 12–24 weeks' treatment compared with oxytetracycline (237 people with at least grade 4 acne on Cook's scale; AR for at least 2 grades' improvement: 90/104 [87%] with minocycline *v* 64/90 [71%] with oxytetracycline; RR 1.22, 95% CI 1.05 to 1.42; completer analysis). The results of the RCT should be interpreted with caution, as they are not analysed by intention to treat, and 43 people (18%) were excluded from the analysis. The clinical relevance of the results is also unclear, because the RCT did not state acne grades after treatment. The RCT did not assess patient perception of improvement. The subsequent double-blind RCT compared five treatments: oral minocycline 100 mg once daily plus topical placebo; oral oxytetracycline 500 mg twice daily plus topical placebo; oral placebo plus topical benzoyl peroxide twice daily; oral placebo plus topical benzoyl peroxide plus topical erythromycin twice daily; and oral placebo plus topical erythromycin in the morning plus topical benzoyl peroxide in the evening. [72] It found no significant difference in the proportion of people reporting moderate improvement in facial acne at 18 weeks between oral minocycline and oral oxytetracycline (5-arm RCT, 649 people with mild to moderate acne [Leeds acne grade 3 or less]; improvement assessed using a 6-point Likert scale; AR for at least moderate improvement: 70/130 [54%] with minocycline *v* 72/131 [55%] with oxytetracycline; OR 0.95, 95% CI 0.58 to 1.55). [72]

Oral minocycline versus oral tetracycline:
We found one systematic review (search date 2002, 6 RCTs, 693 people with moderate to severe acne) comparing oral minocycline versus oral tetracycline. [70] The review did not perform a meta-analysis because of heterogeneity among the trials in outcomes assessed. Five RCTs identified by the review found no significant difference between minocycline and tetracycline in overall acne severity assessed on a variety of scales, including the Samuelson Lesion and Pillsbury Scale. Two RCTs identified by the review found no significant difference between oral minocycline and oral tetracycline in the proportion of people who perceived overall improvement in their acne, or felt that their response was “satisfactory”; the other RCTs did not assess patient perception of improvement. One open-label RCT identified by the review reported a difference in outcomes between minocycline and tetracycline, but the methods used had serious flaws sufficient to question the validity of the result.

Harms:

We found three systematic reviews assessing the adverse effects of minocycline. [70] [73] [74] The first review (search date 2002) identified 21 studies assessing the adverse effects of minocycline. [70] It found that 137/1230 (11%) people had an adverse reaction attributed to minocycline, 36/1230 (3%) of whom withdrew because of adverse effects. It also found that 17/700 (2%) people taking minocycline had abnormal pigmentation. [70] One prospective cohort study identified by the review (700 people) assessed adverse effects in people taking minocycline 100–200 mg daily for a mean 10.5 months. [75] It found that adverse effects were reported in 13.6% of people. They included

vestibular disturbance, candida infection, gastrointestinal disturbance, cutaneous symptoms (pigmentation, pruritus, photosensitive rash, and urticaria), and benign intracranial hypertension. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. [68] [69] They may cause contraceptive failure during the initial weeks of treatment.

Oral minocycline versus placebo: The subsequent RCT of extended-release (ER) minocycline found similar rates of adverse effects in the minocycline and placebo groups during the 12 weeks of follow-up (56% with minocyline *v* 54% with placebo, significance not reported). The most commonly reported adverse effects in the minocycline group were headaches (22.6%), nausea (9.5%), fatigue (9.2%), dizziness (8.8%), diarrhoea (5.2%) and pruritis (4.6%). [71]

Oral minocycline versus oral oxytetracycline:
The subsequent RCT found that adverse events were more common in the first 6 weeks of treatment, and occurred with similar frequency in the minocycline and oxytetracycline groups (skin adverse event: 4% in both groups; gastrointestinal adverse event: 9% with minocycline *v* 8% with oxytetracycline; central nervous system adverse event: 11% with minocycline *v* 17% with oxytetracycline; significance assessments not performed). In the minocycline group, 2% of participants experienced musculoskeletal symptoms at week 12, and 4% experienced musculoskeletal symptoms at week 18 (figures not reported for other groups).

Systemic lupus erythematosus:
We found two systematic reviews. [70] [73] The first review [70] identified one case control study [76] (27,688 people aged 15–19 years with acne) assessing the risk of systemic lupus erythematosus (SLE) in people taking tetracyclines compared with matched controls. Women had a significantly higher risk of developing SLE compared with men (RR 14, 95% CI 1.8 to 111). The case control study found that 29 people (27 women) taking tetracyclines had an SLE-like syndrome. It found that current minocycline use significantly increased the risk of developing SLE (AR 52.8 cases per 100,000 prescriptions; RR 8.5, 95% CI 2.1 to 35). It found no significant difference in the risk of developing SLE with tetracyclines other than minocycline, although use of tetracyclines was associated with an increased risk (RR 1.7, 95% CI 0.4 to 8.1). Cumulative minocycline dose and prolonged exposure (more than 100 days) to minocycline may also be risk factors, but no quantitative data were reported. The second review (search date 1999) identified 57 case reports of SLE in people taking minocycline. [73] It suggested that minocycline may induce SLE, but did not quantify its conclusions. Evidence about adverse effects should be interpreted with caution because of wide variation between studies in numbers of reported adverse events. The prevalence of SLE in the general population is 30/100,000 in white people, rising to 200/100,000 in Afro-Caribbean people. [77]

Liver damage:
We found one systematic review (search date 1998) of case reports and case series, which found 65 cases of liver damage in people taking minocycline. [74] The review did not quantify the increased risk in people taking minocycline. It suggested that minocycline was associated with severe hepatic dysfunction, including hypersensitivity, within a few weeks of taking minocycline (16 cases), autoimmune hepatitis within 1 year or more of taking minocycline (29 cases), or unspecified hepatitis (20 cases).

Comment: See comment on oral erythromycin regarding antibiotic resistance, p 11 .

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and may be supplemented by non-antibiotic topical treatment (e.g. benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) are beneficial, but have different adverse-effect profiles that need to be considered in treatment decisions. Current clinical guidance in the UK suggests that people taking minocycline for more than 6 months should be monitored for hepatotoxicity, pigmentation, and SLE. [78] Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION OXYTETRACYCLINE (ORAL)

Symptom severity
Compared with oral minocycline We don't know whether oral oxytetracycline is more effective at increasing the proportion of people who report moderate improvement or whose acne improves by at least two grades on the Cook's acne grading severity scale at 12–24 weeks (very low-quality evidence).

Compared with oral doxycycline We don't know whether oral oxytetracycline is more effective at reducing the number of lesions at 8 weeks in people with moderate to severe acne (low-quality evidence).

Note
We found no direct information about whether oral oxytetracycline is better than no active treatment in people with acne vulgaris. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. They may cause contraceptive failure during the initial weeks of treatment.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Oral oxytetracycline versus placebo:
We found two systematic review (search date 1999) [16] and (search date not given) [60] which identified no RCTs comparing oral oxytetracycline versus placebo. We found no subsequent RCTs.

Oral oxytetracycline versus oral minocycline:
See benefits of oral minocycline, p 14 .

Oral oxytetracycline versus oral doxycycline:
See benefits of oral doxycycline, p 12 .

Harms:

Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. [68] [69] They may cause contraceptive failure during the initial weeks of treatment.

Oral oxytetracycline versus oral minocycline:
See harms of oral minocycline, p 14 .

Oral oxytetracycline versus oral doxycycline:
See harms of oral doxycycline, p 12 .

Comment:

See comment on oral erythromycin regarding antibiotic resistance, p 11 .

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and may be supplemented by non-antibiotic topical treatment (e.g. benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) are beneficial, but have different adverse-effect profiles that need to be considered in treatment decisions. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION TETRACYCLINE (ORAL)

Symptom severity
Compared with placebo Oral tetracycline may be more effective at reducing severity of acne at 8–12 weeks in people with mild to moderate acne (very low-quality evidence).

Compared with oral erythromycin We don't know whether oral tetracycline is more effective at improving inflammation scores at 6 months, or at reducing the number of pustules, papules, or open or closed comedones at 12 weeks in people with moderate to severe acne (low-quality evidence).

Compared with oral minocycline We don't know whether oral tetracycline is more effective at improving overall acne severity assessed on a variety of scales (including the Samuelson Lesion and Pillsbury Scale) or at increasing the proportion of people with moderate to severe acne who report an overall improvement, or who rate response as satisfactory (very low-quality evidence).

Compared with oral isotretinoin Oral tetracycline is less effective at reducing acne cysts, pustules, and comedones at 24 weeks in people with severe nodulocystic acne (moderate-quality evidence).

Patient perception of improvement
Compared with placebo Oral tetracycline is more effective at increasing the proportion of people with moderate to severe acne who perceive their acne as markedly improved or improved at 8 weeks (moderate-quality evidence).

Compared with oral erythromycin Oral tetracycline and oral erythromycin are equally effective at increasing the proportion of people with moderate to severe acne who perceive their acne as markedly improved or improved at 12 weeks (moderate-quality evidence).

Note
Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. They may also cause contraceptive failure during the initial weeks of treatment.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Oral tetracycline versus placebo:
We found three systematic reviews. [16] [17] [60] The first review (search date 1999, 7 RCTs, 864 people with mild, moderate, or severe acne) compared oral tetracycline 250 mg twice daily versus placebo (see table 5, p 30). [16] The review did not perform a meta-analysis because of heterogeneity among the trials in outcomes assessed. The second review (search date 2004), [17] which had more stringent inclusion criteria, identified one RCT included in the earlier review. [23] The third review (search date not given), did not include any further RCTs. [60] Four RCTs identified by the reviews found that oral tetracycline significantly reduced acne severity compared with placebo. [26] [56] [58] [79] One of these RCTs also found that oral tetracycline significantly increased the proportion of people who perceived that their acne was "markedly improved" or "improved" compared with placebo. [26] A fifth RCT compared three interventions: topical tetracycline plus oral placebo, topical vehicle plus oral tetracycline, and topical vehicle plus oral placebo. [57] It found that more people taking oral tetracycline had improved acne compared with people taking placebo, but did not assess the significance of the difference among groups. A sixth small RCT, which compared four interventions, found no significant difference in the number of inflammatory lesions between oral tetracycline and placebo, but may have lacked power to detect a clinically important difference among groups. [80] The seventh RCT did not compare tetracycline versus placebo directly, although within-group comparisons found that tetracycline significantly reduced the number of inflammatory lesions from baseline, and increased the proportion of people who perceived that their acne was "markedly improved" or "improved". [23]

Oral tetracycline versus oral erythromycin:
See benefits of oral erythromycin, p 11 .

Oral tetracycline versus oral minocycline:
See benefits of oral minocycline, p 14 .

Oral tetracycline versus oral isotretinoin: See benefits of oral retinoids, p 18

Harms:

Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. [68] [69] They may cause contraceptive failure during the initial weeks of treatment.

Oral tetracycline versus placebo:
The review identified five RCTs that assessed adverse effects, and found that 15/579 [3%] people taking tetracycline had adverse effects. [16]

Oral tetracycline versus oral minocycline:
See harms of oral minocycline, p 14 .

Oral tetracycline versus oral isotretinoin: see harms of oral retinoids, p 18 .

Comment:

See comment on oral erythromycin regarding antibiotic resistance, p 11 .

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and may be supplemented by non-antibiotic topical treatment (e.g. benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) are beneficial, but have different adverse-effect profiles that need to be considered in treatment decisions. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION ISOTRETINOIN (ORAL) New

Symptom severity
Compared with placebo Oral isotretinoin is more effective at reducing nodules at 1 month in people with treatment-resistant cystic and conglobate acne (moderate-quality evidence).

Compared with oral tetracycline Oral isotretinoin is more effective at reducing acne cysts, pustules, and comedones at 24 weeks in people with severe nodulocystic acne (moderate-quality evidence).

Adverse effects
Oral isotretinoin is teratogenic and is associated with a wide range of adverse effects, such as skin problems, changes in liver function, and development of psychiatric disorders.

For GRADE evaluation of interventions for acne vulgaris, see table, p 32 .

Benefits:

Oral isotretinoin versus placebo:
We found one RCT (33 people with treatment-resistant cystic and conglobate acne) comparing oral isotretinoin (0.5 mg/kg/day) versus placebo. [82] The RCT found a significant mean reduction of nodules at 1 month in the isotretinoin group of 32%, compared with an increase of 33% in the placebo group (P less than 0.008, no absolute figures reported). The open phase for a further 2–4 months showed further improvement in the treatment group as dose increased to a mean of 0.9 mg/kg/day.

Oral isotretinoin versus oral tetracycline:
One small RCT (29 people with severe nodulocystic acne) compared oral isotretinoin (1–2 mg/kg/day) versus oral tetracycline (0.5–1 mg/day). [81] The RCT found that, compared with tetracycline, isotretinoin significantly reduced acne cysts (reduction in acne cysts: 82% with isotretinoin *v* 52% with tetracycline; P less than 0.01) and pustules and comedones (reduction in pustules and comedones: 85% with isotretinoin *v* 58% with tetracycline; P less than 0.01) at 24 weeks (no absolute figures reported).

Harms:

Oral isotretinoin versus placebo:
The RCT found low rates of adverse effects in the isotretinoin group, including arthralgia, decreased appetite, fatigue, cheilitis, facial dermatitis, conjunctivitis, xerosis, and dryness of the nasal mucosa with nosebleeds. No figures were reported, but no one stopped treatment owing to adverse effects. [82]

Oral isotretinoin versus oral tetracycline:
The RCT found a higher rate of adverse effects with isotretinoin compared with tetracycline. These included xerosis (15/15 [100%] with isotretinoin *v* 2/15 [13%] with oral tetracycline), cheilitis/dry lips (15/15 [100%] with isotretinoin *v* 3/15 [20%] with oral tetracycline), dry nose (10/15 [67%] with isotretonoin *v* 1/15 [7%] with oral tetracycline), and dry mouth (3/15 [20%] with isotretinoin *v* 1/15 [7%] with oral tetracycline). The RCT also reported desquamation, alopecia, erythema, pruritis, epistaxis, dry eyes, conjunctivitis, pterygium (right eye), and photophobia in the isotretinoin group. [81]

Skin: Dry skin and mucosal surfaces are a well-known adverse effect of isotretinion treatment. We found one open study (80 people with a range of acne types failing to respond to oral antibiotics) of intermittent dosing with isotretinion 0.5 mg/kg/daily (1 week in 4 for 6 months), to determine the relative efficacy versus adverse effects. [83] Although there was no control group, the authors reported modest cheilitis at the lower end of the spectrum for isotretinoin adverse effects. [83]
Liver function: Isotretinion treatment affects the metabolic system, and is reflected in altered liver function tests and elevated blood lipids. We found one retrospective analysis of people receiving isotretinoin for acne to determine the necessity for routine testing of lipid profiles and liver function during treatment. The 209 people in the study included 113 people treated with 1 mg/kg/day, and 96 people treated with 0.5 mg/kg/day, who had serial fasting blood samples taken at 0, 8, and 16 weeks. The study found no significant changes in any of the tests of liver function. It concluded that, if the baseline tests are normal, in the absence of clinical indicators or doses greater than 1 mg/kg it is safe to measure just once at about 4 weeks. For prolonged doses, or where there are pre-existing abnormalities or higher doses, more frequent testing may be warranted. [84]
Pregnancy (teratogenesis): Isotretinion is teratogenic. We found two studies evaluating the effect of isotretinoin treatment on pregnancy and unborn infants. The first study (24,503 women self-registered for a pregnancy prevention programme) found that, in 402 pregnancies, 32 went to term; 13 of the infants were examined for teratogenic effects, revealing changes in 5/32 . [85] In the second study (8609 women), 90 women became pregnant, with nine women progressing to live birth. One of the nine infants had a congenital anomaly of the neck and face. [86] It is not clear how many of the 76/90 terminated pregnancies had already identified anomalies by ultrasound that might have biased the results.
Psychiatric adverse effects: There is controversy and conflicting evidence on the association of isotretinoin with a variety of adverse psychiatric effects. We found one systematic review (search date 2004) evaluating isotretinoin's association with depression, psychosis, mood swings, and violent behaviour. [87] The review included one prospective survey [88] and one case control study [89] on psychiatric adverse effects with isotretinoin. The prospective survey reported that the manufacturers had supplied 12 million treatments of isotretinoin by 2001. The data on adverse effects documented 1247 people with mood disorders. The authors also had record of 168 people with suicidal behaviour, 104 with suicide attempts, and 64 with completed suicides, at 10 years' follow-up after the completion of medication. Thirty suicides were confirmed in people while taking the medication. However, this figure should be considered in the context of a very large denominator.In addition, behavioural disorders and suicides are relatively common in the age group typically taking isotretinoin. US healthcare data reviewed in the same publication noted that 5 million people in the US are taking

isotretinoin. The number of suicides expected in that group from national standardised rates would be 190, whereas the number actually reported was 37. [88] The case control study (7195 people treated with isotretinion and 13,700 people treated with oral antibiotics) found no difference in rates of newly diagnosed psychiatric disorders between isotretinoin compared with oral antibiotics or with non-exposure to either drug (RR 0.9, 95% CI 0.3 to 2.4; P value not given). [89] We found one additional and one subsequent cohort study. [90] [91] Both these studies indicated a lack of association between isotretinoin and suicidal thoughts or action. In spite of this, there remain clinical concerns that isotretinoin might be associated with idiosyncratic adverse mood and behavioural effects in a small number of people. This means that guidelines for use and the drug licence include an outline psychiatric history and assessment undertaken by the dermatologist, with relevant monitoring questions at each consultation.

Comment:

Clinical guide: Many of the studies reported here are from the 1990s, assessing data from the 1980s. At that time, the threshold for prescribing oral isotretinoin was higher, where it was typically used on more severe acne. The norms have since shifted, such that it may well be that the milder grades of acne may be effectively managed with lower doses. In addition, adverse effects (see harms, above) may warrant a trial of different regimens in order to achieve clearance with less discomfort. Clinical experience demonstrates that oral isotretinoin is an immensely valuable drug in the management of complex and aggressive acne. It shortens the duration of suffering, and typically reduces the amount of scarring. However, adverse effects are common and sometimes severe. People in their 20s or older may relapse more frequently than adolescents with similar treatment. Those with milder acne may need smaller doses, but the data on the degree of improvement is not as clear for this group as it is in classic severe nodulocystic acne. Measures to prevent pregnancy and screen for psychological factors were revised in 2005, with changes to the drug licence, effective in the US and EU. [92] The current "pregnancy protection programme" recommends monthly pregnancy tests from 1 month before treatment to 1 month after the end of treatment, the use of two different forms of contraception, and the issue of prescriptions for only 4 weeks' medication at a time. The oral contraceptive, or co-cyprindiol, may be commenced before treatment of women of child-bearing age with isotretinoin, and continued for at least 1 month after. This provides some additional and independent therapeutic effect in some instances. As documented in harms (see above), there remains uncertainty about the relevance of isotretinoin treatment to adverse psychological events and suicide. However, it remains important that the medical history and monitoring take close note of psychiatric history and symptoms when reviewed in clinic. A recent systematic review from primary care suggested that, although the general practitioner was best placed to undertake this, it would introduce potential for error through communication between the GP and dermatologist, where the dermatologist would be responsible for prescribing. [92]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Isotretinoin (oral) One RCT added comparing oral isotretinoin versus placebo. The RCT found a mean reduction of nodules in the oral isotretinoin group compared with an increase in the placebo group at 1 month . [82] One RCT added comparing oral isotretinoin versus tetracycline. [81] The RCT found that, compared with tetracycline, isotretinoin reduced acne cysts, pustules, and comedones at 24 weeks. Isotretinoin is teratogenic and is associated with a wide range of adverse effects, such as skin problems, changes in liver function, and development of psychiatric disorders. Categorised as Trade-off between benefits and harms.
Adapalene (topical) One RCT added comparing adapalene with placebo. [47] The RCT found that, at 16 weeks, adapalene 0.1% improved maintenance of at least 50% of the improvement in total lesion count, and reduced lesion counts compared with placebo. Categorised as Likely to be beneficial.
Erythromycin (oral) Two systematic review added comparing oral erythromycin versus placebo. [60] [17] The systematic reviews identified no RCTs. Categorisation unchanged (Beneficial).
Minocycline (oral) One RCT added comparing oral mynocycline with placebo. The RCT found that extended-release oral minocyline reduced the number of inflammatory lesions and total number of lesions at 12 weeks compared with placebo. [71] The RCT reported similar rates of adverse effects between groups. Categorisation unchanged (Trade-off between benefits and harms).
Tetracycline (oral) One systematic review added comparing oral tetracycline versus placebo. [60] The systematic review added no further RCTs. One RCT added comparing oral tetracycline versus oral isotretinoin. [81] The RCT found that, compared with tetracycline, isotretinoin reduced acne cysts, pustules, and comedones at 24 weeks; categorisation unchanged (Trade-off between benefits and harms).

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Disclaimer

TABLE 1 **RCTs comparing benzoyl peroxide versus vehicle.**

Ref	Number of people	Treatment, dose, duration	Results	Comment
[18]	196 people with moderate acne	Benzoyl peroxide 5.5% 4 times daily *v* benzoyl peroxide plus chlorhydroxyquinolone *v* benzoyl peroxide plus chlorhydroxyquinolone plus hydrocortisone *v* vehicle, for 4 weeks	**Total lesion count/severity:** Benzoyl peroxide significantly reduced total lesion count compared with vehicle (% reduction: 37% with benzoyl peroxide *v* 6% with vehicle; P = 0.001) **Non-inflammatory lesions:** No data reported. **Inflammatory lesions:** No data reported **Patient perception of improvement:** No data reported **Adverse effects:** Suggested that peeling and erythema were "negligible" in all groups	
[19]	393 people with moderate acne	Benzoyl peroxide 5% 4 times daily *v* clindamycin *v* benzoyl peroxide plus clindamycin *v* vehicle, for 11 weeks	**Total lesion count/severity:** No data reported **Non-inflammatory lesions:** Benzoyl peroxide significantly reduced number of non-inflammatory lesions compared with vehicle (% change: –30% with benzoyl peroxide *v* +11% with vehicle; P less than 0.005) **Inflammatory lesions:** Benzoyl peroxide significantly reduced number of inflammatory lesions compared with vehicle (% reduction: 39% with benzoyl peroxide *v* 5% with vehicle; P less than 0.002) **Patient perception of improvement:** No data reported **Adverse effects:** More people taking benzoyl peroxide alone or in combination with clindamycin had peeling compared with people taking vehicle (21% with benzoyl peroxide *v* 22% with benzoyl peroxide plus clindamycin *v* 15% with vehicle; P value not reported)	
[20]	150 people with mild to moderate acne	Benzoyl peroxide 5% *v* gluconolactone 14% *v* vehicle for 12 weeks	**Total lesion count/severity:** Benzoyl peroxide significantly reduced total lesion count from baseline (P less than 0.01) **Non-inflammatory lesions:** Benzoyl peroxide significantly reduced number of non-inflammatory lesions from baseline (P less than 0.05) **Inflammatory lesions:** Benzoyl peroxide significantly reduced number of inflammatory lesions from baseline (P less than 0.02) **Patient perception of improvement:** No data reported **Adverse effects:** Benzoyl peroxide 5% significantly increased the proportion of people who had adverse effects, including dryness, scaling, burning, tingling, and redness, compared with vehicle (22/75 [29%] with benzoyl peroxide *v* 5/75 [7%] with vehicle; P = 0.05)	When assessing benefits, did not directly compare benzoyl peroxide and vehicle, but assessed within-group differences from baseline in each group
[21]	77 people with mild to moderate acne	Benzoyl peroxide 5% *v* isotretinoin *v* vehicle, for 12 weeks	**Total lesion count/severity:** Benzoyl peroxide significantly reduced severity scores compared with vehicle (Leeds score where 0 = no acne and 10 = severest acne: 0 with benzoyl peroxide *v* 1 with vehicle; P less than 0.05) **Non-inflammatory lesions:** Benzoyl peroxide significantly reduced number of non-inflammatory lesions compared with vehicle (mean % change –52% with benzoyl peroxide *v* +6% with vehicle; P = 0.01) **Inflammatory lesions:** Benzoyl peroxide significantly reduced number of inflammatory lesions compared with vehicle (mean % change –52% with benzoyl peroxide *v* +9 with vehicle; P = 0.01) **Patient perception of improvement:** No data reported **Adverse effects:** Benzoyl peroxide associated with erythema, dryness, soreness, and burning; 1 person taking benzoyl peroxide withdrew because of adverse effects	
[22]	59 people with mild to moderate acne	Benzoyl peroxide 20% *v* vehicle, for 12 weeks	**Total lesion count/severity:** Benzoyl peroxide significantly reduced total number of lesions after 12 weeks' treatment compared with vehicle (proportion of people with "good" [51–75% reduction] or "excellent" [76–100% reduction] response: 19/26 [73%] with benzoyl peroxide *v* 10/25 [40%] with vehicle; P less than 0.05) **Non-inflammatory lesions:** No data reported **Inflammatory lesions:** No data reported **Patient perception of improvement:** No data reported **Adverse effects:** 21/29 [72%] people using topical benzoyl peroxide and 17/30 [57%] people using placebo had redness and peeling (significance not reported)	

Ref, reference

TABLE 2 **RCTs comparing topical clindamycin versus placebo or vehicle.**

Ref	Number of people	Treatment, dose, duration	Results	Comment
[19]	393 people with mild to moderate acne	Clindamycin 1% *v* benzoyl peroxide 5% *v* benzoyl peroxide plus clindamycin *v* vehicle 4 times daily, for 11 weeks	**Total lesion count:** No data reported **Non-inflammatory lesions:** Clindamycin significantly reduced number of non-inflammatory lesions from baseline at 11 weeks compared with vehicle (mean % change: –9% with clindamycin *v* +11% with vehicle; P = 0.04) **Inflammatory lesions:** Clindamycin significantly reduced number of inflammatory lesions from baseline at 11 weeks compared with vehicle (mean % reduction: –35% with clindamycin *v* –5% with vehicle; P less than 0.001) **Patient perception of improvement:** No data reported **Adverse effects:** No significant difference in adverse effects (erythema, dryness, peeling, burning, or pruritus) between clindamycin and vehicle (reported as NS, CI not reported)	Pooled data from 1 single-centre and 1 multicentre trial
[23]	108 people with mild to moderate acne	Clindamycin phosphate 1% twice daily *v* oral tetracycline 500 mg twice daily *v* placebo, for 8 weeks	**Total lesion count:** No data reported **Non-inflammatory lesions:** No data reported **Inflammatory lesions:** Mean reduction in inflammatory lesion count from baseline with clindamycin 2.38; P = 0.0001. Mean inflammatory lesion count with placebo 6.24; P = NS, CI not reported **Patient perception of improvement:** Proportion of people whose acne had "markedly improved" or "improved" from baseline: 72% with clindamycin; P value not reported. Proportion of people whose acne had "markedly improved" or "improved" from baseline: 3% with placebo; P value not reported **Adverse effects:** 1 person using clindamycin, and 1 using placebo had diarrhoea	No direct comparison of topical clindamycin *v* placebo, as trial designed to compare topical clindamycin *v* oral tetracycline. Completer analysis in 87 people, no intention-to-treat analysis performed
[24]	135 people with moderate acne	Clindamycin phosphate 1% twice daily *v* placebo, for 12 weeks	**Total lesion count:** No data reported **Non-inflammatory lesions:** No data reported. **Inflammatory lesions:** Clindamycin significantly reduced papules at 12 weeks compared with placebo (% reduction: 49% with clindamycin *v* 24% with placebo; P = 0.05). Clindamycin significantly reduced pustules at 12 weeks compared with placebo (% reduction: 59% with clindamycin *v* 31% with placebo; P = 0.05) **Patient perception of improvement:** No data reported **Adverse effects:** Clindamycin was associated with burning. 1 person taking clindamycin and 1 taking placebo had diarrhoea	Unblinded
[25]	40 people with mild to moderate acne	Clindamycin phosphate 1% twice daily *v* vehicle, for 12 weeks	**Total lesion count:** No data reported **Non-inflammatory lesions:** No significant difference between clindamycin and vehicle in non-inflammatory lesions at 12 weeks (% reduction in open comedones: 38% with clindamycin *v* 32% with vehicle; P = NS) **Inflammatory lesions:** No significant difference between clindamycin and placebo in inflammatory lesions at 12 weeks (% reduction in papules: 22% with clindamycin *v* 19% with placebo; P = NS; % reduction in pustules: 12% with clindamycin *v* 22% with placebo; P = NS) **Patient perception of improvement:** No data reported **Adverse effects:** No data reported	Only 76% of people completed the trial, but intention-to-treat analysis performed
[26]	367 people with moderate to severe acne	Clindamycin phosphate 1% *v* oral tetracycline *v* placebo, for 8 weeks	**Total lesion count:** No data reported **Non-inflammatory lesions:** No data reported **Inflammatory lesions:** Clindamycin significantly reduced number of inflammatory lesions at 8 weeks compared with placebo (mean number of papules per person: 8.3 with clindamycin *v* 11.7 with placebo; P less than 0.05; mean number of pustules: 1.1 *v* 2.7; P less than 0.05) **Patient perception of improvement:** Clindamycin significantly increased the proportion of people who thought their acne was "markedly improved" or "improved": 88% with clindamycin *v* 57% with placebo; P less than 0.05 **Adverse effects:** 9 people taking clindamycin and 6 people taking placebo had diarrhoea	Completer analysis in 305/367 [83%] people who completed the trial

Ref	Number of people	Treatment, dose, duration	Results	Comment
[27]	413 people with moderate acne, multicentre	Clindamycin phosphate 1% twice daily *v* clindamycin hydrochloride 1% twice daily *v* vehicle, for 8 weeks	**Total lesion count:** No data reported **Non-inflammatory lesions:** No data reported **Inflammatory lesions:** Clindamycin phosphate or clindamycin hydrochloride significantly reduced number of inflammatory lesions at 8 weeks compared with vehicle (clindamycin phosphate, % reduction in papules: 56% with clindamycin *v* 42% with vehicle; P = 0.002; % reduction in pustules: 72% with clindamycin *v* 43% with vehicle; P = 0.029) **Patient perception of improvement:** Clindamycin significantly increased the proportion of people who rated acne "markedly improved" or "improved" compared with vehicle (77% with clindamycin phosphate *v* 77% with clindamycin hydrochloride *v* 56% with vehicle; reported as significant, P value not reported) **Adverse effects:** 12 people taking clindamycin and 2 people taking placebo had diarrhoea	Completer analysis in 358/413 [87%] people who completed the trial
[28]	46 people with moderate to severe acne	Clindamycin phosphate 1% twice daily *v* placebo, for 12 weeks	**Total lesion count:** No significant difference in mean lesion count: between clindamycin and placebo (0.2 with clindamycin *v* 0.6 with placebo; P = 0.34) **Non-inflammatory lesions:** No significant difference in the number of non-inflammatory lesions at 12 weeks between clindamycin and placebo (mean number of open comedones per person: 3.3 with clindamycin *v* 5.2 with placebo; P = 0.49; mean number of closed comedones per person: 3.4 *v* 5.1; P = 0.47) **Inflammatory lesions:** Clindamycin significantly reduced number of pustules at 12 weeks compared with placebo, but did not reduce papules (mean number of pustules per person: 1.5 with clindamycin *v* 3.1 with placebo; P = 0.02; mean number of papules per person at 12 weeks: 6.8 *v* 10.6; P = 0.16) **Patient perception of improvement:** No data reported **Adverse effects:** 3 people taking clindamycin and 5 taking placebo had diarrhoea. 1 person taking clindamycin had burning and 1 had eczema	

NS, not significant; Ref, reference

TABLE 3 **RCTs comparing topical erythromycin versus vehicle.**

Ref	Number of people	Treatment, dose, duration	Results	Comment
[32]	160 people with mild to moderate acne	Erythromycin 2% alone *v* isotretinoin 0.05% alone *v* isotretinoin plus erythromycin *v* placebo, for 12 weeks	**Overall severity:** Erythromycin significantly reduced total lesions from baseline at 12 weeks whereas placebo did not (mean % change in count per person: –25%, 95% CI –39.04% to –11.44% with erythromycin *v* –10.82%, 95% CI –24.29% to +2.65% with placebo). **Non-inflammatory lesions:** No significant difference in non-inflammatory lesions from baseline within the erythromycin or the placebo group at 12 weeks (mean % change: –17%, 95% CI –38.07% to +4.63% with erythromycin; –7%, 95% CI –28.31% to +14.16% with placebo). **Inflammatory lesions:** Erythromycin significantly reduced inflammatory lesions from baseline within the group at 12 weeks whereas placebo did not (mean % reduction in count per person: –28%, 95% CI –41.29% to –14.14% with erythromycin *v* –10%, 95% CI –24.51% to +5.36% with placebo) **Patient perception of improvement:** Similar proportion of people taking erythromycin compared with vehicle perceived that their acne had improved from baseline at 12 weeks (58% with erythromycin *v* 53% with vehicle; significance of difference not assessed) **Adverse effects:** No data reported	Did not compare erythromycin alone versus placebo directly: assessed changes from baseline within the erythromycin and the placebo groups
[33]	225 people with mild to moderate acne	Erythromycin 2% twice daily *v* vehicle, for 12 weeks	**Overall severity:** Reduction in Cook's severity score at 12 weeks: –40 with erythromycin *v* –22 with vehicle; P = NS, CI not reported **Non-inflammatory lesions:** No data reported **Inflammatory lesions:** Erythromycin significantly reduced inflammatory lesions at 12 weeks compared with vehicle (% reduction: –46% with erythromycin *v* –19% with vehicle; P = 0.01) **Patient perception of improvement:** No data reported **Adverse effects:** No significant difference in erythema or peeling between erythromycin and vehicle (reported as non-significant, CI not reported). No other adverse effects assessed	
[34]	187 people with mild to moderate acne	Erythromycin 2% twice daily *v* vehicle, for 8 weeks	**Overall severity:** No data reported **Non-inflammatory lesions:** Erythromycin significantly reduced open comedones compared with vehicle at 8 weeks (mean reduction in count per person: –7.5 with erythromycin *v* –4.6 with vehicle; P less than 0.01). No significant difference in closed comedones (mean reduction in count per person: –1.7 with erythromycin *v* –2.3 with vehicle; P = NS, CI not reported) **Inflammatory lesions:** Erythromycin significantly reduced papules from baseline (mean reduction in count: –6.2 with erythromycin *v* –4.3 with vehicle; P less than 0.01). No significant difference in pustules (mean reduction in count: –1.7 with erythromycin *v* –1.2 with vehicle; P = NS, CI not reported) **Patient perception of improvement:** No data reported **Adverse effects:** Most frequently reported adverse effects were mild burning and peeling; no significant difference between erythromycin and vehicle	
[35]	175 people with moderate to severe acne unresponsive to oral tetracycline, topical benzoyl peroxide, or topical tretinoin	Erythromycin 2% twice daily *v* vehicle, for 12 weeks	**Overall severity:** Proportion of people rated by physician as having “excellent” or “good” response: 62% with erythromycin *v* 27% with vehicle; P less than 0.001 **Non-inflammatory lesions:** No data reported **Inflammatory lesions:** Erythromycin significantly reduced total inflammatory lesion count at 12 weeks compared with vehicle (856 with erythromycin *v* 1338 with vehicle; P less than 0.01) **Patient perception of improvement:** No data reported **Adverse effects:** Fewer people taking erythromycin had 1 or more adverse effects, including redness, scaling, dryness, and pruritis, compared with people taking vehicle (17/90 [19%] with erythromycin *v* 21/85 [25%] with vehicle; CI not reported). 2 people taking erythromycin withdrew because of adverse effects compared with 4 taking vehicle	Completer analysis in 156 people; no intention-to-treat analysis. People excluded from analysis for poor compliance and failure to complete treatment. Physician rating scale included “excellent”, “good”, “partially improved”, “not improved”, and “worse”. Unclear how ratings were measured

Ref	Number of people	Treatment, dose, duration	Results	Comment
[36]	253 people with moderate to severe acne	Erythromycin 1.5% twice daily *v* vehicle, for 12 weeks	**Overall severity:** Erythromycin significantly reduced total lesion count at 12 weeks compared with vehicle (P = 0.01) **Non-inflammatory lesions:** No significant difference in open or closed comedones between erythromycin and vehicle (reported as NS, P value not reported) **Inflammatory lesions:** Erythromycin significantly reduced papules and pustules at 12 weeks compared with vehicle (P less than 0.025) **Patient perception of improvement:** No data reported **Adverse effects:** 26 people in each group had 1 or more adverse effects, including erythema, scaling, tenderness, and dryness	Absolute results presented graphically
[37]	26 people with moderate to severe acne	Erythromycin 1.5% twice daily *v* vehicle, for 12 weeks	**Overall severity:** Erythromycin significantly increased the proportion of people rated by physician as having "excellent" or "good" response compared with vehicle (92% with erythromycin *v* 20% with vehicle; P = 0.005) **Non-inflammatory lesions:** Reported that erythromycin had less effect on comedones; no further data reported **Inflammatory lesions:** Erythromycin significantly reduced the proportion of people who had more than 50% reduction in papules at 12 weeks (11/12 [32%] with erythromycin *v* 4/10 [40%] with vehicle; P = 0.01) **Patient perception of improvement:** No data reported **Adverse effects:** Reported that "no serious reactions to either formula were observed"	
[38]	28 people with moderate to severe acne	Erythromycin 1% twice daily *v* vehicle, for 4–8 weeks	**Overall severity:** No data reported **Non-inflammatory lesions:** No data reported **Inflammatory lesions:** In 21 people, erythromycin was more effective than vehicle in reducing inflammatory lesions at 8 weeks, in 4 people vehicle more effective, and in 3 no difference; P value not reported **Patient perception of improvement:** No data reported **Adverse effects:** No data reported	Split-face study
[39]	73 people with moderate to severe acne	Erythromycin 2% twice daily *v* vehicle, for 12 weeks	**Overall severity:** No data reported **Non-inflammatory lesions:** No data reported **Inflammatory lesions:** No significant difference in the proportion of people who had more than 50% reduction in inflammatory lesions at 12 weeks between erythromycin and vehicle (30% with erythromycin *v* 20% with vehicle; reported as NS, P value not reported) **Patient perception of improvement:** No data reported **Adverse effects:** No data reported	Split-face study

NS, not significant; Ref, reference

TABLE 4 **RCTs comparing topical tretinoin versus vehicle.**

Ref	Number of people	Treatment, dose, duration	Results	Comment
[40]	256 people with mild to moderate acne	Tretinoin 0.05% *v* tretinoin 0.02% *v* vehicle twice daily, for 8 weeks	**Total lesion count:** No data reported **Non-inflammatory lesions:** Tretinoin at either dose significantly reduced comedones at 7–8 weeks compared with vehicle (measured by total score: 89 with 0.05%, 94 with 0.02% *v* 131 with vehicle; P less than 0.01 for either dose *v* vehicle) **Inflammatory lesions:** Tretinoin 0.05% significantly reduced papules at 7–8 weeks compared with vehicle, no significant difference between tretinoin 0.02% and vehicle (61 with 0.05% tretinoin, 76 with 0.02% tretinoin *v* 83 with vehicle; P less than 0.05 for 0.05% tretinoin *v* vehicle; P = NS for 0.02% tretinoin, CI not reported) **Patient perception of improvement:** No data reported **Adverse effects:** Significantly increased erythema, peeling, or both at 1–3 weeks compared with vehicle (86% with tretinoin 0.05% *v* 81% with tretinoin 0.02% *v* 40% with vehicle; P less than 0.01 for either dose *v* vehicle)	Completer analysis only, no intention-to-treat analysis
[41]	257 people with moderate to severe acne	Tretinoin 0.05% *v* motretinide 0.1% *v* vehicle twice daily, for 8 weeks	**Total lesion count:** No data reported **Non-inflammatory lesions:** Tretinoin significantly reduced non-inflammatory lesions at 8 weeks (number of lesions: 89 with tretinoin *v* 131 with vehicle; P = 0.01) **Inflammatory lesions:** Tretinoin significantly reduced papules at 8 weeks (number of papules: 61 with tretinoin *v* 83 with vehicle; P = 0.05) **Patient perception of improvement:** No data reported **Adverse effects:** Tretinoin significantly increased proportion of people who had erythema and desquamation (76/84 [90%] with tretinoin *v* 16/84 [19%] with vehicle); burning (69/84 [82%] *v* 23/84 [27%]); and pruritis (62/84 [74%] *v* 26/84 [31%]) over 8 weeks. P less than 0.005 for all outcomes	
[42]	60 people with mild to moderate acne	Tretinoin 0.05% *v* tretinoin 0.025% *v* vehicle, for 12 weeks	**Total lesion count:** No data reported **Non-inflammatory lesions:** No data reported **Inflammatory lesions:** No data reported **Patient perception of improvement:** Patient perception of severity on a visual analogue scale (18 with tretinoin *v* 39 with vehicle; range of scale not specified) **Adverse effects:** People taking tretinoin 0.05% or 0.025% had erythema, soreness, and irritation	No results comparing groups directly reported; no assessment of significance in changes in outcomes from baseline within group
[43]	215 people with mild to moderate acne	Tretinoin 0.025% *v* tretinoin 0.025% plus polyolprepolymer-2 *v* vehicle once daily, for 12 weeks	**Total lesion count:** Tretinoin 0.025% significantly reduced total lesion count compared with vehicle (% reduction: 40% with tretinoin *v* 24% with vehicle; P less than 0.05) **Non-inflammatory lesions:** Tretinoin 0.025% alone significantly reduced non-inflammatory lesions at 12 weeks compared with vehicle (% reduction: 39% with tretinoin *v* 19% with vehicle; P less than 0.05) **Inflammatory lesions:** Tretinoin 0.025% alone significantly reduced papules at 12 weeks compared with vehicle (% reduction: 42% with tretinoin *v* 19% with vehicle; P less than 0.05) **Patient perception of improvement:** No data reported **Adverse effects:** Tretinoin 0.025% alone significantly increased proportion of people who had erythema (20% with tretinoin *v* 9% with vehicle); peeling (21% *v* 3%); and dryness (21% *v* 8%). P less than 0.005 for all outcomes	Absolute results estimated from graph
[44]	271 people with mild to moderate acne	Tretinoin 0.025% *v* tretinoin 0.025% plus polyolprepolymer-2 *v* vehicle once daily, for 12 weeks	**Total lesion count:** Tretinoin 0.025% significantly reduced total lesion count compared with vehicle (% reduction: 39% with tretinoin *v* 28% with vehicle; P less than 0.05) **Non-inflammatory lesions:** Tretinoin 0.025% alone significantly reduced non-inflammatory lesions at 12 weeks compared with vehicle (% reduction: 49% with tretinoin *v* 31% with vehicle; P less than 0.05). **Inflammatory lesions:** Tretinoin 0.025% alone significantly reduced papules at 12 weeks compared with vehicle (% reduction: 49% with tretinoin *v* 28% with vehicle; P less than 0.05) **Patient perception of improvement:** No data reported **Adverse effects:** Tretinoin 0.025% alone significantly increased proportion of people who had erythema: 8% with tretinoin *v* 3% with vehicle; burning: 8% *v* 3%; itching: 15% *v* 6%; and tightness: 22% *v* 15%. P less than 0.005 for all outcomes	Absolute results estimated from graph

Ref	Number of people	Treatment, dose, duration	Results	Comment

Ref, reference.

TABLE 5 **RCTs comparing oral tetracycline versus placebo.**

Ref	Number of people	Treatment, dose, duration	Results	Comment
[23]	108 people with mild to moderate acne	Oral tetracycline 500 mg twice daily *v* clindamycin phosphate 1% twice daily *v* placebo, for 8 weeks	**Severity:** No data reported **Inflammatory lesions:** Within-group comparison found that oral tetracycline significantly reduced inflammatory lesions from baseline, whereas placebo did not (mean inflammatory lesion count: 2.66 with tetracycline; P = 0.0001; mean inflammatory lesion count with placebo: 6.24; reported as NS, CI not reported) **Patient perception of improvement:** "Markedly improved" or "improved" from baseline: 72% with tetracycline *v* 3% with placebo; P values not reported **Adverse effects:** 1 person taking tetracycline and 1 taking placebo had diarrhoea	No direct comparison of tetracycline *v* placebo, as trial designed to compare oral tetracycline *v* topical clindamycin. Completer analysis in 87 people, no intention-to-treat analysis performed
[26]	367 people with moderate to severe acne	Clindamycin phosphate 1% *v* oral tetracycline *v* placebo, for 8 weeks	**Severity:** Tetracycline significantly increased the proportion for whom physician assessment of treatment was "excellent" or "good" compared with placebo (64% with tetracycline *v* 46% with placebo; P less than 0.05) **Inflammatory lesions:** No data reported **Patient perception of improvement:** Tetracycline significantly increased the proportion of people who thought their acne was "markedly improved" or "improved" compared with placebo (84% with tetracycline *v* 57% with placebo; P less than 0.05) **Adverse effects:** 9 people taking tetracycline *v* 6 people taking placebo had diarrhoea. 4 people taking tetracycline had epigastric pain	Completer analysis in 305/367 [83%] people who completed the trial. Unclear how assessments by physician or patient were defined
[56]	75 people with moderate acne	Oral tetracycline 250 mg twice daily plus topical placebo *v* topical tetracycline 0.5% plus oral placebo *v* topical plus oral placebo, for 13 weeks	**Severity:** Tetracycline significantly reduced severity compared with placebo at 6 weeks (mean reduction in acne severity grade measured or a scale from 0 [least severe]–8 [most severe]: 1.14 with tetracycline *v* 0.43 with placebo; P less than 0.05) and 13 weeks (mean reduction in acne severity grade: 1.91 *v* 0.62; P less than 0.05) **Inflammatory lesions:** No data reported **Patient perception of improvement:** No data reported **Adverse effects:** No data reported	Observer blinded only. Results should be interpreted with caution because intention-to-treat analysis not performed, and 11/75 [15%] people withdrew from the trial
[57]	60 male adolescents with mild to moderate acne	Oral tetracycline plus topical vehicle *v* oral placebo plus topical tetracycline *v* oral placebo plus topical vehicle, for 8 weeks	**Severity:** Improvement from baseline of 1 or more on a scale from 0 to 8: 12/18 [67%] with oral tetracycline *v* 14/19 [74%] with topical tetracycline *v* 6/17 [35%] with placebo **Inflammatory lesions:** No data reported **Patient perception of improvement:** No data reported **Adverse effects:** No data reported	Did not assess the significance of the difference among groups
[58]	135 people aged 18–25 years with mild to moderate acne, Cook's grades 0 to 8)	Topical tetracycline 0.22% plus oral placebo *v* oral tetracycline plus topical vehicle *v* topical vehicle plus oral placebo, for 12 weeks	**Severity:** Tetracycline significantly reduced acne severity at 7, 10, and 12 weeks compared with placebo (P less than 0.05) **Inflammatory lesions:** No data reported **Patient perception of improvement:** No data reported **Adverse effects:** No data reported	Absolute results presented graphically
[79]	51 people (severity of acne unclear)	Tetracycline 250 mg twice daily *v* placebo, for 12 weeks	**Severity:** Tetracycline significantly reduced severity compared with placebo at 12 weeks (change in Pillsbury modified score –2 with tetracycline *v* 0 with placebo; P = 0.001). Tetracycline significantly increased the proportion of people assessed as "improved" at 12 weeks (23/24 [96%] with tetracycline *v* 15/27 [56%] with placebo; P = 0.01) **Inflammatory lesions:** No data reported **Patient perception of improvement:** Reported in discussion section of article that patient perception of improvement "close" to clinical assessment; no further data provided **Adverse effects:** No data reported	Pillsbury modified score: assigns 1 point for a change equivalent to half a grade. Score of +1 to +4 = "improved", 0 = "no change" and –1 to –4 = "worse"

Ref	Number of people	Treatment, dose, duration	Results	Comment
[80]	68 people with mild to moderate acne	Tetracycline plus placebo *v* ibuprofen plus placebo *v* tetracycline plus ibuprofen *v* placebo for 8 weeks	**Severity:** No data reported **Inflammatory lesions:** No significant difference in inflammatory lesions between tetracycline and placebo (% reduction: 26% with tetracycline *v* 16% with placebo; P = NS, CI not reported) **Patient perception of improvement:** No data reported **Adverse effects:** No data reported	May have lacked power to detect a clinically important difference among groups

NS, not significant; Ref, reference

TABLE **GRADE evaluation of interventions for acne vulgaris**

Important outcomes	**Symptom severity, patient perception of improvement, psychological distress, quality of life, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of topical treatments in people with acne vulgaris?									
4 (875) [18] [19] [21] [22] [20]	Symptom severity	Benzoyl peroxide *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for assessing different outcomes and for no direct comparison between groups in one RCT
7 (1354) [19] [23] [24] [25] [26] [27] [28]	Symptom severity	Clindamycin *v* placebo/vehicle	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and methodological flaws (no intention-to-treat analysis, or poor follow-up)
3 (750) [23] [27] [28]	Patient perception of improvement	Clindamycin *v* placebo/vehicle	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and methodological flaws (no intention-to-treat analysis, poor follow-up)
8 (1104) [32] [33] [34] [35] [36] [37] [38] [39]	Symptom severity	Erythromycin *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for assessing different outcomes
1 (160) [32]	Patient perception of improvement	Erythromycin *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between groups
4 (999) [40] [41] [43] [44]	Symptom severity	Tretinoin *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and no intention-to-treat analysis
1 (60) [42]	Patient perception of improvement	Tretinoin *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data, and incomplete reporting of results. Directness point deducted for no direct comparison between groups
2 (890) [48] [46] [47]	Symptom severity	Adapalene *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (132) [49] [50]	Symptom severity	Azelaic acid *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about duration and severity of acne in one RCT
2 (222) [52] [53]	Symptom severity	Erythromycin plus zinc *v* placebo	4	0	0	–2	0	Low	Directness points deducted for uncertainty about severity of acne in one RCT and for assessing different outcomes
4 (632) [21] [54] [55] [32]	Symptom severity	Isotretinoin *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct comparison between groups
1 (160) [32]	Patient perception of improvement	Isotretinoin *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between groups
4 (344) [56] [79] [57] [58] [59]	Symptom severity	Tetracycline *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results and for methodological flaws (no intention-to-treat analysis, uncertainty about method of analysis of results)
1 (55) [59]	Patient perception of improvement	Tetracycline *v* placebo	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
What are the effects of oral treatments in people with acne vulgaris?									

Important outcomes	Symptom severity, patient perception of improvement, psychological distress, quality of life, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (56) [61]	Symptom severity	Erythromycin *v* oral doxycycline	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (300) [62] [63] [64]	Symptom severity	Erythromycin *v* oral tetracycline	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct comparison between groups in one RCT
1 (200) [64]	Patient perception of improvement	Erythromycin *v* oral tetracycline	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (62) [66]	Symptom severity	Doxycycline *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and poor follow-up. Directness point deducted for no direct comparison between groups
1 (28) [67]	Symptom severity	Doxycline *v* oxytetracycline	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (967) [70] [71]	Symptom severity	Minocycline *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct comparison between groups
1 (43) [70]	Patient perception of improvement	Minocycline *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, poor follow-up, and methodological flaws. Directness point deducted for no direct comparison between groups
5 (419) [70]	Symptom severity	Minocycline *v* oral doxycycline	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, and methodological flaws. Directness points deducted for assessing different outcomes and comparing different doses
1 (144) [70]	Symptom severity	Minocycline *v* oral lymecycline	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (144) [70]	Patient perception of improvement	Minocycline *v* oral lymecycline	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (498) [70] [72]	Symptom severity	Minocycline *v* oral oxytetracycline	4	–2	–1	–2	0	Very low	Quality points deducted for no intention-to-treat analysis, and open-label RCT. Consistency point deducted for conflicting results. Directness points deducted for uncertainty about clinical relevance of results, and differences in symptom severity between groups
6 (693) [70]	Symptom severity	Minocycline *v* oral tetracycline	4	–2	0	–1	0	Very low	Quality points deducted for not reporting results. Directness point deducted for assessing different outcomes
7 (621) [26] [56] [58] [79] [57] [80] [23]	Symptom severity	Tetracycline *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and methodological weaknesses (no intention-to-treat analysis and blinding flaws). Directness point deducted for no direct comparison between groups
1 (305) [26]	Patient perception of improvement	Tetracycline *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about definitions of assessments
1 (33) [82]	Symptom severity	Oral isotretinoin *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	Symptom severity, patient perception of improvement, psychological distress, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (29) [81]	Symptom severity	Oral isotretinoin *v* oral tetracycline	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio