Minocycline for acne vulgaris: Efficacy and safety

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Minocycline for acne vulgaris: efficacy and safety

Review information

Review number: #05

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What's new

Date	Event	Description
6 July 2012	Updated	New search for studies
6 July 2012	New citation: conclusions not changed	A substantial amount of new information has been added in the form of 12 newly-included studies.

History

Date	Event	Description
30 September 2009	Amended	Converted to new review format.
1 November 2006	New citation: conclusions changed	Substantive amendment
18 November 2002	Amended	New studies found and included or excluded.
1 June 2000	Amended	Minor update.

Abstract

Background

Minocycline is an oral antibiotic used for acne vulgaris. Its use has lessened due to safety concerns (including potentially irreversible pigmentation), a relatively high cost, and no evidence of any greater benefit than other acne treatments. A modified-release version of minocycline is being promoted as having fewer side-effects.

Objectives

To assess new evidence on the effects of minocycline for acne vulgaris.

Search methods

Searches were updated in the following databases to November 2011: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library*, MEDLINE (from 1946), EMBASE (from 1974), and LILACS (from 1982). We also searched trials registers and checked reference lists for further references to relevant randomised controlled trials (RCTs).

The Cochrane Skin Group's Trials Search Co-ordinator undertook searches exploring minocycline's adverse effects in EMBASE and MEDLINE in February 2012.

Selection criteria

We selected randomised controlled trials (RCTs) comparing minocycline, at any dose, to an active or a placebo control, in participants with inflammatory acne vulgaris. For adverse effects, we selected additional studies that reported the number of adverse effects and the number of participants treated.

Data collection and analysis

Outcome measures used in the trials included lesion counts, acne grades/severity scores, doctors' and participants' global assessments, adverse effects, and dropout rates. Two authors independently assessed the quality of each study. Effect sizes were calculated, and meta-analyses were undertaken where possible.

Sixteen studies met the inclusion criteria for the review of adverse effects.

Main results

We included 12 new RCTs for this update, giving a total of 39 RCTs (6013 participants). These additional 12 RCTs have not changed the original conclusions about the clinical efficacy of minocycline.

The identified RCTs were generally small and poor quality. Meta-analysis was rarely possible because of the lack of data and different outcome measures and trial durations. Although minocycline was shown to be an effective treatment for moderate to moderately-severe acne vulgaris, there was no evidence that it is better than any of the other commonly-used acne treatments. One company-sponsored RCT found minocycline to be less effective than combination treatment with topical erythromycin and zinc. No trials have been conducted using minocycline in those participants whose acne is resistant to other therapies. Also, there is no evidence to guide what dose should be used.

The adverse effects studies must be interpreted with caution. The evidence suggests that minocycline is associated with more severe adverse effects than doxycycline. Minocycline, but not other tetracyclines, is associated with lupus erythematosus, but the risk is small: 8.8 cases per 100,000 person-years. The risk of autoimmune reactions increases with duration of use. The evidence does not support the conclusion that the more expensive extended-release preparation is safer than standard minocycline preparations.

Authors' conclusions

Minocycline is an effective treatment for moderate to moderately-severe inflammatory acne vulgaris, but there is still no evidence that it is superior to other commonly-used therapies. This review found no reliable evidence to justify the reinstatement of its first-line use, even though the price-differential is less than it was 10 years ago. Concerns remain about its safety compared to other tetracyclines.

Plain language summary

Minocycline for acne vulgaris: efficacy and safety

Acne is the most common skin disease of adolescence, and in most cases it clears spontaneously. However, in some people it persists in to adulthood. There are many different treatment options, but there is little good evidence to inform doctors and individuals about which to choose.

Minocycline was the most prescribed antibiotic used to treat acne because it was thought to be better than other options, despite the original version of this review finding no reliable evidence that it was any better than other treatments. Over recent years it has been used less, which was due to serious concerns about its safety, including skin pigmentation, which in some cases is irreversible. It was also more expensive than other treatments.

Since the first version of this review, minocycline's cost has fallen. In the UK, the daily cost of generic minocycline is now one third the cost of tetracycline. This update was undertaken to identify whether there was any new evidence that might change the conclusions of the original review or provide information on risks associated with minocycline therapy. Twelve new RCTs were identified, making a total of 39 RCTs (6013 participants).

In summary, there is no evidence to support the first-line use of minocycline in the treatment of acne. All of the trials showed

that, on average, people treated with minocycline experienced an improvement in their acne. However, no study conclusively showed any important clinical difference between minocycline or other commonly-used therapies. The analysis found that minocycline may act more quickly than oxytetracycline or tetracycline, but there is no overall difference in the end. There is no evidence that it is more effective in acne that is resistant to other therapies, or that the effects last longer. Although it is often claimed that the more expensive once-daily slow-release preparation is a more attractive option to teenagers with acne, the evidence in this review does not show it to be any better or safer compared to other oral antibiotics that have to be taken more frequently.

Despite a thorough search for evidence, it is still not known which of the tetracyclines are the safest to take overall as they are all associated with side-effects. The only conclusion that we could make was that people treated with minocycline for acne are at a significantly greater risk of developing an autoimmune (lupus-like) syndrome than those given tetracycline or no treatment.

Background

Please see the Glossary in Table 1 for an explanation of terms used in this review.

Description of the condition

Acne is the most common skin disease of adolescence, and few teenagers escape the experience (Williams 2012). The severity of acne varies considerably, and in some individuals, acne persists well beyond the teens for reasons that are not yet clear (Goulden 1997). Acne usually begins before or during puberty when the output of sebum (grease) by tiny hair follicles on the face and upper trunk increases substantially (Rothman 1993). The production of sebum is controlled by male hormones (androgens) in both sexes. Spots form in follicles that respond abnormally to the hormones producing sebum. At the same time that sebum production increases, some of the openings through which the sebum flows (pores) become blocked by horny impactions made up of dead skin cells. The sebum acts as a nutrient for a resident skin bacterium called *Propionibacterium acnes (P. acnes)*, which colonises both healthy and diseased follicles. The role of *P. acnes* in the pathogenesis of acne has never been formally proven, and there is some doubt that it has any role to play (Shaheen 2011).

In the absence of effective treatment, acne persists for an average of 8 to 12 years in most sufferers (Cunliffe 1989; Cunliffe 1996), before it resolves spontaneously, usually but not always, by the early 20s.

Description of the intervention

Conventional treatments act by interfering with one or more of the factors (described above) that cause spots to form. Thus, drug treatments that reduce sebum production or the blockage of the pores, inhibit the growth of the acne bacillus, or both, are commonly used (Leyden 1997). Alternative approaches, such as dietary manipulation, relaxation therapy, homeopathy, Chinese herbs, and counselling, have been tried in acne management, especially in those people who do not want to use conventional methods for extended periods. Most available treatments, such as antibiotics, antiandrogens (including the combined oral contraceptive), and agents that unblock pores, only stop spots forming whilst the drug is being used, and therefore must be used extensively and continuously. The only potential cure for acne is oral isotretinoin (Roaccutane™), which reduces sebum production permanently (Saurat 1997). However, oral isotretinoin is a teratogen (a drug that, like thalidomide, may cause abnormalities in unborn babies) and causes significant side-effects; therefore, prescribing is limited to individuals whose acne is severe, persistent, or unresponsive to alternative medications. It is also recommended in people who scar easily as well as those who are emotionally distressed (Ortonne 1997). Thus, oral and topical antibiotics continue to be widely prescribed.

Minocycline is an orally-taken antibiotic that belongs to a class of drugs known as the tetracyclines. These can be subdivided into two classes: the original or 'first-generation' tetracyclines (oxytetracycline and tetracycline) and the 'second-generation' tetracyclines (such as minocycline, doxycycline, and lymecycline), which were chemically adapted to provide additional benefits. Historically, the preferential use of minocycline in the treatment of acne arose because of several perceived advantages over the other tetracyclines (that were fostered by a very successful marketing strategy).

One of the well-publicised benefits of minocycline was its convenience - because of its extended half-life, it only needs to be taken orally once-daily, and absorption is not affected by food. This is in contrast to tetracycline and oxytetracycline, which need to be taken on an empty stomach up to four times a day. It is also widely perceived by clinicians to have a faster onset of action than tetracycline or oxytetracycline and to be beneficial in acne that does not respond to other therapy (Knaggs 1993). In addition, although the exact relationship between bacterial levels and acne severity has not been clearly defined, in vivo studies have shown that minocycline produces a greater reduction of skin *P. acnes* levels compared to tetracycline (Eady 1990a), and there is a lower level of bacterial resistance to it (Eady 1993). The effects of minocycline are also commonly believed to persist post-treatment because of its high lipophilicity (fat solubility) and resultant distribution within the body (Chopra 1992; Leyden 1982).

Many of the pharmacological advantages of minocycline over the first-generation tetracyclines (oxytetracycline and tetracycline) have been ascribed to its increased lipid solubility (Colaizzi 1969). A greater per cent of the drug is absorbed from the intestinal tract, and the serum half-life is extended by several hours (Agruh 2006). The sustained blood levels are thought to translate biologically into higher skin concentrations and enhanced sebum penetration (Luderschmidt 1985; Macdonald 1973), although this view has been challenged (Aubin 1989). The absorption profile and steady state concentration also varies significantly between individuals, which cannot be explained by participant size and weight (Leyden 1985). There is considerable variation and overlap in serum concentrations that are achieved following doses of 100 mg or 200 mg per day (Eady 1993; Gardner 1997). The observation that the absorption profile of minocycline is minimally affected by the stomach contents (Leyden 1985) has been disputed by a later study, which showed that the presence of food in the

stomach reduced minocycline absorption between 2% and 51% (Meyer 1996).

As a result of the enhanced absorption of minocycline, lower doses are required and less of the active drug remains in the gastro-intestinal tract, minimising the disturbances to the resident microflora that often result in gastro-intestinal upset (Fanning 1977). However, minocycline and other second-generation tetracyclines exhibit an increased spectrum and incidence of adverse effects, which has been linked to their accumulation in fatty tissue and to their longer half-life (Ruef 1996).

The once-daily dosage advantage of minocycline is not unique; lymecycline and doxycycline are typically prescribed as a single-daily dose. In recent years, lymecycline has gained in popularity following the publication of a series of manufacturer-sponsored trials attesting to its efficacy in acne.

Initially, attention focused on the vestibular side-effects of minocycline (Gump 1977; Williams 1974). The vestibular system is in the inner ear and contributes to balance and the sense of spatial orientation. Diseases of the vestibular system usually induce vertigo and instability, and they are often accompanied by nausea. Prior to 1974, reports of these side-effects were rare, but that year saw a marked increase from less than 10% to over 70% of individuals in the U.S. who were treated. A similar increase was not evident in other countries (Allen 1976). With widespread and continued use, other side-effects have become apparent, leading to periodic debate over the safety of minocycline use for acne (Basler 1979; Davies 1989; Wright 1988). All tetracyclines bind to calcified tissues and are deposited and persist where normal bone forms. Minocycline causes pigmentation in a variety of tissues including skin, thyroid, nails, sclera, teeth, conjunctiva, tongue, and bone. The pigmentation can be irreversible.

Three patterns of serious reactions to minocycline have been described:

- early onset dose-related toxicity reactions resulting in single organ dysfunction;
- hypersensitivity reactions (presenting as pneumonitis, eosinophilia, nephritis, and serum-sickness-like syndrome); and
- autoimmune disorders (systemic lupus erythematosus-like syndrome, autoimmune hepatitis, and polyarteritis nodosa).

Safety concerns increased markedly following the publication of an article in the BMJ that highlighted the risk of potentially fatal liver failure with two documented deaths (Gough 1996). Further reports followed (Beneton 1997; Crosson 1997; Knowles 1996; MacNeil 1997; Shapiro 1997), and consequently, the level of minocycline prescribing fell by 38% in the UK (Ferguson 1998; Walsh 2012). The ensuing controversy over the safety of minocycline provoked several articles, with differing opinions amongst dermatologists as to the relative risks and benefits of minocycline, tetracycline or oxytetracycline for the treatment of acne (Beneton 1997; Cunliffe 1996; Ferner 1996; Fessler 1996; Seukeran 1997).

In 2010 the U.S. Food and Drug Administration (FDA) approved an extended-release (ER) formulation of minocycline (Solodyn® by Medicis pharmaceutical Corporation) for once-daily treatment of non-nodular moderate to severe acne at a dose of 1 mg/kg. The packaging insert states that a 135 mg dose has a longer T max (time to maximum dose in the blood) (3.5 to 4 hours versus (vs) 2.25 to 3 hours), a lower C max (maximum blood concentration) (2.63 mcg/ml vs 2.92 mcg/ml), and a smaller AUC (area under the curve, which represents how much of the drug is in the body over time) (33.32 vs 46.35 mcg/hr/ml). It is claimed that the extended-release formulation has reduced side-effects, particularly vertigo. Three included studies tested this formulation (Fleisch 2006a (MP010404); Fleisch 2006b (MP010405); Stewart 2006 (MP010401)).

As well as considering the relative risks and benefits of interventions, unfortunately, in today's climate of rising healthcare expenditure, the comparative cost-benefit must be considered. Since the original publication of the review, the relative costs of antibiotics have changed dramatically. Minocycline is no longer the most expensive (Table 2).

How the intervention might work

The fact that acne responds to antibiotics is one of the strongest pieces of evidence that acne is a bacterial disease caused by the bacterium *P.acnes*. However, all of the antibiotics used to treat acne, including minocycline, also exhibit multiple anti-inflammatory effects. For example, the tetracyclines as a group are matrix metalloproteinase inhibitors, and this action may contribute to therapeutic efficacy in acne by limiting proteolytic tissue damage (Soory 2008). Hence, the relative contributions of antibacterial activity and anti-inflammatory activity to clinical efficacy of the tetracyclines, including minocycline, is not known.

Why it is important to do this review

Prescribing of minocycline for acne has fallen dramatically in the last decade since the publication of the original review (Walsh 2012). However, its use is potentially increasing again due to the recent licensing in the United States of a extended-release version (Solodyn®). There appears to have been a non-evidence based switch back to first-generation tetracyclines (such as oxytetracycline or tetracycline) or to the second-generation tetracycline, lymecycline. The main reason for updating this review was to examine new data on the relative efficacy of the tetracyclines in acne and, especially, any head-to-head comparisons of minocycline with lymecycline. Whilst the emphasis was on clinical efficacy, we also sought to examine new safety data, especially any that shed light on the relative risks of the tetracyclines when used chronically, as in acne management.

Objectives

The primary aim of updating this review was to determine whether evidence from newer studies was persuasive enough to justify amending our original conclusions about the efficacy or safety of minocycline for acne, or both. Specifically the objectives were as follows:

1. To identify any new RCTs comparing the efficacy of minocycline against placebo and other drug treatments for acne (both oral and topical) with the aim of undertaking meta-analysis.

2. To examine any new safety data on the incidence of adverse effects associated with minocycline therapy, and to determine whether the risk increases with dose or duration of therapy.

Methods

Criteria for considering studies for this review

Types of studies

All prospective randomised controlled trials (RCTs) in which minocycline was compared either to placebo or to another active therapy in participants with acne vulgaris were eligible for inclusion, if at least one generally-accepted outcome measure was used. We did not exclude trials on the basis of language, and we included open trials.

It is recognised that rare adverse drug reactions (ADRs) are unlikely to occur in clinical trials involving relatively-small numbers of participants with short follow-up periods; therefore, estimates of the frequency of such events cannot be obtained by pooling data from several small trials. In addition, spontaneous report systems and case reports are not reliable sources of evidence, as the actual number of events that individuals experience is uncertain because of selective reporting and the fact that the number of participants who received the therapy overall is not known. Therefore, information on the incidence of the less common and more severe ADRs associated with minocycline was sought from systematic reviews, cohort studies, or case-control studies that provided a clear indication on the numerator (i.e. the number of adverse effects) and the denominator (the number of participants treated).

Types of participants

Participants with a diagnosis of acne vulgaris on the face, upper trunk, or both. We accepted studies that used the diagnosis of papulopustular, inflammatory, juvenile, or polymorphic acne. Restrictions were not made on age, gender, or acne severity. We included trials that recruited only participants with nodular acne, but they were considered separately.

Types of interventions

Studies that examined minocycline at any dose, compared either to placebo or another active therapy (topical or oral). We included studies that permitted the use of concomitant topical or oral antiacne medications if both treatment groups were treated equivalently, and the results of the study were interpreted accordingly.

Types of outcome measures

In accordance with the methods used in the original version of the review, this update did not select primary and secondary outcome measures. This is because there is no evidence on which to differentiate the reliability and validity of measures. The outcome measures of interest were those that estimated clinical efficacy, participant acceptability, or both, in a defined way. There are many different methods used to assess clinical efficacy, and there is no evidence at present on their relative validity, reliability, or responsiveness. Therefore, we included lesion counts (total, inflamed, and non-inflamed, separately), acne severity scores, physicians' global evaluation, and participants' self-assessment. The abbreviations used throughout this review are non-inflamed lesion (NIL), inflamed lesion (IL), and total lesion (TL).

Data on the overall incidence of ADRs, the incidence of gastro-intestinal (GI) disturbances, and the incidence of ADRs necessitating withdrawal of therapy were analysed for each study to assess the relative safety of each intervention. We judged the acceptability of each therapy either directly or through evidence of compliance and overall dropout rates. We excluded studies that used only surrogate markers of efficacy (such as numbers of cutaneous propionibacteria).

Search methods for identification of studies

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

Electronic searches

For this update, we revised the search strategies for the databases below and searched up to 8th November 2011:

- the Cochrane Skin Group Specialised Register using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* using the strategy in Appendix 2;
- MEDLINE (from 1946) using the strategy in Appendix 3;
- EMBASE (from 1974) using the search strategy in Appendix 4; and
- LILACS (Latin American and Caribbean Health Science Information Database, from 1982) using the search strategy in Appendix 5.

Trials registers

We searched the following trials registers, using the terms 'minocycline' and 'acne', on 16th April 2012.

- The metaRegister of Controlled Trials (www.controlled-trials.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The Ongoing Skin Trials Register on (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

Adverse effects

For this update, we revised the adverse effects search strategy for MEDLINE and developed a new strategy for EMBASE, in order to make our search more comprehensive. We ran our searches up to 9th February 2012.

- EMBASE (from 1974) using the strategy in Appendix 6.
- MEDLINE (from 1946) using the strategy in Appendix 7.

Reference lists

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

Correspondence

For the original review, a list of the identified RCTs was sent to the first author of each study and 42 acne experts to enquire about their knowledge of any further published or unpublished trials. This list was also sent to Wyeth-Lederle, the original developers of minocycline; and Medicis, who market minocycline in the United States. We also contacted the drug information departments of 16 pharmaceutical companies who manufactured other acne therapies.

For the 2012 update, we contacted 15 companies and authors for data that had not been included in the published article.

Data collection and analysis

Selection of studies

Once a study had been identified, we recorded the citation and located a copy of the report. We translated studies written in languages other than English if it could not be ascertained that it was randomised or controlled from the initial inspection. Two reviewers (SEG and EAE for the original; SEG and CB for the update) then independently assessed each study to see whether it met the inclusion criteria for the review. We resolved any discrepancies, other than those of simple error, by discussion. Where resolving disagreement by discussion was not possible, we added the article to those awaiting assessment and contacted the authors of the study for clarification. We considered duplicate publications in tandem.

Data extraction and management

We designed and piloted data extraction forms on a sample of five trials to detect any confusing or incomplete coding instructions. After we made revisions, we re-piloted the resulting forms. The team performed a double abstraction process, with EAE and SEG (SEG and CB for the update) independently extracting data. We resolved disagreements other than those of simple error by discussion or contacted the authors of the studies.

We extracted from each study the following information on key variables characterising participants, interventions, and outcomes, entering it into the tables of included studies:

- study information - author, publication status (full report/abstract/unpublished data, publication date, sponsorship, setting, dual publication);
- key variables characterising the study - overall design, trial type (parallel or cross-over), number of participants allocated to each treatment group, study duration, participant/provider and outcome assessor blinding, number and reason for dropouts, method of analysis;
- key variables characterising the intervention - dose, duration, use of concomitant therapy, skin hygiene, previous treatment withdrawal (oral and topical), control for ultraviolet light exposure, instructions to the participant, whether the dose was taken on an empty stomach, evidence of compliance monitoring; and
- key variables characterising the participants - number of participants enrolled, recruitment method, overall mean age, initial acne severity, comparability of study groups at entry, number at final assessment, percentage of participants not accounted for, and inclusion and exclusion criteria.
- outcome data - For continuous outcome measures, such as lesion count or grade, we extracted raw data on means and dispersion. Where categorical outcomes had been used, we recorded the number of participants in each group and the denominator.
- adverse effects - We sought data on the number and type and how the information was obtained. In some cases, information was only available on the number of events, so no denominator could be determined; therefore, we considered this information separately.
- other information - We examined publication bias by comparing the outcomes of published and unpublished trials. We assumed expectation bias in all open trials and in those in which the principal investigators were responsible for the collection of subjective data.
- We collected 'Risk of bias' information for all studies for the 2012 update.

Assessment of risk of bias in included studies

We assessed each study for specific methodological and substantive components that may have influenced the validity of the results. Methodological components relate to the overall trial design and execution, whilst substantive components are specific to the topic under consideration (Glass 1981). We used the following criteria:

(a) methodological components (The Standards of Reporting Trials Group 1994), including whether an adequate sample size enrolled, whether the correct randomisation protocol followed, whether allocation was concealed, whether there was baseline comparability of the groups, whether the reliability and validity of outcome measures were examined, whether the withdrawals (number and reason) were clearly stated, whether all participants were accounted for, and whether the appropriate method of analysis was used; and

(b) substantive components (Eady 1990b), including whether there was adequate study duration, whether the acne severity at inclusion was clearly stated, whether there were explicit and appropriate inclusion/exclusion criteria, whether there was

adequate withdrawal of the previous therapy (four weeks oral and two weeks topical), whether the use of concomitant medication was prohibited, whether there was monitoring of participant compliance, whether the tetracycline was taken on an empty stomach, whether clear instructions were given to participants, whether there was standardisation of the skin hygiene routine, whether there was control of exposure to UV light, whether there was a uniform site of evaluation, whether the number and timing of assessments were standardised, and whether there was evaluation of inter-assessor variability.

Two reviewers (EAE and SEG for the original; SEG and CB for the update) independently assessed the trials, resolving disagreements by discussion. We did not exclude open and single-blind studies from the review, but we took the degree of blinding and the resultant potential for bias into consideration in the interpretation of the results.

Measures of treatment effect

In this review, our analyses attempted to include all people who had been randomised to minocycline or control treatments (an intention-to-treat analysis).

Where continuous data, such as lesion counts or grades from baseline, were used, we extracted the mean and standard error/deviation of the change from baseline to each assessment and calculated the mean difference. In most cases, it was not possible to extract these data directly from the trial report or obtain them from the authors/trial sponsors. If the calculated P value or T statistic was given, we used it to estimate the effect size; otherwise, we used the authors' report of significance.

If the authors of the study had designated a cut-off point for determination of clinical effectiveness (e.g. a 40% reduction in inflamed lesion counts, or attainment of grade 2 on a grading scale), we used this to calculate the risk ratio (RR). Similarly, we dichotomised the results of the participant and doctor evaluations where necessary (e.g. into either 'improved' or 'not improved') and calculated RRs. The RR compares the risk of the event in people receiving minocycline versus people who are receiving an alternative treatment.

- A RR of 1 means there is no difference in risk between the 2 groups.
- A RR of < 1 means the event is less likely to occur in the experimental group than in the control group.
- A RR of > 1 means the event is more likely to occur in the experimental group than in the control group.

We summarised data on the more common adverse effects as number of participants experiencing an event compared to the number of participants treated with the drug. We calculated RRs for the overall incidence of any adverse effect, for adverse effects necessitating withdrawal, and for the incidence of gastro-intestinal complaints.

Unit of analysis issues

We collected data from only the first stage of cross-over trials to exclude potential additive effects in the second phase.

Dealing with missing data

Where possible, we used results from intention-to-treat analyses, rather than those from the per-protocol/efficacy analyses. If the data were not clear or not included in the trial report, we contacted the primary author of the paper for assistance and clarification. If the data could not be attained by any method and only the partial data from the report were available, we calculated values where possible, and if not, we reported the authors' report of significance in tabular form.

Data synthesis

We reported fixed-effect meta-analyses as the default. Where significant heterogeneity was detected, we also undertook random-effects analyses.

Subgroup analysis and investigation of heterogeneity

No subgroup analysis was possible because of the lack of data. We quantified the levels of heterogeneity using I^2 statistic.

Sensitivity analysis

We undertook sensitivity analyses where possible by comparing the per-protocol analyses with the intention-to-treat. Where data were not available for dichotomous outcomes, we made a 'worse case' assumption, i.e. we assumed that the people with missing data had poor outcomes.

For the analysis of adverse effects in the trials, we re-ran the meta-analysis excluding open (non-blinded) studies where the participant and investigator knew their treatment allocation.

Results

Description of studies

Results of the search

The original review contained 27 RCTs. The searches for the update identified a further 12 RCTs. Thirty-nine RCTs in total were identified comparing minocycline to another comparator, with a total of 6013 participants. All but seven were published in English: Two studies were published in German (Blecschmidt 1987; Laux 1989), three studies were published in French (Dreno 1998 [pers comm]; Lorette 1994; Waskiewicz 1992), and one study each were published in Italian (Fallica 1985) and Spanish (Campo 2003).

Included studies

Design

The duration of the trials ranged from 4 to 24 weeks, with a median of 12 weeks. There is no agreed minimum duration of

acne trials, but 12 weeks is commonly used. Nineteen of the trials were conducted under double-blind conditions where neither the assessor nor the participant knew the treatment allocation. In another six, the investigator was unaware of the treatment allocation, but the participant was. Both the participant and the investigator knew the treatment allocation in 14 RCTs. One cross-over trial was identified (Hersle 1976).

Sample sizes

The numbers of participants included in the individual RCTs ranged from 18 (Smit 1978) to 649 (Ozolins 2005). The median number of participants was 100. Twenty-four of the studies included 109 individuals or fewer.

Only four RCTs - all conducted in the UK - stated that a power calculation had been undertaken to ensure sufficient numbers of participants had been included to exclude the effects of chance (Bossuyt 2003 (TETRABUK); Cunliffe 1998; Darrah 1996; Ozolins 2005).

Bossuyt 2003 (TETRABUK) used a non-inferiority design (80% probability, using a one-sided test performed at the 0.025 level of significance and a maximum difference of 15% in inflamed lesions). Non-inferiority trials are designed to demonstrate that the efficacy of a new treatment is not worse than the chosen control by more than a specified margin (in this case a 15% difference in inflamed lesion count). There are a number of inherent weaknesses in this type of design.

Cunliffe 1998 based calculations on the ability to detect a 15% difference in the per cent reduction in inflammatory lesion count with 80% probability, using a two-sided test performed at the 0.05 significance level. They estimated that 67 evaluable participants per treatment group were required.

Darrah 1996 estimated that 150 evaluable participants were required to demonstrate with 80% probability that the 95% confidence interval of the true difference in response rates was within ± 15% in respect of the percentage of participants who achieved at least a 40% reduction from baseline to the end of treatment in the number of acne lesions.

Ozolins 2005 estimated that based on participants' evaluation of overall improvement, 132 would be needed for a 20% relative treatment effect between the test regimen and 5% benzoyl peroxide to be detected with a 75% response rate (80% probability, using a two-sided test at the 0.05 level of significance) on the assumption of a 23% dropout rate.

Setting

In total, 28 studies were conducted in more than 1 centre. Of the 39 RCTs, 36 were conducted in dermatology clinics and only 3 in general practice, which were all in the UK (Darrah 1996; Ozolins 2005; Peacock 1990).

The RCTs were conducted in different countries: U.S. (nine), UK (seven), France (six), Germany (three), Italy (three), Chile (one), Columbia (one), Japan (one), Sweden (one), India (one), Iceland (one), Netherlands (one), and Belgium (one). Three further RCTs were conducted over three sites in different EU countries.

Participants

The 39 RCTs enrolled a total of 6013 participants. The ages ranged from 9 to 47, although most trials (29) insisted on a minimum age of between 12 to 17 years. Where it was stated in 29 of the RCTs, the maximum age was above 24 and generally over 30. Post-adolescent acne is generally regarded as harder to treat, so the degree to which the results can be generalised to adolescents is questionable. We didn't identify any subgroup analyses by age.

Two of the RCTs enrolled only men (Gollnick 1997; Pigatto 1986) because they were comparing minocycline with oral isotretinoin, which is known to cause foetal abnormalities. One further RCT of an oral contraceptive inevitably only included women (Monk 1987). Otherwise, there was a fairly even distribution of men and women or boys and girls across the studies, with a few notable exceptions (Blecschmidt 1987; Cullen 1976; Darrah 1996; Dreno 1998 [pers comm]; Dreno 2001; Fallica 1985; Hersle 1976; Fleisch 2006a (MP010404); Fleisch 2006b (MP010405); Ozolins 2005; Peacock 1990; Pelfini 1989).

All trials reported the entry and exclusion criteria, but there was a lot of variation. The severity of acne varied from mild to severe, but most RCTs included mainly participants with 'moderate to moderately severe inflammatory disease'. Only four trials included participants with mild as well as moderate acne (Darrah 1996; Hersle 1976; Ozolins 2005; Revuz 1985), and none only included non-inflammatory acne. Almost all included moderate acne (33), and 24 included severe acne. Three trials only included severe acne, two compared minocycline to oral isotretinoin (Gollnick 1997; Pigatto 1986), and one assessed combination treatment with adapalene (Smit 1978).

Exclusion criteria almost always included hypersensitivity to tetracyclines or the comparator as well as pregnancy and lactation. In addition, some authors specifically excluded participants with renal or hepatic dysfunction, vertigo (a common side-effect of minocycline therapy), or any intercurrent illness. Participants with secondary acne and acne conglobata or fulminans were specifically mentioned as excluded by a minority of authors. Such participants should not have been included in any of the trials.

Interventions

Among the trials identified, there was considerable variation in the choice of comparator and in the dose of minocycline. Treatment regimens varied from 100 mg per day in 1 or 2 divided doses, to 100 mg or 200 mg initially followed by 50 mg or 100 mg after the first 4 weeks. In 1 instance, 100 mg was given on alternate days after the first 2 weeks, as is recommended in France by the manufacturer (Cunliffe 1998).

Six RCTs included a placebo comparison, and three RCTs examined different doses of minocycline. The following oral antibiotics were compared with minocycline: oxytetracycline (2 RCTs), tetracycline (7), doxycycline (5), lymecycline (4), roxithromycin (1), faropenem (1), and josamycin (1). Minocycline was compared against zinc gluconate in one RCT and two different hormonal treatments; cyproterone acetate/ethinyloestradiol (1 RCT) and a type 1 5-alpha reductase inhibitor (1

RCT). The comparisons against topical treatments were topical clindamycin (3 RCTs), topical erythromycin/zinc(1), topical fusidic acid (1) and benzoyl peroxide and benzoyl peroxide/erythromycin (1). Combination treatments were evaluated in four RCTs, and two RCTs compared minocycline with isotretinoin. Finally, one RCT evaluated minocycline as a maintenance therapy.

Minocycline was compared with the following: zinc gluconate in one RCT, two different hormonal treatments (cyproterone acetate/ethinyloestradiol) in one RCT, a type 1 5-alpha reductase inhibitor in one RCT. The comparisons against topical treatments were as follows: topical clindamycin in three RCTs, topical erythromycin/zinc in one RCT, topical fusidic acid in one RCT, and benzoyl peroxide and benzoyl peroxide/erythromycin in one RCT. Combination treatments were evaluated in four RCTs, and two RCTs compared minocycline with isotretinoin. Finally, one RCT evaluated minocycline as a maintenance therapy.

Outcomes

Almost all the trials used more than one outcome measure, and over 50 different methods were used. Thirty-five RCTs counted various combinations of lesions, but there was once again considerable variation in how this was carried out, what was included, and how it was reported (e.g. separate and total lesion counts, absolute changes from baseline, and percentage lesion counts). Although most authors reported mean reductions in grade or lesion count, a minority reported medians instead or in addition (Gollnick 1997; Monk 1987). Four used grades only (Blecschmidt 1987; Fallica 1985; Hubbell 1982; Samuelson 1985), and only 17 included any assessment made by the participants.

A variety of significance tests were used with both acne grades and lesion counts: the commonest being the student's t-test, the Mann-Whitney U test, and analysis of covariance. In two instances, non-parametric tests, such as Mann-Whitney or Wilcoxon, had been carried out on means instead of medians (Smit 1978; Stainforth 1993). As far as it could be ascertained, most studies were analysed on a per-protocol basis. A minority of trials used intention-to-treat analysis. It was not always clear how withdrawals and participants who failed to attend at one or more visits had been dealt with, and few studies specified how many of the participants enrolled had been included in the final analysis.

Two studies used a simple quality of life (QOL) questionnaire (Dreno 1998 [pers comm]; Peacock 1990), and one included recognised QOL instruments suitable for cost-utility analysis (Ozolins 2005).

Adverse effects

All evaluable trials collected data on unwanted effects, and all but one reported these data in some form. However, some collected data on adverse events, some on side-effects, and some on tolerance. Details of how unwanted effects were identified were given only occasionally and were rarely adequate. Twelve studies gave no detail whatsoever, and five merely stated that they asked the participant. Revuz 1985 recorded those adverse effects that were spontaneously reported by participants or observed by the doctor. Khanna 1993 questioned participants about four specific categories of side-effect (photosensitivity, signs of benign intracranial hypertension, hyperpigmentation, and vaginal candidiasis). Ruping 1985 reported tolerance on a five-point scale as separately assessed by participants and physicians. Harrison 1988 asked the specific question, 'Has the treatment upset you in any way?'. Waskiewicz 1992 and Lorette 1994 assessed tolerance on the basis of subjective criteria (e.g. dizziness) and objective signs (e.g. urticaria). Darrah 1996 recorded adverse effects as observed by the physician and as reported spontaneously by the participant in response to a non-leading question. There was clearly confusion about definitions, and some authors had apparently made quite arbitrary decisions about which adverse effects were possibly drug-related. For example, Cullen 1976 ruled that joint pain and swelling of the fingers in a minocycline-treated participant was unlikely to be drug-related. In the vast majority of studies, it was impossible to ascertain what proportion of participants had been included in the safety analysis. In 6/26 studies, side-effects were only reported if they led to withdrawal of the participant. Only one of these six studies actually made it clear that participants who hadn't been withdrawn did not report any side-effects.

For the additional review of adverse effects, we identified 16 studies (please see Table 3), of which 3 used a number of different designs simultaneously. Three studies used nationally-reported pharmacovigilence data, and four examined cohorts of consecutive participants attending clinics. Large prescribing databases were the subject of two cohort studies and three case-control studies. Finally, we identified seven systematic reviews.

Excluded studies

We excluded 64 studies that are commonly cited as evidence of the effectiveness of minocycline: Most were uncontrolled cohort studies. However, six were actually RCTs, but they did not meet the inclusion criteria for this review, primarily due to the non-clinical outcomes used in the studies (Bodokh 1997; Goulden 1996; Kligman 1998; Leyden 1997a; Nishijima 1996; Pablo 1975). In one trial, all participants were given minocycline and then randomised to receive either streptokinase (Varidase) or placebo (Randazzo 1981); therefore, this trial was excluded. Please see the 'Characteristics of excluded studies' tables.

Risk of bias in included studies

It is clear from the above description of the included trials that there was considerable variation between them with respect to numerous factors, which might affect study quality or introduce bias, or both. We sought further information from trial investigators when there was insufficient information in the trial report to make a judgement.

Allocation (selection bias)

Only six of the RCT reports (published and unpublished) mentioned any specifics about how the randomisation was carried out and were rated as low risk of bias (Blecschmidt 1987; Cunliffe 1998; Darrah 1996; Leyden 2006 (Part 2); Ozolins 2005;

Peacock 1990). The remainder of the included studies did not provide additional information beyond the fact that the study was randomised. One study matched pairs of participants in the treatment groups prior to randomisation on the basis of age, sex, and baseline acne severity (Sheehan-Dare 1989). Pelfini 1989 and Waskiewicz 1992 were rated as high risk of bias. In Pelfini 1989, the trial design was compromised by a number of participants who were also given 5% benzoyl peroxide, which is very active. Also, two different treatments schedules and the method of randomisation was unclear and possibly based on severity. In Waskiewicz 1992, the investigators stated that three participants dropped out and were re-included in the trial three to six months after their dropout. In the meantime, their acne did not improve spontaneously or with other treatments. The re-inclusion of dropouts was judged to have compromised the randomisation.

Four RCTs provided adequate descriptions of allocation concealment (Cunliffe 1998; Hayashi 2011; Leyden 2006 (Part 2); Ozolins 2005). We rated 10 studies as high risk (Blecschmidt 1987; Cabezas 1993; Fallica 1985; Gollnick 1997; Laux 1989; Monk 1987; Pigatto 1986; Ruping 1985; Schollhammer 1994; Waskiewicz 1992) as no allocation was attempted or it was judged to be inadequate. We rated the remainder of the studies (25) as unclear.

Blinding (performance bias and detection bias)

We included 13 open trials (Blecschmidt 1987; Darrah 1996; Fallica 1985; Gollnick 1997; Hayashi 2011; Khanna 1993; Laux 1989; Monk 1987; Pelfini 1989, Pigatto 1986; Ruping 1985; Schollhammer 1994; Waskiewicz 1992) in this review and rated them as high risk of bias. We decided not to exclude these studies but to interpret the results in consideration of the bias that is often associated with open trials.

In total, we described 20 trials as 'double-blind', which were therefore classified as at low risk of bias: Cabezas 1993; Cullen 1976; Cunliffe 1998; Drake 1990; Dreno 1998 [pers comm]; Dreno 2001; Hersle 1976; Hubbell 1982; Leyden 2004; Leyden 2006 (Part 2); Lorette 1994; Stewart 2006 (MP010401); Fleisch 2006a (MP010404); Fleisch 2006b (MP010405); Olafsson 1989; Pierard 2002; Revuz 1985; Samuelson 1985; Sheehan-Dare 1989; Smit 1978. In a further six RCTs, the participant knew what treatment they were allocated to, but the assessor did not. Five of these (Bossuyt 2003 (TETRABUK); Campo 2003; Harrison 1988; Peacock 1990; Stainforth 1993) were rated as unclear as they are more open to biases. The sixth (Ozolins 2005) was classed as low risk of bias because it stated, "Participants were given specific written and spoken instructions not to discuss the nature of their medication with assessors. Instances of treatment unmasking to assessors during the study were recorded."

Incomplete outcome data (attrition bias)

Only 19 of the 39 included studies provided sufficient information to assess them as being at low risk of attrition bias, with reasons for dropouts fully accounted for and dropouts balanced between the groups (Cullen 1976; Cunliffe 1998; Darrah 1996; Dreno 2001; Fallica 1985; Gollnick 1997; Harrison 1988; Hayashi 2011; Khanna 1993; Leyden 2006 (Part 2); Stewart 2006 (MP010401); Olafsson 1989; Ozolins 2005; Peacock 1990; Pelfini 1989; Pierard 2002; Pigatto 1986; Smit 1978; Stainforth 1993). We judged 14 studies to be at high risk of bias due to the proportion of dropouts, incomplete reporting of dropouts, or imbalanced rates of dropout between the groups, with the remaining 5 studies being judged as unclear due to the lack of information.

Selective reporting (reporting bias)

We only judged three studies (Leyden 2004; Lorette 1994; Waskiewicz 1992) to be at high risk of bias. Leyden 2004 only reported inflammatory lesions from prespecified outcomes that included lesion counts, investigator and participant assessments, and photographs. It may be that these data were collected but not included in the published report of the study. Lorette 1994 did not provide the number of participants in each group who experienced adverse effects. Although the types of adverse effects were listed, clinical tolerability is described only as 'satisfactory'. Waskiewicz 1992 provided only percentage improvements and acne count.

We rated nine studies as unclear risk of bias as we were unable to assess, from the report of the study, whether all outcomes had been fully reported or where further information was not available from the trial investigator (Campo 2003; Dreno 1998 [pers comm]; Gollnick 1997; Hubbell 1982; Monk 1987; Ozolins 2005; Ruping 1985; Samuelson 1985; Schollhammer 1994).

The remaining 27 studies reported all prespecified outcomes and therefore were rated as low risk of bias.

Effects of interventions

The outcome measures of interest were those that estimated clinical efficacy, participant acceptability, or both, in a defined way. There are many different methods used to assess clinical efficacy, and there is no evidence at present on their relative validity, reliability, or responsiveness. Therefore, lesion counts (total, inflamed, and non-inflamed, separately), acne severity scores, physicians' global evaluation, and participants' self assessment have all been included in the description of the effects of interventions.

1. Minocycline versus placebo

Six RCTs included a placebo comparison (Cabezas 1993; Hersle 1976; Leyden 2004; Stewart 2006 (MP010401); Fleisch 2006a (MP010404); Fleisch 2006b (MP010405)).

We identified one trial that used a cross-over design, comprising two five-week treatment phases (Hersle 1976). It is not clear whether the 43 participants completing the study were aware of the cross-over, as the tablets in each phase were identical. There was no wash-out period between the two phases, which meant that the results for placebo in the second phase could not be considered reliable. A summed weighted acne lesion score was used as the sole outcome measure, and during the first phase, the minocycline group demonstrated a significant reduction ($P < 0.05$, paired student's t-test), whilst the placebo-treated group did not. No measures of dispersion were presented, and no statistical comparison was performed between the

groups.

A placebo arm was included in a trial that compared minocycline to a drug in the experimental stages (see comparison 4b). The 34 participants treated with minocycline were reported to have a 49.2% reduction in inflamed lesion counts compared to 26.8% in the 37 participants treated with placebo (Analysis 1.1) (means difference (MD) 22.40, 95% CI 4.34 to 40.46) (Leyden 2004). Non-inflamed lesion counts did not appear to be undertaken, and no usable data on adverse effects were reported.

Three RCTs evaluated a extended-release formulation of minocycline and were all sponsored by Medicis Pharmaceutical Corporation. The two 3-month phase 3 trials (Fleisch 2006a (MP010404); Fleisch 2006b (MP010405)) included a total of 615 participants receiving minocycline 1 mg/kg and 309 participants receiving placebo. The results of the phase 2 dose-finding trial are further discussed under '2. Dose response' (Stewart 2006 (MP010401)). The similarities between the trial designs in the three RCTs meant that meta-analysis could be undertaken. Minocycline ER resulted in a statistically significant greater percentage reduction in inflamed lesion counts (45.5% reduction versus 32.4%) in Analysis 2.1 (MD 13.43, 95% CI 7.10 to 19.76) and total lesion counts in Analysis 2.2 (MD 9.84, 95% CI 4.84 to 14.84), but not non-inflamed lesion counts (14.9 vs 6.3 mean per cent reduction from baseline - data not presented in poolable format); the authors stated it as being 'not inferior' and not causing an exacerbation. Pooled treatment success as evaluated by the investigator was Analysis 2.3 (RR 1.89, 95% CI 1.26 to 2.82). For all three analyses I^2 statistic = 0%. There was no statistically significant difference between the numbers of participants at different doses of minocycline and the placebo group whose skin was clear or almost clear after 12 weeks in Analysis 2.4 (RR 1.62, 95% CI 0.81 to 3.24). Adverse effect data were not presented for the individual trials.

One small Spanish-language study conducted in Chile (80 participants) compared minocycline to tetracycline and placebo (Cabezas 1993). Very sparse data on the trial methodology and results were available in this publication. The authors did not report any statistical comparison between the minocycline and placebo group. No further data could be obtained from either the trial authors or sponsors.

2. Dose response

In most countries, the manufacturer's recommended dose of minocycline for acne is 100 mg per day, which is half the normal therapeutic dose used for other indications. Therefore, it is surprising that no study was located that compared 100 mg to 200 mg per day in the treatment of acne.

Pierard 2002 compared 50 mg a day for 12 weeks with 50 mg twice-daily for 4 weeks, followed by 50 mg a day for 8 weeks. There were only 28 and 31 participants randomised to each group, respectively; very few methodological details were provided; and there were no baseline assessments of equivalence. The authors concluded that the inflammatory papule counts in the 100/50 mg group showed a statistically significant greater reduction compared to the 50 mg daily group ($P < 0.05$, non-parametric pairwise Wilcoxon rank sum test). No details were provided on open comedones, closed comedones, and pustules. There was also a significant difference in the investigator and participant global assessments ($P < 0.05$, Chi^2 test). The trial was primarily an evaluation of in vivo antibacterial efficacy, and therefore few protocol details were presented and few clinical data were available from the publication. The authors did not respond to requests for additional information. The authors concluded that the "microbial response to minocycline 100/50 mg was also superior", although no data were provided for further assessment, only a graph. There was insufficient information mentioned in the trial report to allow for proper assessment.

A publication of a double-blind, phase two, dose-ranging trial that explored the appropriate dose of a extended-release form of minocycline was identified (Stewart 2006 (MP010401)). The randomisation was stratified by body weight with 233 participants with moderate to severe acne given either placebo or 1 mg/kg, 2 mg/kg, or 3 mg/kg minocycline ER for 12 weeks. There was a high dropout of 57 participants (24%). By day 84, the number of inflammatory lesions had decreased by 39% in the placebo group and 57%, 49%, and 47%, respectively, in the minocycline groups. The authors concluded that no dose-dependent effect was observed in either global assessment scores, inflamed lesion counts, non-inflamed lesions, or total lesion counts. Although it is probable that insufficient numbers of participants were recruited to ensure the trial was adequately powered, no power calculation was included in the publication. Compared to placebo, the only difference in per cent change from baseline in inflammatory lesions that reached statistical significance was the 1 mg/kg group at 84 days. There were no statistically significant differences between any of the groups for the changes in the number of non-inflamed lesions, total lesion counts, or number of participants who were clear/almost clear as rated by the assessor (Analysis 3.1). Subgroup analyses were conducted (it was not stated whether they were planned or post hoc). The analyses indicated that minocycline ER "seemed to be somewhat less effective in the heaviest subjects".

One RCT compared minocycline at a continuous dose of 100 mg per day for 8 weeks with the same initial regimen, but at a reduced dose of only 50 mg per day after 2 weeks. The lead investigator supplied the full report of outcomes from the trial report, but it is as yet unpublished (Dreno 1998 [pers comm]). A total of 325 participants were included in the tolerance analysis: 307 in the intention-to-treat and 214 in the per-protocol. After eight weeks, no significant differences between the dosage regimens were noted in any of the outcome measures using either per-protocol or intention-to-treat analysis (Analysis 4.1; Analysis 4.2; Analysis 4.3). However, because of the short duration of the study, inferences cannot be made concerning their relative efficacies in long-term treatment.

3 Minocycline versus other oral antibiotics

a. Minocycline versus tetracycline or oxytetracycline (abbreviated as (oxy)tetracycline)

Tetracycline and oxytetracycline are in the first-generation class of tetracyclines.

The original version of the review included 7 RCTs, and 2 further RCTs were identified in the 2012 update. Of these nine

studies, the authors of five reported no statistically significant differences between minocycline and (oxy)tetracycline: The methodology of these five studies reflected standards at the time, but by today's standards, it would not be considered robust. They were also likely to be underpowered due to the small total numbers of participants included: Cullen 1976 included 100 participants (Analysis 5.8), Fallica 1985 included 100 participants, Hubbell 1982 included 104 participants (Analysis 5.7), Samuelson 1985 included 62 participants (Analysis 5.4), and Khanna 1993 included 44 participants (Analysis 5.9).

The sixth study was more recent, well-designed, and a larger observer-blind study conducted in those with mild to moderate acne in primary care in the UK (Ozolins 2005). The trial was funded independently. The initial plan was to compare 11 treatments, but slow-recruitment meant that 6 arms were discontinued. Power calculations were undertaken at the start of the study, and approximately 130 participants were randomised to each arm (649 participants in total). Minocycline and oxytetracycline obtained comparable results at 18 weeks with a decrease in inflamed lesion count from baseline (MD 3.60, 95% CI -1.56 to 8.76) (Analysis 5.2) and in those participants with at least moderate improvement, as assessed by the participants themselves (Analysis 5.3) and by the assessors (Analysis 5.4). However, at 12 weeks the minocycline-treated group had a statistically significantly greater reduction in the mean number of inflamed lesions (RR 7.30, 95% CI 1.12 to 13.48) (Analysis 5.2).

The overall numbers of participants experiencing adverse effects were not reported, and there were no differences in the numbers of participants withdrawing because of adverse effects. The oral antibiotic-treated groups experienced more gastro-intestinal and musculoskeletal events at week six. Using 2005 acquisition costs, oxytetracycline was reported as being more cost-effective and of similar effectiveness at approximately 1/7th of the cost at that time. The acquisition costs have now changed as generic minocycline has become available. The clinical efficacy of both tetracyclines was reported as being compromised in individuals who were colonised by tetracycline-resistant propionibacteria. Most of the treatment effect was seen after the first six weeks of treatment.

Three studies found minocycline to be superior to (oxy)tetracycline (Blecschmidt 1987 (Analysis 5.1); Cabezas 1993; Ruping 1985). The first two RCTs were however conducted under open conditions and had a number of serious methodological flaws. Therefore, the results must be interpreted with extreme caution. Ruping 1985 reported that minocycline was significantly superior to tetracycline in terms of the reduction in inflamed lesion count at week 12, but presented the results only in graphical form and did not include any measures of dispersion or state the method used to calculate its P values. Visual inspection of the graphical data does not support the conclusion that minocycline is superior. The study included participants with acne conglobata, and assessments were performed only on one side of the face, back, or chest, with the assessment intervals grouped into 14-day periods without standardisation. The trial also reported that 36 participants could not be evaluated because of faulty or inadequate statements, with no details as to which treatment they were randomised to, and no information was provided on dropouts or the number of participants included in the analysis. The total number of adverse effects in each group was not reported, and the text is contradictory about the numbers withdrawing due to adverse effects. The second study (Blecschmidt 1987) enrolled 237 participants and had similar design faults, with 43 participants being excluded from the analysis and duration of treatment varying between 12 and 20 weeks. The outcome measure used was the number of participants improving by at least two grades at each assessment point, with no indication of what grade they improved from or to.

Cabezas 1993 was a small (80 participants) placebo-controlled, double-blind study. It was conducted in Chile, and a very brief report was published in Spanish with few methodological details. Neither the company nor the authors responded to requests for more information. There were no statistical comparisons with the placebo group, but the authors reported that there was a statistically significant difference in favour of minocycline in the average numbers of 'lesions', papules, and pustules after 45 days of treatment.

It has been suggested that minocycline has a faster onset of action than first-generation tetracyclines because it is more fat-soluble, and therefore higher levels are obtained in sebum. Khanna 1993 recorded a statistically significant difference in favour of minocycline compared to tetracycline in the 'acne lesion score' at six weeks but not 12 weeks (Analysis 5.9). This effect was also reported by Hubbell 1982 in the number of participants converting to grade 1 acne (indicating mild acne), although data for only 55 of 104 enrolled participants were included in the data analysis (Analysis 5.7). Compared to tetracycline Samuelson 1985 reported statistically significant differences in the change in acne grade from baseline in favour of minocycline at weeks two and eight, but only as assessed by the investigator and not when self-assessed by participants. However, the only data provided were the mean grade at each time point, which showed no difference between the groups (Analysis 5.5; Analysis 5.6).

Blecschmidt 1987 found that, statistically significantly, more participants treated with minocycline had improved by 2 or more grades by the end of weeks 2, 4, 8, and 12 than those treated with oxytetracycline (Analysis 5.1). Visual inspection of the survival curves presented in Ruping 1985 also suggested minocycline had a faster onset of action against papules and pustules (with the caveat about the methodology as described in the paragraph). In all cases where the initial response to minocycline was faster, the magnitude of the reduction in acne severity produced by both drugs at the end of the treatment period was similar (Analysis 5.3; Analysis 5.4).

The concerns about the robustness of the RCTs not withstanding, some limited meta-analysis of the 'overall improvement' results could be undertaken (Analysis 5.8). This indicated that, as assessed by the investigator, more participants receiving minocycline had improved compared to those receiving tetracycline at week 6 (RR 1.43, 95% CI 1.04 to 1.96, I^2 statistic = 72%), but not week 12 (RR 0.97, 95% CI 0.72 to 1.31, I^2 statistic = 0%). However, this difference was not evident when a random-effects meta-analysis was undertaken, reflecting the heterogeneity identified.

b. Minocycline versus lymecycline (Tetralysal)

Lymecycline is a second-generation tetracycline, which, like minocycline, is typically given as a single-daily dose. It has become the most commonly prescribed first-line antibiotic for acne in Europe.

The original version of the review included two RCTs that compared lymecycline with minocycline, both of which used reducing doses of each drug (as is common practice in France). The first was a 144-participant double-blind, double-dummy trial in 5 centres (Cunliffe 1998), which was sponsored by Galderma, who manufacture lymecycline. A variety of outcome measures were used, but the primary end point was declared in advance as the per cent reduction in inflamed lesion count at week 12. Using both intention-to-treat (ITT) and per-protocol analyses, no significant difference was found between minocycline and lymecycline for this or any other outcome measure (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4; Analysis 6.5). The sample size had been calculated to enable the study to detect a 15% difference in the percentage reduction in the inflamed lesion count with an 80% probability using a two-sided test performed at the 0.05 significance level. The second study was a small (71 participants) 12-week open study and additionally included participants treated with doxycycline (Schollhammer 1994). The authors reported a 68.4%, 72.7%, and 62.4% reduction in inflamed lesion counts in the minocycline, lymecycline, and doxycycline groups, respectively. These differences were not found to be statistically significant ($P > 0.05$, test not reported); however, the trial was likely to be very underpowered.

The 2012 update identified a further two 12-week RCTs trials that both compared 300 mg lymecycline daily with 2 different minocycline regimens.

Pierard 2002 compared 300 mg lymecycline per day for 12 weeks with 2 different minocycline regimens (50 mg a day for 12 weeks or, alternatively, 50 mg twice-daily for 4 weeks, followed by 50 mg a day for 8 weeks). Double-dummy treatments were used. One of the authors was affiliated with Wyeth-Lederle. There were only 28 and 31 participants randomised to each group, respectively; very few methodological details were provided; and there were no baseline assessments of equivalence. The trial was primarily an evaluation of in vivo antibacterial efficacy; therefore, few protocol details were presented, and few clinical data were available from the publication. The authors concluded that the 100/50 mg group compared to the lymecycline group showed statistically significant ($P < 0.05$, non-parametric pair-wise Wilcoxon rank sum test) "less severe" acne lesions, a greater reduction in inflammatory papule counts, and "significantly less lesions" at week 12. "Approximately one third" of participants in the lymecycline and minocycline 50 mg groups reported "the clearance of acne lesions" compared to "over half" in the minocycline 100 mg/50 mg group. Total lesions counts are not a good measure of outcome because inflamed and non-inflamed lesions respond differently to treatments. There was also a significant difference in the investigator and participant global assessments ($P < 0.05$, Chi^2 test). The authors concluded that the "microbial response to minocycline 100/50 mg was also superior" as assessed by percentage of live bacteria and percentage of dead bacteria and debris, which were assessed by dual-flow cytometry analysis. The authors did not respond to requests for additional information.

Bossuyt 2003 (TETRABUK) was sponsored and organised by Galderma, who manufacture lymecycline. The study compared extended-release minocycline 100 mg with 300 mg lymecycline daily for 12 weeks in 68 and 66 participants, respectively. At the end of 12 weeks, there was no significant difference between the 2 groups in the lesion count data (IL, NIL, TLC). There were similarly no difference in global severity grade or participant or physician global assessment of improvement. There were some discrepancies in the publication with regard to the numbers of participants included in the per-protocol analysis, which potentially indicated that approximately one third of participants randomised to each group did not complete the study. The "economic evaluation" included in the paper was a cost-minimisation analysis that compared the most expensive minocycline preparation (extended-release) with lymecycline. The prices of both minocycline and tetracycline have changed since 2003.

Limited pooling of data could be undertaken from Cunliffe 1998 and Bossuyt 2003 (TETRABUK); lymecycline appeared to have a greater effect on both the participant and doctor global assessments of overall improvement using intention-to-treat analysis, but the result was not significant (Analysis 6.6). Further data would increase the statistical power of this analysis.

c. Minocycline versus doxycycline

Doxycycline is a second-generation tetracycline.

All 5 trials of minocycline versus doxycycline contained less than 80 participants. Therefore, not surprisingly, because of inadequate statistical power, they did not detect any overall difference between the drugs. Four were 12 weeks, with Lorette 1994 being 17 weeks. All three open studies had deficiencies in either the outcome measures used, the trial design, or both, (Laux 1989; Schollhammer 1994; Waskiewicz 1992) and included very small numbers of participants: 74, 50, and 77, respectively. Neither of the two double-blind studies contained sufficient information to allow effect sizes to be calculated directly (Lorette 1994; Olafsson 1989). The included participant numbers were 79 and 71, respectively.

The physician-assessed improvement could be pooled in three trials (RR 0.99, 95% CI 0.88 to 1.12, I^2 statistic = 0%) (Analysis 7.2).

d. Minocycline versus roxithromycin

Roxithromycin is a semi-synthetic macrolide antibiotic derived from erythromycin and with a similar mode of action. Roxithromycin is licensed for acne in Japan, but it is not licensed in the United States or the United Kingdom.

A Japanese RCT compared 4-week treatment with 100 mg daily minocycline (given as single dose once a day or 50 mg twice a day) with 150 mg roxithromycin daily (Hayashi 2011) in 49 and 50 participants with moderate acne. A third trial group of 51 participants received faropenem 200 mg three times a day. A second four-week follow-up period occurred in which no treatment was given. The only acne-treatment-related exclusion was if participants had received oral antibiotics within the past month. Concomitant use of acne treatments was prohibited in the treatment period, but permitted during the

observational follow-up period. Unsurprisingly, given the small numbers of participants treated and the short (four-week) treatment duration, the authors reported no significant differences between the reductions in inflammatory and non-inflammatory lesion counts from baseline, or quality of life. A significant reduction in all groups was seen for all outcomes from baseline at all time points. Data were reported in graphical format only. The microbiological outcomes suggested resistance had developed to roxithromycin in some participants. Dizziness and nausea were reported in two minocycline-treated participants.

e. Minocycline versus faropenem

Faropenem is a member of the class of antibiotics known as penems. These antibiotics are broad spectrum and related to penicillins and cephalosporins. Faropenem is licensed for acne in Japan, but to date, the FDA have not approved it for any indication because of a lack of efficacy data. It is not licensed in the UK. One small trial compared minocycline versus faropenem (Hayashi 2011). The results are described in the section on minocycline versus roxithromycin. Three participants in the faropenem group had diarrhoea.

f. Minocycline versus josamycin

Josamycin is a macrolide antibiotic related to erythromycin and with a similar mode of action. It is not approved in the UK or US.

122 participants with severe or refractory acne were allocated to 2 different treatment schedules depending on severity (Pelfini 1989). The first group received 500 mg josamycin or 100 mg minocycline once daily for 8 weeks. The second received 1000 mg josamycin and 200 mg minocycline. Some participants also received topical 5% benzoyl peroxide. It is unclear how the groups were allocated. The authors reported a statistically significant reduction in the number of papulopustules, comedones, and nodulo-cysts, and the intensity of seborrhoea and erythema. They reported that josamycin was more effective than minocycline (Analysis 8.1; Analysis 8.2; Analysis 8.3; Analysis 8.4; Analysis 8.5). The standard of the publication was however very poor, and the results cannot therefore be substantiated given the potential biases introduced by the likelihood of the trial being open, the dosing schedule, and use of benzoyl peroxide. One participant receiving josamycin had mild gastric discomfort, one minocycline-treated participant had a rash, and a third had to discontinue minocycline due to severe gastric intolerance.

4. Minocycline versus hormonal treatments

Excessive oil production in the skin contributes to acne. The oil-producing glands in the skin are controlled by hormones called androgens (for example, testosterone). One potential mechanism of treating acne is to manipulate the hormones.

a. Minocycline versus cyproterone acetate/ethinyloestradiol (Diane™)

In the UK, the oral contraceptive Dianette™ containing 2 mg of cyproterone acetate (an antiandrogenic progestogen that competes with dihydrotestosterone) and 0.035 mg ethinyloestradiol offers an alternative to antibiotics in women with moderately-severe inflammatory acne. Diane™, the product compared with minocycline in the open trial of Monk 1987, contained a higher concentration of ethinyloestradiol (0.05 mg) than in the currently available product known as Dianette™. The authors found no overall difference between the treatments after 24 weeks, but as the trial only included 98 participants, it was likely to be inadequately statistically powered to conclude that the treatments are equivalent. 17% (6 out of 36 participants) of the Diane™-treated group and 20% (7 out of 35 participants) of the minocycline group thought their acne had completely cleared (RR 1.20, 95% CI 0.45 to 3.22) (Analysis 9.1). The methodology used reflects the standards in 1987 when the trial was conducted; there were serious flaws by today's standards. There is a Cochrane review of the use of hormonal treatments to treat acne (Arowojolu 2009).

b. Minocycline versus compound A: inhibitor of type I 5-alpha reductase

It is unusual for companies and journals to publish trials with negative findings as in the case of an experimental drug code-named Compound A, which was compared to minocycline. Compound A inhibits the enzyme (called 5-alpha reductase type 1) in the hair follicles that converts testosterone into the active hormone, dihydrotestosterone (DHT). This is one of the chemicals that causes sebum to be produced by the hair follicles. The experimental drug reduces the amount of DHT in the blood and sebum, but was shown to be ineffective in treating acne; therefore, the authors concluded that more research is required into sebaceous gland control at the cellular level (Leyden 2004). The trial was intended to last six months, but only three-month data were reported. It is probable that the trial was stopped early due to lack of efficacy in the group receiving compound A.

After 3 months, the 34 men treated with 100 mg minocycline twice a day were reported to have a 49.2% reduction in inflamed lesion counts compared to 25.7% in the 37 men treated with 25 mg of compound A daily (MD 23.50, 95% CI 3.8 to 43.2) (Analysis 10.1). Two other arms in the study included a total 74 participants who received a combination of Compound A and minocycline, and they achieved similar results to those treated with minocycline alone. No usable data on overall adverse effects were reported, but one man receiving minocycline was reported as having a transient elevation in liver enzymes.

5. Minocycline versus zinc gluconate

Oral zinc salts (sulphate, citrate, and gluconate) have been used to treat acne since 1970. Their mechanism of action is poorly understood.

The 2012 update identified 1 double-blind 'equivalence' RCT that compared 100 mg minocycline a day with 30 mg of zinc gluconate in 332 participants (Dreno 2001). The sponsoring company (Labcatal Pharmaceuticals) also kindly supplied additional information. Minocycline produced a greater reduction in both inflamed and non-inflamed lesion counts, at all time

points, and was evaluated as more effective by both clinicians and participants. Interestingly, for both treatment groups, significantly more women were reported as responding. After 90 days of treatment, the mean difference between the percentage change in inflamed lesions from baseline was as follows: MD -16.42, 95% CI -25.10 to -7.74 (Analysis 11.1). The clinician assessed 102/161 minocycline-treated participants as having a successful treatment (defined as a two thirds reduction in IL) compared to 49/157 of those treated with zinc (RR 2.03, 95% CI 1.56 to 2.63) (Analysis 11.2). The results for the doctor and participant overall assessment of effectiveness were similar (Analysis 11.3).

Two minocycline-treated participants had to withdraw for GI disturbances compared to 4 zinc-treated participants (RR 0.04, 95% CI -0.01 to 0.09). 36/169 participants treated with minocycline experienced an adverse effect compared to 55/163 treated with zinc (RR -0.12, 95% CI -0.22 to -0.03). These led to the withdrawal of 4 participants in the minocycline group and 5 in the zinc group (RR -0.01, 95% CI -0.04 to 0.03).

6. Minocycline versus topical acne treatments

a. Clindamycin

Three trials compared minocycline 50 mg twice-daily with 1% clindamycin applied topically twice-daily (Drake 1990; Peacock 1990; Sheehan-Dare 1989). The trials were of similar design and duration, and all included lesion counts. However, data could not be pooled as the results were presented graphically, and no further information could be obtained from the authors or sponsors.

In all three trials, there was a statistically significant decrease in lesion counts in all groups. Although there was conflicting data in the two Sheehan reports with one saying there was no statistically significant reduction in non-inflamed lesions, there was a definite trend in Sheehan-Dare 1989 for superiority of topical clindamycin. However, this did not reach statistical significance, probably due to the large range of lesion counts included, and the small number of participants (66). The other two trials obtained virtually identical results for both minocycline and clindamycin. This is to be expected given both trials were very small (52 participants in Drake 1990 and 80 in the Peacock 1990 trial completed the trial). Peacock 1990 also reported on aspects of quality of life obtained via participant questionnaires, with no significant difference between the groups (Analysis 12.1).

Both treatments were reported as well-tolerated.

b. Fusidic acid

Fusidic acid is an antibiotic that is especially useful in the treatment of staphylococcal infections. Fusidic acid is widely-available internationally, but not in the United States. Topical use for a chronic condition like acne is contra-indicated because fusidic acid promotes resistance when used alone. Awareness of this issue was low when the trial was conducted.

Twice-daily 2% fusidic acid (Darrah 1996) was compared with 50 mg oral minocycline twice a day in participants with mild to moderate facial acne in UK general practice. Although spots were always counted on the right side of the face, participants were instructed to apply the topical medication to the affected area only. This trial included both a power calculation and declared the primary end point in advance. However, the end point defined was rather loose, namely a 40% reduction in either total lesion count or total non-inflamed lesion count or total inflamed lesion count by the end of the treatment period. Using this criterion, no significant difference was found between the treatments; 188 participants were included in the non-inferiority design (Analysis 13.1). At the end of treatment, the overall reduction in the inflamed lesion count due to minocycline was significantly superior (P = 0.04, Chi² test with Yate's continuity correction) than that due to fusidic acid (MD 3.00, 95% CI 0.06 to 5.94) (Analysis 13.2). The authors' concluded this was unlikely to be of clinical significance. There was a trend for fusidic acid to be superior against non-inflamed lesions. The fusidic acid-treated participants may have done better by applying treatment to the whole face to prevent new lesions forming. As to be expected, topical fusidic acid was associated with more skin adverse effects: 13/90 compared to 3/84. Minocycline was associated with more gastro-intestinal disturbances: 4/84 compared to 1/90.

c. Erythromycin/zinc

Stainforth 1993 evaluated a twice-daily topical application of 4% erythromycin and 1.2% zinc acetate against minocycline 50 mg twice a day in 109 participants. There was a significant reduction in lesion counts in both groups at 12 weeks compared to baseline, with good results seen after 2 weeks. The combination topical was significantly better than minocycline against both inflamed and non-inflamed lesions at the end of the 12-week treatment period (Analysis 14.1; Analysis 14.3; Analysis 14.2). However, there was no significant difference between the groups in terms of acne grade at any time point nor in the participants' self-assessment using a visual analogue scale (Analysis 14.4). The minocycline-treated participants recorded the lowest percentage reductions in inflamed and non-inflamed lesions of all the trials that presented data in this form. After 12 weeks, there was only a 23% reduction in non-inflamed lesions and 36% reduction in inflamed lesions. It is possible that the results may be biased as the authors admit that, in at least seven cases, therapy became known to the assessor during the trial. The topical treatment was associated with dryness and irritation in five participants. Four participants receiving minocycline reported transient headache, with one having symptoms suggestive of benign intracranial hypertension.

d. Benzoyl peroxide or benzoyl peroxide/erythromycin

Extended-release minocycline was compared to 5% benzoyl peroxide and 2 different combination regimens of benzoyl peroxide and erythromycin in a large, 18-week, community-based, independently-funded study in the UK (see the oxytetracycline comparison for more details). The combination treatments were (a) separate formulations of 2% erythromycin in the morning, 5% benzoyl peroxide at night; and (b) a single formulation containing 3% erythromycin and 5% benzoyl peroxide to be applied morning and night. The participants had mild to moderate acne (Ozolins 2005). The outcomes were change in inflammatory lesion count from baseline and the number of participants assessed by participants having at least

'moderate improvement' as determined by investigators and the participants themselves.

Minocycline and 5% benzoyl peroxide produced similar results, with an average of 22.3 less inflamed lesions (Analysis 15.3) and similar improvements (Analysis 15.1; Analysis 15.2). The results for the two different combination regimens were similar: a trend towards the combination treatments being more effective, which was not statistically significant (Analysis 16.1; Analysis 16.2; Analysis 16.3; Analysis 17.1; Analysis 17.2; Analysis 17.3). The numbers of adverse effects at each time point were reported. As to be expected, there were more systemic adverse effects in the minocycline group and more local irritation in the topical groups. The two erythromycin-containing regimens produced the largest reductions in the frequency and population density of viable organisms. The three topical regimens significantly lowered the frequency and population density of erythromycin-resistant propionibacteria.

7. Combination therapy

Harrison 1988 compared 50 mg minocycline twice-daily versus 50 mg doxycycline once-daily in a group of 43 participants with acne of unspecified severity, who also received separate formulations of 4% chlorhexidine and 5% benzoyl peroxide. After 12 weeks, only 34 participants remained. Unsurprisingly, because of the very small number of participants enrolled and the additional active treatments used in both groups, no significant differences were detected in any of the reductions in lesion counts: A 59% reduction in total lesion counts was seen for each group, with a 67% to 84% decrease in the number of papules and pustules (Analysis 18.1). There was some apparent discrepancy between the adverse effect data, with tolerance being reported as less than good or excellent in 7% of participants receiving doxycycline and 21% receiving minocycline. The study authors reported that four participants in the doxycycline group and three in the minocycline group experienced side-effects, but it was unclear what they were as only those designated as treatment-related were reported.

Revuz 1985 compared minocycline against placebo over 60 days in 90 participants who were also applying topical erythromycin/tretinoin gel (of unknown strength). Reductions in the number of lesions in both groups were reported, with minocycline reported as having a statistically significant greater effect against the total number of 'retentional' lesions (thought to be cysts, plus inflamed lesions), but not non-inflamed lesions. Significant reductions in the number of papules and pustules were noted with no significant differences between the two groups. 69% of participants reported good or very good response in the minocycline group compared to 57% in the placebo group (RR 1.20, 95% CI 0.84 to 1.72) (Analysis 19.1). The data for the physician-reported good/very good response was 77% versus 54% (RR 1.41, 95% CI 0.99 to 2.01) (Analysis 19.1). The latter was reported as statistically significant. Unsurprisingly, the rate of skin adverse effects was similar, although more burning was reported in the placebo group (26/34 compared to 21/39).

Smit 1978 randomised 18 participants with severe acne to either 100 mg minocycline or 100 mg doxycycline. Both groups received a topical 5% salicylic acid and 5% resorcinol preparation to be applied twice daily for the 12-week duration of the RCT. The trial did not find any difference between the two groups in the change in overall score from baseline. However, too few participants were included to infer anything about the relative effectiveness.

The 2012 update identified the abstract of a 24-week investigator-blinded RCT that compared 100 mg minocycline daily to 300 mg lymecycline for 2 weeks, followed by 150 mg for another 8 weeks in 152 participants who were also being treated with 0.1% adapalene gel once daily (Campo 2003). Most, but not all, of the RCTs included in this review found a minimal effect of minocycline (and other antibiotics) on non-inflamed lesions; however, this study used adapalene in both groups, which is active, against non-inflamed lesions. Lymecycline was reported as having a statistically significant greater reduction than minocycline in total lesion counts (67% and 77%, respectively) and non-inflamed lesions (64% versus 77%), but there was no difference in inflamed lesions or global assessments. There were however some contradictions in the abstract, so clarification is required. Data appeared to only be reported from the 122/152 evaluable participants; therefore, the study was likely not to have included sufficient numbers of participants to be able to conclude there was no difference between the groups. Further information was requested from the company, but no response was received. The treatments were reported as 'well tolerated'.

8. Minocycline versus oral isotretinoin in nodular acne

Isotretinoin is the only treatment that often cures acne after a single course. It works primarily by stopping the production of sebum. However, it is associated with severe side-effects; therefore, it is reserved for severe or refractory acne. It can also harm the foetus, so it is not used in women of childbearing age without adequate contraception.

Two open trials compared oral isotretinoin with minocycline in nodular acne; participants and investigators will always be able to tell who receives isotretinoin due to its distinctive side-effect profile.

In one study, the minocycline-treated group of 50 men also received topical azelaic acid (Gollnick 1997); the second group of 35 men were treated with isotretinoin dosed according to their weight. The authors stated that the study was randomised, but there were unequal numbers of participants in each group. Furthermore, whilst at the start of the trial the two groups were demographically comparable for age, there appeared to be other differences. Only the abstract was available for the original review, but the trial had been published in full by the update, and there were some minor differences in the reported results. The study had two phases; an initial six-month study phase followed by a second three-month maintenance phase (topical azelaic acid only in the minocycline group). The full publication notes that, "Participants in whom a very good clinical improvement was achieved prematurely, i.e. before completing the 6 months of study phase 1, were transferred early to study phase 2". This makes the findings difficult to interpret.

Very high percentage reductions in all types of lesion count were reported for both isotretinoin and the minocycline/azelaic acid combination. The authors reported a statistically significant difference in favour of oral isotretinoin against non-inflamed lesions (66% reduction from baseline vs 80%) (Analysis 20.2) and papules and pustules (88% vs 97%) after 24 weeks of

treatment (Analysis 20.3). The clinical significance of these differences is unclear. Changes in the nodule count were 100% in both groups. The investigator reported that 100% of participants in both groups improved. The speed of onset of improvement in this study with the minocycline/azelaic acid combination was rapid and equivalent to oral isotretinoin after just one month of treatment. The adverse effect rates reflected the better tolerance of minocycline/azelaic acid, which is to be expected. In the maintenance phase, 37% of participants who continued on azelaic acid (AA) but had their minocycline stopped showed marked deterioration compared to 4% in the isotretinoin group who stopped treatment. These findings warrant further investigation and a robust trial being undertaken. Because of the side-effects associated with isotretinoin, the combination would be a good option particularly in female participants with nodular acne.

The second study focused on the biochemical impact of isotretinoin, included only 24 men (Pigatto 1986), and reported few clinical outcomes. The results showed that oral isotretinoin was significantly superior to minocycline with respect to reductions in the number and diameter of nodular lesions. This study is of note because it recorded a total of 16 adverse effects in 7 of 12 minocycline-treated participants, which is a much higher rate than in any other trial. Laboratory testing was undertaken as part of the study-examined changes in the metabolism of lipids: Three participants treated with minocycline had slight but persistent abnormal elevations of alkaline phosphatase during therapy, and five had initial transient minor abnormal elevations of the liver enzymes aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT).

9. Minocycline as a maintenance therapy

The 2012 update found 1 randomised double-blind 12-week trial that evaluated minocycline as a maintenance therapy after participants with moderately-severe acne had shown 75% or greater global improvement after 12 weeks of treatment with 0.1% tazarotene gel each evening, plus 100 mg minocycline twice daily (Leyden 2006 (Part 2)). Tazarotene gel is not available in the UK. The three regimens that were compared (minocycline 100 mg twice daily, 0.1% tazarotene each evening, or a combination of the 2 regimens) were all effective at maintaining improvement over a 12-week period, and there were no statistically significant differences between the groups for the following outcomes: severity score, maintenance of a 50% or greater global improvement, maintenance of a 75% or greater global improvement, mean percentage change in inflamed lesion count or non-inflamed lesion count, or percentage of participants showing good or excellent maintenance. There was however a gradual increase in the number of inflamed lesions whilst the non-inflamed lesions continued to reduce in number. However, the trial was not powered to detect differences, and no power calculation was reported. The data suggest that the minocycline-containing regimens may be more effective at maintaining a reduction in inflamed lesions compared to tazarotene alone, and that tazarotene-containing regimens had more impact on non-inflamed lesions. Both findings are consistent with their mechanisms of action. However, further evaluation is required in a larger sample of participants before any conclusions can be drawn. All regimens were reported as being well-tolerated (Analysis 21.1; Analysis 21.2; Analysis 21.3; Analysis 21.4; Analysis 21.5; Analysis 21.6).

10. Minocycline in tetracycline recalcitrant acne

No RCTs were located that evaluated minocycline in therapy-resistant acne. The only evidence available was from five open, uncontrolled studies, which did not meet the inclusion criteria for this review because the results were considered unreliable due to the inadequacy of the study design (Becker 1974; Cullen 1978; Degreef 1983; Knaggs 1993; Rossman 1981).

Adverse effects

a) Results from the included RCTs

There were numerous differences between the RCTs in the way adverse effect data were collected, interpreted, reported, and analysed, which means that pooled estimates must be interpreted with caution. Accurate denominators could not be ascertained for many of the studies. Most trials only reported the most significant adverse effects; others did not report numbers or percentages of adverse effects. Furthermore, many trials were conducted under 'open' conditions.

Twenty-nine of the RCTs reported adverse events that they attributed to minocycline therapy; of the 1906 participants treated, 332 (17.4%) experienced 1 or more events.

Thirty-four RCTs reported the number of participants who withdrew due to adverse events; this was, in total, 79 (3.6%) out of 2143 treated.

There was a trend for minocycline to be associated with more adverse effects than placebo (RR 1.25, 95% CI 0.95 to 1.65, I^2 statistic = 24%) (Analysis 22.1.1) and higher-dose minocycline more than lower-dose (Analysis 22.1). Meta-analysis indicated that the rates of adverse effects in minocycline-treated participants were less than in those who were treated with (oxy)tetracycline (RR 0.73, 95% CI 0.53 to 1.01, I^2 statistic = 28%) (Analysis 22.1.5). However, a sensitivity analysis that removed the 4 'open'-label studies (in which the reporting could have been influenced by the participants' and investigators' knowledge of treatment assignment) removed this difference (RR 1.07, 95% CI 0.59 to 1.95, I^2 statistic = 34%) (Analysis 22.1.6). The largest study (Ozolins 2005) did not report data on overall adverse effects in a comparable format. The only other statistically significant differences identified were that minocycline-treated participants experienced fewer adverse effects than those receiving zinc, as shown in Dreno 2001 (RR 0.63, 95% CI 0.44 to 0.91) (Analysis 22.1.15). Minocycline alone or in combination with azelaic acid also produced fewer side-effects than isotretinoin, as shown in Pigatto 1986 (RR 0.60, 95% CI 0.37 to 0.97) (Analysis 22.1.21) and Gollnick 1997 (RR 0.55, 95% CI 0.35 to 0.85) (Analysis 22.1.20). The results for those adverse effects necessitating treatment withdrawal when being treated with minocycline were similar to those for all adverse effects. Minocycline was associated with more withdrawals, due to adverse effects, than placebo (risk difference (RD) 0.08, 95% CI 0.03 to 0.13, I^2 statistic = 0%) (Analysis 22.2.1) and less than (oxy)tetracycline (RD -0.03, 95% CI -0.06 to -0.00, I^2 statistic = 44%) (Analysis 22.2.8). There were no other notable differences (Analysis 22.2).

The focus of the 233-participant phase 2 study, Stewart 2006 (MP010401), was on acute vestibular adverse effects, which are hypothesised as being dose-related. The researchers defined vestibular events as one or more of the following symptoms: nausea, vomiting, dizziness, vertigo, and ringing in the ears; the symptoms being attributed to the rapid rise in serum minocycline levels with standard minocycline. The authors reported that the results of the trial indicated this was dose-dependent (10%, 24%, and 28% in the 1, 2, and 3 mg/kg minocycline groups, respectively, compared to 16% in the placebo group). These differences were non-significant statistically, although the study may not have been powered adequately. However, it is not clear whether the symptoms included in the composite measure were actually due to vestibular effects; nausea and vomiting were common symptoms. These adverse effects were more common in the first five days of treatment and in the heaviest participants. In summary, the data reported do not support the study authors conclusions that "the key benefit of this new minocycline preparation is safety", because no standard-release formulation was included as a comparison.

b) Results from other studies of adverse events

It is recognised that rare adverse effects are unlikely to occur in clinical trials involving relatively small numbers of participants with short follow-up periods. Estimates of the frequency of such events cannot be obtained by pooling data from several small trials. In addition, spontaneous report systems and case reports are not reliable sources; the number of adverse effects is uncertain because of selective reporting, and the number of participants who received the therapy overall is not known. Therefore, information on the incidence of the less common and more severe adverse effects associated with minocycline in any condition was sought from controlled studies that provided a clear indication on the numerator (i.e. the number of adverse effects) and the denominator (the number of participants treated). These studies are subject to different biases than RCTs.

The results of the 16 studies that met the inclusion criteria for the review of adverse effects are summarised in Table 3.

The notable findings of the studies were as follows.

1. FDA data on prescription rates and spontaneous reports of adverse effects estimated that rates of any adverse effect is 13 per million with doxycycline and 72 per million with minocycline. Gastro-intestinal reactions were the most common with doxycycline, whereas changes affecting the central nervous system and gastro-intestinal disturbances were more common with minocycline (Smith 2005).
2. The proportion of severe adverse effects were higher with minocycline than doxycycline (Lebrun-Vignes 2012) (29.5% of events versus 19.5%).
3. The most common adverse effects of minocycline were cutaneous disorders (42%) and neurological disorders (12.5%) (Lebrun-Vignes 2012).
4. Hypersensitivity reactions were more common with minocycline compared to doxycyline (4% versus 1.6%) (Lebrun-Vignes 2012).
5. The minocycline-associated pigmentation in rheumatoid arthritis participants seemed to increase with age (Fay 2008).
6. The incidence of adverse effects was greater in women compared to men (13.5% compared to 7.5%) (Goulden 1997).
7. The incidence of adverse effects was greater in those over the age of 35 (27% compared to 11.8%) (Goulden 1997).
8. The incidence of adverse effects did not seem to rise significantly with dose, with the exception of pigmentation (Goulden 1997).
9. There were two different types of liver damage associated with minocycline: hypersensitivity with rapid onset (usually within one month) and autoimmune hepatitis generally after a year or more of therapy (more common in women). The authors noted that they could not make any recommendations about whether or not participants should have routine liver function monitoring (Lawrenson 2000).
10. There were 51 cases of lupus (0.05% of acne cohort of 97,694 participants); of these, 24 had been exposed to minocycline (Margolis 2007). The hazard ratio (HR) for association of minocycline and lupus erythematosus (LE) was 2.64 (95% CI 1.51 to 4.66) and when adjusted for age and gender, the hazard ratio was 3.11 (95% CI 1.77 to 5.48). A strong relationship between the duration of exposure and LE was noted, but cases have still occurred with exposures of less than six months. The frequency of LE in people treated with minocycline was estimated at 8.8 cases per 100,000 person-years (Margolis 2007).
11. Antineutrophil antibody (ANA) positivity was seen in participants with acne, irrespective of exposure to minocycline. However, antineutrophil cytoplasmic antibody positivity appeared to be a serological marker for developing autoimmune disease in participants receiving minocycline (Marzo-Ortega 2007).
12. Minocycline was associated with a greater risk of lupus than controls with an OR of 4.23 (95% CI 1.03 to 42.74) (Schoonen 2010).
13. There was an 8.5 fold greater risk of lupus-like syndrome in young women currently using minocycline for acne compared with non-users or past users, and this effect is strongest for longer-term use. The absolute risk of lupus-like syndrome is 52.8 cases per 100,000 prescriptions, and minocycline increases the risk 8.5 times (95% CI 2.1 to 35) compared to other tetracyclines, which carry a risk of 1.7 (95% CI 0.4 to 8.1) (Sturkenboom 1999).
14. The adjusted odds ratio of liver dysfunction associated with exposure to minocycline compared with non-use was 2.10 (95% CI 1.30 to 3.40), and for oxytetracycline/tetracycline it was 1.46 (95% CI 0.81 to 2.64). Overall, the incidence of liver dysfunction was rare: 1.04 cases/10,000 exposed person months (EPM) for minocycline and 0.69 cases/10,000 EPM in those exposed to oxytetracycline/tetracycline (RR 1.51, 95% CI 0.63 to 3.65) (Seaman 2001).

Recommendations were as follows:

1. periodic liver function tests and ANA tests should be performed on those receiving long-term minocycline therapy (Angulo 1998; Schlienger 2000); and

2. since lupus-like syndrome is uncommon and reversible after stopping minocycline treatment, the increased risk associated with minocycline use only moderately affects the risk/benefit balance (Sturkenboom 1999).

Discussion

Summary of main results

Clinical efficacy

The 39 RCTs that were included in this updated systematic review demonstrated that minocycline is active against both inflamed and non-inflamed lesions, although there were large variations between trials in both the absolute and percentage decreases attained. Per cent reductions in lesion counts were the most frequently-used outcome measure.

The most robust data from the 6 placebo-controlled trials indicated that minocycline is more active than placebo against inflamed lesions, producing a 45.5% reduction compared to 32% after 12 weeks but with large in-group variations in response (Analysis 2.1). There is no evidence to suggest this is a clinically meaningful difference or whether participants were more satisfied with their treatment. The effect against non-inflamed lesions was smaller (14.9% versus 6.3%; no standard deviations were reported). There was no difference in the number of participants ascertained to be 'clear' or 'almost clear' at the end of 12 weeks of treatment (Analysis 2.4).

There is no robust evidence to indicate whether or not the effects of minocycline are dose-dependent; it is likely that all three of the RCTs that looked at this issue contained insufficient numbers of participants. However, one indicated that after 8 weeks of therapy, there was no difference between a 100 mg a day dose compared to 100 mg a day for 2 weeks, followed by 50 mg a day.

The most robust data from an independently-funded RCT in UK general practice (Ozolins 2005) suggested that, when used to treat facial acne, minocycline produces similar results to oxytetracycline, benzoyl peroxide, and combination treatment with erythromycin/benzoyl peroxide. Out of the nine RCTs that compared minocycline to a first-generation tetracycline, five did not find any difference in efficacy, but did not contain sufficient numbers of participants to conclude that there is no difference. The most robust study (Ozolins 2005) found minocycline had a greater effect than oxytetracycline against inflamed lesions at 12 weeks, but not 18 weeks (Analysis 5.2). Three other studies found minocycline to be superior, but all had serious flaws (Blecschmidt 1987; Cabezas 1993; Ruping 1985). Seven of the nine RCTs that compared minocycline to other second-generation tetracyclines had serious methodological flaws. None of these trials found any difference between the treatments, but all but two (Bossuyt 2003 (TETRABUK); Cunliffe 1998) were unlikely to contain sufficient numbers of participants. The former was a non-inferiority design. Minocycline was compared to three other non-tetracycline antibiotics (roxithromycin, faropenem, and josamycin) that are not licensed in the UK or U.S. As with the tetracycline RCTS, all had methodological flaws. There is some evidence to suggest that minocycline may have a more rapid onset of action than low-dose (500 mg/day) tetracycline; further evaluation is required, including the clinical significance of this.

Only three other studies were able to detect any difference between treatments; minocycline was found to have greater activity against inflammatory lesions than 2% topical fusidic acid (Darrah 1996) and oral zinc gluconate (Dreno 2001). It was also superior to zinc against non-inflamed lesions (Dreno 2001). Minocycline was found to be inferior to a topically applied combination of 4% erythromycin and 1.2% zinc against both inflamed and non-inflamed lesions (Stainforth 1993), although the mean lesion counts did not change in the minocycline group after the second week. Another finding of note that warrants further evaluation is that a minocycline/azelaic acid combination may produce good results in nodular acne.

It is now widely-accepted that tetracycline and erythromycin should be given for acne in full therapeutic doses, and yet minocycline and doxycycline are still given at lower doses (usually one half the full therapeutic dose). It is surprising that no adequate dose-response study has been done to confirm that doses of 200 mg and 100 mg are equivalent in terms of clinical efficacy. Therefore, no recommendations can be made concerning the appropriate dose of minocycline that should be used.

The efficacy of minocycline in tetracycline-recalcitrant acne cannot be confirmed or refuted as no RCT was located, and similarly, no evaluation of the rate of relapse of participants treated with minocycline was retrieved. Only three studies attempted any measure of the impact of treatment of participant quality of life (Dreno 1998 [pers comm]; Ozolins 2005; Peacock 1990). There was no indication from the trials as to whether minocycline was more acceptable to participants than other forms of acne therapy, and the five trials that monitored compliance did not report the results. It is important that some measure of compliance is included in clinical trials as differences between treatment and control groups can seriously distort the outcome, and where compliance is poor, the sample size will have to be increased to detect the true treatment effect. In the case of acne therapy, compliance and acceptability are important issues and will impact on the clinical results seen.

There is one very important issue that this review has not addressed and that is the emerging problem of antibiotic resistance in *P. acnes*. Available data suggests that up to one in four antibiotic-treated acne participants are colonised by tetracycline-resistant strains of propionibacteria (Coates 1999). The resistant strains may or may not show decreased sensitivity to minocycline (Eady 1993). However, the minimum inhibitory concentration of minocycline for all of them is within the National Committee for Clinical Laboratory Standards guidelines for sensitive strains (less than or equal to 4 mg/ml), and all could potentially be inhibited by serum levels of the drug achieved on a higher dose of 200 mg. The question therefore arises as to whether minocycline is the drug of choice when tetracycline-resistant strains are present on the skin.

Adverse effects

Prescribers should inform people that there are extremely rare cases of hypersensitivity to minocycline and tell them what signs and symptoms to look out for. If hypersensitivity occurs, it may be fatal, so medical help should be obtained immediately.

Despite the large volume of data collected, it is still not possible to produce a reliable estimate of the likelihood of experiencing an adverse effect during a course of minocycline for acne. Moreover, it is not possible to predict who might be at increased risk of a serious adverse event on the basis of age, gender, pre-existing health conditions, or dose or duration of minocycline therapy (except in the case of lupus and skin pigmentation - see below).

The most robust study that used spontaneous adverse effect reports coupled with sales data suggested that the overall rate of adverse effects is extremely low at 72 per million people treated with minocycline (0.0072%), but is higher than for doxycycline (Smith 2005). This is likely to be a gross underestimate as there is no mandate for clinicians, pharmacists, or people to report adverse effects when receiving therapy; reporting is done on a voluntary basis. The inadequacy of this system is highlighted by the fact that 332 of the 1906 (17.4%) participants receiving minocycline in the 39 included RCTs reported an adverse effect, a rate that is over 2400 times higher.

The studies do support a conclusion of an increased risk of lupus associated with minocycline that is not seen with other tetracyclines, and which increases with duration of treatment (Margolis 2007; Marzo-Ortega 2007; Schoonen 2010; Sturkenboom 1999). It should however be noted that the absolute risk is small: One study estimated it to be 52.8 cases per 100,000 prescriptions (Sturkenboom 1999). Similarly, there is an increase in the risk of liver dysfunction associated with minocycline use, but the incidence is rare: 1.04 cases/10,000 exposed person months (Seaman 2001). This would support monitoring and periodic liver function tests and ANA tests in those receiving long-term treatment.

Relating to the extended-release version of minocycline, the RCT data reported do not support the conclusions that "the key benefit of this new minocycline preparation is safety", because no standard-release formulation was included as a comparison, and the placebo-controlled trial was likely to be underpowered (Fleisch 2006a (MP010404); Fleisch 2006b (MP010405); Stewart 2006 (MP010401)).

Overall completeness and applicability of evidence

Systematic reviewing is a retrospective study, and the conclusions are therefore dependent on the primary studies that have actually been conducted, are successfully identified, and then included. In order to prevent any bias arising from the inherent observational nature of the review, a strict systematic review protocol was developed prior to the onset of the review. This was not published as a Cochrane Protocol as this was not a requirement when the review was initially undertaken.

Two authors independently assessed each study. An exhaustive search was conducted and successfully located three unpublished RCTs, Cunliffe 1998 (which has since been published) and Drake 1990 and Dreno 1998 [pers comm], all of which met the inclusion criteria for the review. It is unlikely that any publication bias existed, as the majority of the studies failed to find any differences between the comparators. And any positive study, in either direction, would probably have been widely-publicised and cited in the retrieved studies. Language bias was avoided by inclusion of any RCT regardless of language of publication.

In many cases, the individual study results were not analysed by intention-to-treat, and therefore sensitivity analysis was used to compare the results obtained from efficacy analysis, intention-to-treat, or when dropouts were treated as non-responders. In some cases where categorical outcomes were used, the results had to be dichotomised; therefore, sensitivity analyses were used to validate these assumptions by examining the effect that different cut-off points had on the overall results. In no case were these different analyses found to affect the outcome of any study. Similarly, no study that used both intention-to-treat analysis and per-protocol/efficacy analysis found any difference in outcome.

Quality of the evidence

Please see Figure 1.

The objective of this review was to evaluate the efficacy and safety of minocycline in acne vulgaris by systematically reviewing the evidence from randomised controlled trials (RCTs). The intention was to pool the results of individual trials to produce overall summary measures of effect. In practice, this was hard to do because the internal validity of most of the studies was severely compromised on account of inadequate design. As well as the use of many disparate outcome measures, there were numerous methodological differences between the retrieved studies that could not be reconciled. This meant that pooling was not appropriate. In addition, the methodological reporting in many of the trial reports was poor, and as a result, the legitimacy of their conclusions could not be properly evaluated.

Only 1 trial conclusively stated funding sources independent from any sponsor (Ozolins 2005): 28 cited industry-sponsorship, and 10 made no declaration.

Most of the trialists made some attempt to show that the different treatment groups were comparable at baseline. However, a variety of criteria were used, and some of them were of questionable validity in this context (e.g. height, age of onset of acne). The following criteria were used by a majority of trialists: age, gender, lesion count, or lesion score. In addition, a minority of trialists used weight, duration of acne, and acne grade/severity.

Most trialists specified how long previous acne treatments or other therapies that might have affected acne severity, should have been stopped prior to entry in the trial. However, there was absolutely no consensus on how long this should be. The specified wash-out period for antibiotics was as short as 48 hours (Revuz 1985) and up to 4 months (Hubbell 1982). For retinoids and hormonal therapy, wash-out periods varied from 14 days (Peacock 1990) to 1 year (Darrah 1996). Some studies used similar wash-out periods for oral and topical acne therapy (Samuelson 1985; Sheehan-Dare 1989); others used shorter periods for topical therapy (Drake 1990; Lorette 1994). Approximately a third of reports mentioned that the trial was not conducted during the summer to avoid the beneficial/camouflaging effects of ultraviolet light.

Concomitant therapy that might affect acne severity was specifically mentioned as being disallowed in nine trials; three

others mentioned that no prescribed topical therapy was permitted. It was unclear in the majority of cases whether participants taking potentially interfering medications were excluded from the per-protocol analysis or continued to be included in the study. It was not usually possible to tell whether concomitant medications had been recorded. Skin hygiene regimens were standardised, usually by the provision of a simple non-mediated soap, in seven trials. Two trials (Dreno 1998 [pers comm]; Ozolins 2005) additionally provided a moisturiser. Compliance is a significant problem in acne, and only a minority of the authors indicated what instructions were given to participants. Only five trials apparently included some form of compliance monitoring. Of the studies for which details were available, in one instance, medication was taken under supervision (Samuelson 1985); two studies counted unused medication (Cunliffe 1998; Peacock 1990); and two studies used a participant-completed diary card (Ozolins 2005; Stainforth 1993).

In some cases, minocycline was taken on an empty stomach, in others before, with, or after a meal. Six reports mentioned that antacids were among the non-permitted medications, and only four specified exclusion of participants taking divalent metal ions (three iron and one zinc).

Potential biases in the review process

The limitations of this review stemmed from the methodological insufficiencies and the subsequent heterogeneity in the primary studies, and the inadequacies of the reported data. The studies generally included insufficient numbers of participants, and the majority were only of 12 weeks duration, so assumptions could not be made about the impact of longer-term therapy. Although additional data were obtained from several authors, the manufacturers of minocycline, who sponsored many of the studies, failed to provide any of the requested information, despite an initial agreement (Brock 1998 [pers comm]). Subgroup analysis was also impossible due to the poor characterisation of participant groups and lack of adequate outcome data. It was also not possible to examine the impact of study design on the results, particularly with reference to the degree of blinding, as many studies were inconclusive.

Authors' conclusions

Implications for practice

The additional 12 RCTs that were located for the update have not changed the original conclusions about the clinical efficacy of minocycline. The 39 RCTs now included in this review do not provide any evidence to support the first-line use of minocycline in the treatment of acne. Although it has been shown to be an effective treatment for moderate to moderately-severe acne vulgaris at a dose of 100 mg per day, no study has conclusively shown any important clinical difference between minocycline and other commonly-used therapies. Meta-analysis indicated that minocycline may have a more rapid onset of action than tetracycline or oxytetracycline, but overall efficacy in the longer-term is similar. There is no evidence that minocycline is more effective in acne resistant to other therapies, or that it has a more prolonged effect. Insufficient information was found to make any recommendations concerning the appropriate dose that should be used.

The relative safeties of the tetracyclines have still not been adequately determined, and little further information could be derived from the included RCTs because of their inherent inability to detect rare events. Recent reviews of case reports and case series (Gough 1996; Shapiro 1997) suggest that minocycline therapy for acne may be associated with a broader spectrum and a higher incidence of severe adverse effects than other tetracyclines. The lack of a denominator in nearly all of the studies means that the risks for minocycline compared to other tetracyclines cannot be compared. Only in the case of lupus-like syndrome has it been conclusively shown that acne participants treated with minocycline are at a significantly greater risk than those given tetracycline or no treatment (Sturkenboom 1999). The risk of developing pigmentation (which can be irreversible) and lupus-like syndrome increases with cumulative dose.

Implications for research

The poor methodological quality of the acne trials was highlighted in the original version of this review. This was also the case for many of the trials identified in this update, with a few notable exceptions. In order to enable comparison of acne treatment, either directly or indirectly through modelling, an agreed set of core outcome measures should be developed. Until this has been done, trialists are encouraged to include lesion counts and quality of life as outcome measures.

It is surprising that very basic information about acne therapy with the tetracycline group of antibiotics is still unavailable.

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Contributions of authors

SEG was the contact person with the editorial base; SEG coordinated contributions from the co-authors and wrote the final draft of the review.
SEG and CB screened papers against eligibility criteria.
SEG obtained data on ongoing and unpublished studies.
SEG and CB appraised the quality of papers.
SEG and CB extracted data for the review and sought additional information about papers.
SEG and CB entered data into RevMan.
SEG analysed and interpreted data.
SEG and EAE worked on the methods sections.
SEG and EAE checked the manuscript for inconsistencies.
SEG, CP, and JN drafted the clinical sections of the background and responded to the clinical comments of the referees.
SEG responded to the methodology and statistics comments of the referees.
KT was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes were relevant to consumers.
SEG is the guarantor of the update.

Declarations of interest

One of the reviewers (EAE) has previously received research funds from one of the manufacturers of minocycline, and she was the co-author of published studies on minocycline, including the following included study: Ozolins M, Eady EA, Avery AJ, Cunliffe PWJ, Wan Po PAL, O'Neill PC, et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet 2004;364(9452):2188-95.

Associate Professor Catalin Popescu has received honoraria for speaking at Astellas Pharma-sponsered meetings and symposia. Astellas Pharma is the producer of Unidox (doxycycline) tablets, but none of Associate Professor Popescu's talks and none of these meetings were about Unidox. Unidox is not actively promoted by Astellas, as there are lots of generic doxycycline products. Moreover, minocycline has never been available in Romania, which is the country in which Associate Professor Popescu works.

Differences between protocol and review

This review was first published in 2000 when there was no requirement to publish a Cochrane Protocol. It was however conducted according to a prespecified systematic review protocol according to best methodological practice. There have been no subsequent amendments to this protocol.

For the 2012 update, an additional 12 RCTs were included, and 16 studies were reviewed to evaluate adverse effects. Changes were made to most sections of the review to reflect the impact of the included studies. Two additional tables were added: Table 2 documented the relative costs of oral antibiotics for acne (BNF April 2012), and Table 3 summarised the included adverse effect studies.

Published notes

Characteristics of studies

Characteristics of included studies

Blecschmidt 1987

Methods	• This was an open-label RCT in a hospital setting (7 centres). • The duration of the trial was 12 to 20 weeks. • Randomisation was by 'list'. • Industrial support came from Cyanamid. • The use of UV control was not stated. • Oral and topical treatment was withdrawn 28 days prior to the trial. • Evaluation was at 0, 2, 4, 8, 12, 16, and 20 weeks. • The area evaluated was unspecified (- face?). • The assessor was not specified. • A per-protocol analysis was used.
Participants	194 participants were enrolled. 104 participants were randomised in the minocycline group, and 90 participants were randomised in the oxytetracycline group. (For 43 there were no data.) There were at least 4 dropouts. The mean age was 20.9 +/- 5 (range = 13 to 45). Recruitment was fulfilled by hospital out-patients. **Inclusion criteria of the trial** • Minimum of Cook grade 4 papulopustular acne (Cook 1979) with 10 to 20 PA, PU over half the face, or both **Exclusion criteria of the trial** • SENS, PREG, BF, ACID, IRON, or vertigo
Interventions	• Minocycline 50 mg twice a day • Oxytetracycline 250 mg 4 times a day for 4 weeks then 250 mg bd Concomitant therapy: not permitted Appearance: standard Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Grade: Cook and Centner (0 to 8) (Cook 1979) 2. Number of participants improving by at least 2 grades at each time point 3. Adverse drug reactions as reported by the participants
Notes	Country: Germany Language: German Review version: 2002 The trial report was inadequate for 'Risk of bias' assessment. The outcome measures were inappropriate. The dose reduction was not adhered to in 46 participants. There was variable duration of treatment. There was unclear dropout reporting. No further information was obtainable.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred according to a prepared randomisation schedule.
Allocation concealment (selection bias)	High risk	This was not used.
Blinding (performance bias and detection bias)	High risk	There was no blinding.
Incomplete outcome data (attrition bias)	High risk	The number of dropouts in each group was unclear; 43 participants were not included in the efficacy analysis. There were 18 dropouts in the minocycline group, and 23 in the oxytetracycline group were treated for only 12 weeks because of the side-effects and low compliance. 6 participants were lost to follow up: 6 dropped out due to unspecified treatment, and 31 dropped out due to the use of topical treatment.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Bossuyt 2003 (TETRABUK)

Methods	• This was an observer-blinded RCT in a multicentre/multicountry setting. • The duration of the trial was 12 weeks. • Randomisation was "balanced by centre and by block". • Industrial support and funding came from the Galderma organisation. • The use of UV control was not stated. • All oral and topical treatment that had been used for acne was stopped 4 weeks prior to the start of the trial. • Evaluation was at 0, 4, 8, and 12 weeks. • The area evaluated was the face (including the forehead, cheeks, and chin). • The assessor was not specified. • The method of statistical analysis used was non-parametric for NIL; the median of the difference between treatments was calculated, and 2-tailed 95% confidence intervals were calculated; an intention-to-treat analysis was undertaken using the method of last observation carried forward for missing data. Safety was evaluated for all participants who took at least 1 dose.
Participants	136 participants were enrolled. 68 participants were randomised in the minocycline group, and 66 participants were randomised in the lymecycline group. There were 30 dropouts, plus 2 were screened but not treated. The mean age was 18.6 (range = 12 to 29). Recruitment was fulfilled by hospital out-patients. Power calculation: To demonstrate the non-inferiority of lymecycline compared to minocycline - 80% power, based on a 1-tailed alpha risk of 0.025, the difference of at most 15% in the reduction in ILC - 64 participants per group would be required. There was baseline comparability for demographic data and baseline severity. **Inclusion criteria of the trial** • 15 to 120 IL including a maximum of 2 nodules (diameter > 1 cm), </= 60 NIL, Leeds 1 to 5, OC but for more than 3 months continuous prior to study or 12 months for cyproterone acetate, 12 to 30 years of age **Exclusion criteria of the trial** • BF, pregnancy, acne conglobata, acne fulminans, secondary acne, topical acne preparations, topical anti-inflammatories on the face, systemic anti-inflammatory, systemic antibiotics (except short penicillin courses during the previous 4 weeks), systemic retinoids in the previous 6 months, known renal or hepatic disease, known or suspected allergy to tetracyclines, known or suspected systemic lupus erythematosus

Interventions	• Minocycline 100 mg - extended-release once daily • Lymecycline 300 mg once daily No other antiacne/anti-inflammatory, topical, oral, or systemic antibiotics, with the exception of short penicillin courses; corticosteroids; or any other treatment likely to interfere with tetracyclines were allowed. Appearance: standard Instructions: taken before, during, or after meals at the same time of day Skin hygiene: not specified - cosmetics were allowed but listed as concomitant Empty stomach: no Compliance: not reported
Outcomes	Outcomes of the trial 1. ILC (PA, PU, NOD) and NILC (Cc, Co) of the face, including the forehead, cheeks, and chin 2. Grade: Leeds 0 to 10 3. Overall improvement (5-point scale) as rated by the assessor 4. Overall improvement (5-point scale) as rated by the participant 5. Mean per cent reduction in IL at week 12 in those participants completing the study as planned (per-protocol) (primary outcome) 6. Adverse drug reactions at each visit 7. Global tolerance (3-point scale) 8. Pharmacoeconomic analysis on ITT population at 12 weeks
Notes	Country: UK and Belgium Language: English Review version: 2012 There were discrepancies in the reporting of the participant numbers: 136 enrolled, 2 were not treated, 66 were assigned to lymecycline, and 68 were assigned to minocycline, so the total number was 134. Per-protocol figures stated in the tables (42 minocycline and 44 lymecycline) did not match the numbers of withdrawals (16 and 14, respectively).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 131): "Randomization was balanced by center and by block." Comment: This was unclear; it was stated to be randomised, but no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear. No details were given.
Blinding (performance bias and detection bias)	Unclear risk	This was probably done as the study is described as "investigator masked", but no details were given.
Incomplete outcome data (attrition bias)	High risk	136 participants enrolled: 2 were not treated, 66 were assigned to lymecycline, 68 were assigned to minocycline, so the total number was 134 (Table 3 page 132). Per-protocol figures stated in the tables (42 minocycline and 44 lymecycline) did not match the number of withdrawals (16 and 14, respectively, Table II). The text stated that 56 lymecycline and 53 minocycline participants were evaluable for the per-protocol efficacy analysis (total n = 109) (number of inflammatory lesions, see statistical methods, page 131). This does not match the number of dropouts in table II, which was 14 lymecycline participants and 16 minocycline participants, so the total number of participants left was 130, or the total number of participants in table 3 was 86 (44 lymecycline participants and 42 lymecycline participants).
Selective reporting (reporting bias)	Low risk	All outcomes were reported on: inflammatory lesions count, assessor-rated overall improvement, participant-rated overall improvement, adverse drug reactions, tolerance, and economics at 12 weeks.

Cabezas 1993

Methods	• This was a double-blind RCT comparing minocycline, tetracycline, and placebo. • The duration of the trial was 45 days. • The method of randomisation was not stated. • Any industrial support was not stated. • The use of UV control was not stated. • It was not stated whether all previous oral and topical treatment was stopped prior to the start of the trial. • Evaluation was at days 0, 15, 30, and 45. • The area evaluated was unspecified. • The assessor was a dermatologist.
Participants	80 participants were enrolled. 28 participants were randomised in the minocycline group, 27 participants were randomised in the tetracycline group, and 25 participants were randomised in the placebo group. No dropouts were stated. Recruitment was fulfilled by students using the medical service at the University of Chile. **Inclusion criteria of the trial** • Mild to moderate inflammatory acne **Exclusion criteria of the trial** • Recent acne treatment, ingestion of acne-genic drugs, drug allergies, concomitant illness, or chronic disease
Interventions	• Minocycline 50 mg twice a day • Tetracycline 250 mg twice a day • Placebo twice daily All were identical capsules. Concomitant therapy: none Appearance: identical Instructions: none Skin hygiene: no details Empty stomach: no details Compliance: no details
Outcomes	**Outcomes of the trial** 1. Grade: not used 2. Number of papules, pustules, and summary of lesions (means and percentages) at each checkpoint (0, 15, 30, and 45 days) (primary outcome) 3. Adverse drug reactions at each checkpoint (0, 15, 30, and 45 days)
Notes	Country: Chile, participants of the student medical service of the University of Chile Language: Spanish Review version: 2012 Additional information was sought from the authors, but it was not obtained.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	There were no details; it was only stated to be 'double blind'.
Allocation concealment (selection bias)	High risk	No allocation concealment was employed.
Blinding (performance bias and detection bias)	Low risk	Administation of the medicines was carried out under the following conditions: Packets of medicine were coded using a key. The dermatologist, who did not know the contents of the packets or the coding key, gave the participant 2 packets of pills in the first consultation; the order of delivery was determined by the numerical key on the packaging. It was unclear if outcome assessors were blinded.
Incomplete outcome data (attrition bias)	High risk	No details were given about the dropouts. There was no apparent dropout of any participants.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Campo 2003

Methods	• This was an investigator-blinded, parallel RCT in a multicentre setting. • The duration of the trial was 24 weeks. • The method of randomisation was not stated. • Any industrial support was not specified. • The use of UV control was not stated. • It was not stated whether all previous oral and topical treatment was stopped prior to the start of the trial. • Evaluation was at baseline and 24 weeks. • The area evaluated was unspecified. • The assessor was not specified. • A per-protocol analysis was used.
Participants	152 participants were enrolled. 58 participants were randomised in the minocycline group, and 64 participants were randomised in the lymecycline group. There were 30 dropouts. The ages of the participants were not specified. It was not stated where participants were recruited from. **Inclusion criteria of the trial** • Not specified **Exclusion criteria of the trial** • Not specified
Interventions	• Minocycline 100 mg per day for 24 weeks • Lymecycline 300 mg per day for 2 weeks followed by 150 mg per day for 22 weeks Concomitant therapy: adapalene gel 0.1% once daily Appearance: not specified Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. IL count, NIL count, and TLC 2. Per cent reduction in lesion counts from baseline 3. Adverse drug reactions (tolerance described but not reported in detail) 4. Baseline and follow-up visits up to 24 weeks 5. Local cutaneous tolerance and adverse events
Notes	Country: Colombia Language: English Review version: 2012 Only the abstract was available. Galderma Columbia were contacted for more information, but there was no response. The time points for the assessment of outcomes were unclear.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details were given; it was stated to be randomised.
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding (performance bias and detection bias)	Unclear risk	No details were given; it was stated to be investigator-blinded.
Incomplete outcome data (attrition bias)	High risk	152 participants were recruited: 122 were evaluable. No further details were given.
Selective reporting (reporting bias)	Unclear risk	Outcomes were the mean number of total inflammatory lesions and mean number of lesions at each time point. Both were reported.

Cullen 1976

Methods	• This was a double-blind RCT in a private practice setting. • The duration of the trial was 18 weeks. • The method of randomisation was not stated. • Any industrial support was not specified. • UV control was conducted in the fall and the winter. • All previous oral treatment for acne was stopped 30 days prior to the start of the trial. It was not stated whether topical treatment was stopped. • Evaluation was at 0, 2, 4, 6, 8, 12, 14, 16, and 18 weeks. • Assessments were done on the right side of the face. • There was a single assessor for each participant. • A per-protocol analysis was used.
Participants	100 participants were enrolled. 50 participants were randomised in the minocycline group, and 50 participants were randomised in the tetracycline group. There were 8 (16%) dropouts in the minocycline group, and 10 (20%) in the tetracycline group. The mean age was 20 (range = 14 to 31). Recruitment was fulfilled by students at a private dermatology clinic. **Inclusion criteria of the trial** • Pillsbury grade II, III, or IV - minimum of 30 lesions on the right side of the face **Exclusion criteria of the trial** • ILL, MDR, SENS, PREG, or BF
Interventions	• Minocycline 50 mg twice a day • Tetracycline 250 mg twice a day Concomitant therapy: not permitted Appearance: identical Instructions: empty stomach Skin hygiene: non-medicated soap Empty stomach: yes Compliance: not specified
Outcomes	**Outcomes of the trial** 1. NIL count, PA count, PU count, and cysts 2. Per cent reduction in lesion counts from baseline (primary outcome) 3. Overall evaluation (satisfactory/unsatisfactory) 4. Participant and doctor improvement evaluation (4-point scale) 5. Adverse drug reactions
Notes	Country: United States Language: English Review version: 2002 The assessment intervals were variable. There was a contradiction in terms of the numbers of participants completing the trial. 2 participants with acne conglobata were included. There was no statistical analysis of the results.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated as 'random distribution' and 'random assignment'. There were no further details.
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding (performance bias and detection bias)	Low risk	Quote (page 1209): "Neither participant nor physician knew the identity of the medication dispensed." Comment: It was stated as double-blind. There were identical medications, which were coded, and the identity of the medication was only revealed at the end of the study. (All lesion counts and evaluations were made only by a senior trialist.)
Incomplete outcome data (attrition bias)	Low risk	3/100 participants dropped out; reasons were given. This was unlikely to introduce bias.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Cunliffe 1998

Methods	• This was a double-blind, double-dummy RCT in a hospital setting (5 centres). • Randomisation was by balanced treatment by centre and blocks of 4. • Allocation was by sealed envelopes. • The duration of the trial was 12 weeks. • Industrial support came from Galderma, France. • UV control was used. • All previous oral and topical treatment for acne was stopped 4 weeks prior to the start of the trial. • Evaluation was at 0, 4, 8, and 12 weeks. • Assessments were done on the right side of the face, forehead, cheeks, and chin. • There was a single assessor. • Per-protocol and ITT analyses were used.
Participants	144 participants were enrolled. 73 participants were randomised in the minocycline group, and 71 participants were randomised in the lymecycline group. There were 14 (20%) dropouts in the minocycline group, and 15 (21%) in the lymecycline group. The mean age was 19.0 (range = 12 to 32). Recruitment was fulfilled by hospital out-patients. Inclusion criteria of the trial • Moderately-severe, 15 to 120 IL (facial) with a maximum of 2 NOD (diameter > 1 cm) and fewer than 60 NIL, severity grade 1 to 5 Leeds (Burke 1984), 12 to 30 years, use of contraceptive methods for women throughout the study and post-study for 1 month Exclusion criteria of the trial • Acne conglobata, fulminans or secondary; isotretinoin within 6 months; concomitant retinoids; anticoagulants; ACID; IRON; hepatic enzyme inducers; corticosteroids; renal or hepatic disease; SENS; or beard or moustache

Interventions	• Minocycline 100 mg once-daily for 2 weeks then 100 mg on alternate days • Lymecycline 150 mg bd for 2 weeks then 150 mg od Concomitant therapy: not permitted Appearance: double-dummy Instructions: avoid extensive exposure to sun/UV; ingest with sufficient liquid; avoid concomitant dairy products, iron, and calcium; antacids within 2 hours prior- or post-caps Skin hygiene: Cetaphil cleansing lotion Empty stomach: no Compliance: capsule count at each visit
Outcomes	**Outcomes of the trial** 1. ILC (PA, PU, and NOD) and NILC (Cc, Co) 2. Grade: Leeds 0 to 8 modified (Burke 1984) 3. Change in ILC from baseline to week 12 (primary outcome) 4. Lesion counts transformed to per cent reduction from baseline and categorised by Mills and Kligman scale: > 75% = excellent, 50% to 75% = good, 25% to 50% = fair, < 25% = poor 5. Participant and assessor global improvement at week 12 (-1 to 3) 6. Adverse events: numbers of participants and numbers of events obtained by direct questioning and doctor observation 7. Participant and physician global tolerance assessment (-1 to 1)
Notes	Country: UK and France Language: English Review version: 2002 Power calculation: In order to demonstrate with 80% probability using a 2-sided test performed at the 0.05 significance level that the true response was within +/- 15% in respect of the percentage reduction in the ILC from baseline to the end of treatment, 144 participants would be needed (67 evaluable per group).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The following was stated: "Within each center participants were assigned to one of the 2 treatment groups using a randomisation procedure by blocks of 4 assuring therefore that treatments are balanced every 4 consecutive participants."
Allocation concealment (selection bias)	Low risk	The identification of each participant's treatment was inserted in a sealed envelope provided by the sponsor and retained by the investigator. In an emergency, the investigator had access to the code of the concerned participant. In practice, no such event occurred.
Blinding (performance bias and detection bias)	Low risk	Quote (page 2): "A double-dummy technique involving administration of placebo minocycline capsules with lymecycline and placebo lymecycline capsules with minocycline was employed to ensure the blinding of the study." Comment: It was stated as double-blind. Participants were blinded to treatment type by use of a placebo.
Incomplete outcome data (attrition bias)	Low risk	Reasons for dropouts were reported, and results were reported as ITT and per-protocol.
Selective reporting (reporting bias)	Low risk	All outcomes were reported at each time point as planned. There was access to the trial report.

Darrah 1996

Methods	• This was an open-label RCT in a general practice setting (38 centres). • Randomisation was computer-generated in balanced blocks of 4 participants. • The duration of the trial was 8 weeks. • Industrial support came from Leo pharmaceuticals. • UV control was used. • All previous oral antibiotics were stopped 4 weeks prior to the start of the trial. All previous topical antibacterials were stopped 2 weeks prior to the start of the trial. • Evaluation was at 0, 2, 4, 6, and 8 weeks. • The area evaluated was the right half of the face. • The assessor was not specified. • Per-protocol and ITT analyses were used.
Participants	188 participants were enrolled. 93 participants were randomised in the minocycline group, and 95 participants were randomised in the fusidic acid group. There were 19 (20%) dropouts in the minocycline group, and 18 (19%) dropouts in the fusidic acid group. The mean age was 17.8 (range = 11 to 29). Recruitment was fulfilled through general practice. Groups were matched for age, gender, duration of acne, and previous treatment. **Inclusion criteria of the trial** • Age 12 to 25, acne of a minimum of 3 months duration • Mild to moderate facial acne vulgaris (mild: 5 to 20 PA, PU, or both; moderate: 21 to 50 PA, PU, or both > 5 mm in diameter on the right side of the face) **Exclusion criteria of the trial** • Women not using an adequate contraception, severe acne, presence of cysts or nodules, established or suspected dermatological facial disease, UV treatment in the past 4 weeks, systemic retinoid/hormone prep/corticosteroids in previous 52 weeks, PREG, BF, or SENS
Interventions	• Minocycline 50 mg twice-daily • Fusidic acid lotion 2% topically applied twice-daily Concomitant therapy: not permitted Appearance: standard Instructions: apply to acne-affected area after washing with provided soap Skin hygiene: non-medicated soap Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. PA count, PU count, NIL count, and TLC on right side of the face 2. Overall response as assessed by the investigator (very good, good, average, poor, or very poor) 3. Successful treatment defined as the number of participants attaining > 40% reduction in any lesion count (primary outcome) 4. Adverse events reported by the participants or noted events, observed or reported (spontaneous or open-questioned) 5. Observation of skin and recording of uncharacteristic changes 6. Microbiological evaluation: week 0 and week 8 anaerobic culture. Standard disc diffusion to test *P. acnes* susceptibility to fusidic acid, minocycline, erythromycin, and clindamycin. Bacteriological treatment: positive culture at baseline but negative at week 8 7. Face: hairline and jawline excluding ear and neck

Notes	Country: UK Language: English Review version: 2002 Power calculation: In order to demonstrate with 80% probability that the 95% confidence interval (CI) of the true response was within +/- 15% in respect of the percentage of participants achieving at least a 40% reduction in the number of acne lesions from baseline to the end of treatment, 150 participants would be needed (75 per group). The primary outcome measure was inappropriate. Lotion was applied to the acne-affected area only. There were 38 centres, but no reporting of inter-assessor variability. The full trial report was made available by the manufacturer. Adverse effects were reported in 84 minocycline participants and 90 fusidic acid participants. This was a well-conducted study.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred according to a computer-generated, random numbers table in balanced blocks of 4. Each block of 4 treatments contained 2 treatments with fusidic acid and 2 with minocycline.
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding (performance bias and detection bias)	High risk	This was not used - open-label trial.
Incomplete outcome data (attrition bias)	Low risk	Reasons for the dropouts were described in full (in the results on page 101).
Selective reporting (reporting bias)	Low risk	The outcomes described were as follows: • number of participants attaining > 40% reduction in any lesion count; • adverse events reported by the participants, or noted events, observed or reported (spontaneous or open-questioned); and • observation of skin and recording of uncharacteristic changes. These were reported adequately in the Results. Microbiological evaluation (culture for *P. acnes*) was reported in the results, but was described in the Discussion (but not for each treatment group at each time point). There was access to the full trial report.

Drake 1990

Methods	• This was a double-blind, double-dummy RCT in a university clinic setting. • Randomisation was by list - separate male and female. • The duration of the trial was 12 weeks. • Industrial support came from Upjohn. • The use of UV control was not stated. • All previous oral antibiotics were stopped 30 days prior to the start of the trial. All previous topical treatments for acne were stopped 14 days prior to the start of the trial. • Evaluation was at 0, 3, 6, 9, and 12 weeks. • The area evaluated was the face and jawline. • The assessor was not specified. • The statistical analysis used a per-protocol analysis. Baseline differences were tested using the 'analysis of variance' technique. The following statistical tests were used: t-tests for between groups, paired t-test for within-group changes, and Chi² test for categorical variables.

Participants	74 participants were enrolled. The number of randomised participants was not specified. There were 22 (30%) dropouts (allocation unknown). Baseline comparability of groups: demographics and baseline variables. The age range was 14 to 35. Recruitment was fulfilled through a university clinic. **Inclusion criteria of the trial** • Moderate to severe acne vulgaris (15 to 70 PA/PU with < 6 nodulo-cystic lesions) • Age 14 to 35 **Exclusion criteria of the trial** • SENS (tet/clin), PREG, BF, ACID, VERT, severe renal disease, oral steroid/androgenic drug within 30 days of the start of the trial, women not taking adequate contraceptive measures, or history of chronic bowel disease or frequent periodic diarrhoea
Interventions	• Minocycline 50 mg bd • Clindamycin phosphate 1% topical gel bd Concomitant therapy: not permitted Appearance: double-dummy Instructions: wash face apply gel morning/evening Skin hygiene: non-medicated soap wash face morning and evening Empty stomach: not specified Compliance: not specified Duration of therapy: unclear - at least 6 weeks to be included in the analyses
Outcomes	**Outcomes of the trial** 1. PA count, PU count, NOD count, Cc count, and Co count 2. Grade: Cook (0 to 8) (Cook 1979) 3. Mean change in lesion count from baseline (primary outcome) 4. Skin tolerance: dryness, oiliness, erythema, burning, and itching - mild, moderate, or severe 5. Adverse drug reactions as reported by the participants (assessed at the following time points: baseline; 3, 6, 9, and 12 weeks)
Notes	Country: United States Language: English Review version: 2002 Unpublished data were only available in the form of a technical report. There were no details of the number of participants randomised to each group, or dropouts. The results were only presented graphically with no measures of dispersion. The manufacturers were unable to supply further details about the unpublished data. The duration of therapy was unclear; each participant needed at least 6 weeks of therapy to be included in the analysis. The numbers of participants allocated to each group or dropouts in each group, were not reported.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was described as randomised. No detail was given about the generation of the sequence other than that "separate randomisation lists for males and females were used to assure that there were equal numbers of participants of each sex." (Page 3)
Allocation concealment (selection bias)	Unclear risk	This was unclear. No details were given.
Blinding (performance bias and detection bias)	Low risk	It was stated to be double-blind (abstract), but no details were given. A double-dummy was used.
Incomplete outcome data (attrition bias)	High risk	Quote (page 4): "Of the 74 participants that enrolled into this study, 52 were deemed evaluable for efficacy analysis; the other 22 participants did not complete at least 6 weeks of treatment." Comment: No reasons were given for the discontinuation other than that 4 participants withdrew due to adverse effects (reasons given: vaginitis in 2 receiving clindamycin, gastro-intestinal distress in 1 receiving minocycline, and another minocycline participant developed a rash and abdominal distress).
Selective reporting (reporting bias)	Low risk	All outcomes were reported at each time point, but most outcomes were reported graphically.

Dreno 1998 [pers comm]

Methods	• This was a double-blind RCT in a hospital/clinic setting (45 centres). • The duration of the trial was 8 weeks. • The method of randomisation was not stated. • Industrial support came from Wyeth-Lederle. • UV control was used. • The period of time in which previous treatment was stopped prior to the start of the trial was as follows: 1 month for oral antibiotics; 15 days for topical treatments; 3 months for Dianette™ or isotretinoin. • Evaluation was at days 0, 15, 30, and 60. • The area evaluated was the whole face. • Per-protocol and ITT analyses were used.
Participants	325 participants were enrolled. 169 participants were randomised in the constant-dose group, and 156 participants were randomised in the reducing-dose group. ITT: 160/147 There were 59 (35%) dropouts in the constant dose group, and 52 (33%) in the reducing dose group. The mean age was 19.54 +/- 4.58 (range = 12 to 41). Recruitment was fulfilled through hospitals and clinics. **Inclusion criteria of the trial** • 20 or more IL on face • 13 to 30 years **Exclusion criteria of the trial** • Nodulo-cystic acne, beard or moustache, weight < 40 kg, SENS, OC taken for less than 3 months, UV exposure
Interventions	• Minocycline 100 mg od • Minocycline 100 mg od for 12 days then 50 mg od Concomitant therapy: not permitted Appearance: identical Instructions: with breakfast but not with milk Skin hygiene: non-medicated soap and moisturiser Empty stomach: no (during breakfast but not with milk) Compliance: monitored
Outcomes	**Outcomes of the trial** 1. NIL, IL, and TL count 2. Grade: ECLA 3. Assessor global improvement (0 to 5) 4. Participant (100 cm VAS) global efficacy, importance of acne, impact of acne on relationships/sexual relationships/physical appearance 5. Reduction in lesion counts from baseline/ECLA (primary outcome) 6. Adverse drug reactions as reported by the participants
Notes	Country: France Language: not published Review version: 2002 The full trial report of the results section was provided by the lead investigator.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated to be randomised, but the details supplied by the investigator did not clarify the method used.
Allocation concealment (selection bias)	Unclear risk	This was unclear. No details were given.
Blinding (performance bias and detection bias)	Low risk	It was stated to be double-blind; it was unclear how this was achieved. Medications were identical in appearance.
Incomplete outcome data (attrition bias)	High risk	The dropouts were as follows: 59/169 participants on a constant dose and 52/156 on a reducing dose. The reasons for dropout were unclear. Although dropouts were evenly distributed between the groups, the dropout rate was high.
Selective reporting (reporting bias)	Unclear risk	This was unclear; insufficient data were available. There was potential for large inter-assessor variability.

Dreno 2001

Methods	• This was a double-blind RCT in a multicentre (56 centres: 43 private dermatologists, 3 care units, and 10 hospital dermatologists) setting. • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • Industrial support came from Labcatal Pharmaceuticals (manufacturers of zinc gluconate). • UV control was undertaken in the autumn and winter months; participants were asked to avoid exposure to sunlight/UV during this time. • For details on the time frame for when oral and topical acne treatments were stopped prior to the start of the trial, see the section on exclusion criteria. • Evaluation was at days 30, 60, and 90. • The area evaluated was the entire face. • The assessor was trained in the ECLA, but there were no details of standardisation. • The following statistical analyses were undertaken: Logistic regression analysis was used to identify clinical response criteria in terms of successes/failures within each group. Criteria were age, gender, age at onset of acne, history of acne, existence of an adverse event during the first 30 days, baseline papule/pustule, and comedone counts. An intention-to-treat analysis was used. • To calculate the number of participants that had to be included in the study to ensure that any findings had not occurred by chance, it was assumed that (1) the clinical success rate in the reference group would be 60%; the method of statistical analysis would be 15% equivalence hypothesis with 1-tailed testing. It was assumed that the chance of a type I error was 5% and a type II error was 20%. This led to a total of 264 and therefore 150 per group adopted as a precautionary measure.

Participants	332 participants were enrolled. 169 participants were randomised in the minocycline group, and 163 participants were randomised in the zinc group. There were 44 (13%) dropouts (24 in the minocycline group and 20 in the zinc group). Age: 19.2 mean range Recruitment was fulfilled through private dermatologists, care units, and hospitals. Baseline comparability of groups tested for age, gender, family history of acne, age at onset, use of concomitant treatment, Oc, Cc, PA, PU, previous topical or systemic use. Minocycline was previously prescribed for 30% of participants in the minocycline group and 19% in the zinc group. **Inclusion criteria of the trial** • >/= 12 years of age, inflammatory acne vulgaris >/= 20 IL on the face, and no nodules or cysts • Participants of childbearing age had to be on oral contraception except Diane™ or Dianette™ **Exclusion criteria of the trial** • Less than 2 weeks topical treatment (vitamin A, topical antibiotics, benzoyl peroxide, azelaic acid); less than 1 month of systemic tetracyclines, cyproterone acetate, or zinc salts; less than 2 months of oral isotretinoin; treatments potentially inducing acne during the month prior to inclusion; individuals on prolonged treatment likely to interfere with the metabolism of zinc or minocycline (antacids, iron or calcium, dietary); participants taking zinc for therapeutic purposes other than acne
Interventions	• Minocycline 100 mg once daily • Zinc gluconate (Rubozinc) - 1 capsule of active substance (30 mg of elemental zinc) twice-daily Concomitant therapy: not reported Appearance: identical and placebo used for second dose of minocycline Instructions: not reported Skin hygiene: only those provided in trial permitted and no facial cosmetics with antiseptic properties; high-fat soap and moisturiser Empty stomach: yes, unless GI disturbance then could be taken at night Compliance: very good and comparable: 95.1% +/- 6.2% zinc versus 95.9% +/- 6.5% - no details of how evaluated
Outcomes	**Outcomes of the trial** 1. PA lesion count, PU lesion count, open comedone count, closed comedone count 2. Grade: ECLA scale 3. Investigator global clinical efficacy (100 mm VAS) 4. Participant global clinical efficacy (100 mm VAS) 5. Percentage of the clinical success rate in each group on day 90 (clinical success = decrease by more than 2/3 of PA and PU on the face) (primary outcome) 6. Adverse drug reactions
Notes	Country: France Language: English Review version: 2012 Additional data were provided by Labcatal.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated to be multicentre randomisation, but no details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding (performance bias and detection bias)	Low risk	It was stated to be double-blind, but there were no further details other than the following quote on page 136: "Both groups received look-alike capsules."
Incomplete outcome data (attrition bias)	Low risk	All participants accounted for each time point (please see Figure 1, page 137).
Selective reporting (reporting bias)	Low risk	All outcomes were reported at each time point.

Fallica 1985

Methods	• This was an open-label RCT in a hospital setting (3 centres). • The duration of the trial was 12 weeks plus 8 weeks post-study. • The method of randomisation was not stated. • Any industrial support was not specified. • The use of UV control was not stated. • It was not specified whether previous treatment was withdrawn prior to the start of the trial. • Evaluation was at 0, 2, 4, 8, and 12 weeks plus post-study at weeks 16 and 20. • The area evaluated was the whole face. • The assessor was not specified. • A per-protocol analysis was used.
Participants	100 participants were enrolled. 50 participants were randomised in the minocycline group, and 50 participants were randomised in the tetracycline group. There were 4 (8%) dropouts in the minocycline group and 4 (8%) in the tetracycline group. The mean age was 19.22 (range = 12 to 36). Recruitment was fulfilled by hospital out-patients. **Inclusion criteria of the trial** • Inflammatory acne **Exclusion criteria of the trial** • Not specified
Interventions	• Minocycline 100 mg once a day • Tetracycline 250 mg 4 times a day Concomitant therapy: not permitted Appearance: standard Instructions: minocycline to be taken 1 hour before main meal Skin hygiene: not specified Empty stomach: yes Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Grade: Cook (0 to 8) (Cook 1979) 2. Overall improvement (5-point scale) as reported by the assessor 3. Overall improvement (5-point scale) as reported by the participant 4. Reduction in grade from baseline (primary outcome) 5. Adverse drug reactions as reported by the participants
Notes	Country: Italy Language: Italian and English Review version: 2002 The results were presented graphically and as statistical analysis values. The report was inadequate for 'Risk of bias' assessment. The age and sex distribution with the 2 groups after randomisation was homogeneous.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was unclear; it was described as controlled randomised. There were no further details in the published report.
Allocation concealment (selection bias)	High risk	This was not used.
Blinding (performance bias and detection bias)	High risk	This was not blinded.
Incomplete outcome data (attrition bias)	Low risk	In the minocycline group, 3 participants did not present at the 7th control due to good improvement, while 1 was suspended for nausea; 4 were not present at the 6th week, due to optimal improvement; and 2 were suspended after 4 weeks (of these, 1 was for complete resolution of acne and 1 was for refusal to continue). In the tetracycline group, 4 were absent at the 7th control for good or modest improvement, and 6 did not attend for the 6th visit (of these, 1 was for optimal improvement, 1 was for gastralgia, and 4 were for refusal to continue).
Selective reporting (reporting bias)	Low risk	The outcomes were reported at each time point for each group.

Fleisch 2006a (MP010404)

Methods	• This was a prospective, double-blind, placebo-controlled RCT in a multicentre setting. • The duration of the trial was 12 weeks. • Randomisation details were not given, but a participant's assignment to a treatment group was stratified by severity of acne. • Industrial support came from Medicis Pharmaceutical Corporation who produce Solodyn®, the extended-release minocycline preparation. • The use of UV control was not stated. • The period of time before the trial in which all oral and topical treatment for acne was stopped was as follows: within 6 months for oral isotretinoin, within 4 weeks for oral antibiotics (e.g. tetracyclines, erythromycin), within 4 weeks for systemic corticosteroids, within 2 weeks for topical retinoids or retinol-containing products for facial acne, within 2 weeks for topical antibiotics for facial acne, within 2 weeks for topical corticosteroids applied to the face, and within 2 weeks prior to baseline for topical benzoyl peroxide for facial acne or topical over-the-counter remedies (e.g. salicylic acid) for facial acne. • Evaluation was at days 28, 56, and 84. • The area evaluated was the face. • The assessor was not stated. • An intention-to-treat analysis was possibly used, as data using last observation carried forward were imputed.

Participants	451 participants were enrolled (n = 300 minocycline, n = 151 placebo). After screening and baseline evaluations in the phase 3 studies, participants were randomised in a 2:1 ratio to 2 treatment groups (ER-minocycline 1 mg/kg [n = 615] or placebo [n = 309]). Each participant's study drug supply was determined by body weight and available tablet strength (Table 2). Assignment to treatment groups was stratified by the severity of acne (moderate or severe). The number of dropouts was not given by group (21% in both phase RCTs). The mean age was 19.2 years in the minocycline group and 21.3 years in the placebo group. It was not stated where participants were recruited from. Inclusion criteria of the trial • 12 to 30 years of age • 39.1 kg to 102.3 kg (86 to 225 lb) • Moderate to severe facial acne vulgaris - they were required to have >/= 25 and < 75 facial IL; < 2 facial nodules or cysts • Women of childbearing potential had to have a negative urine pregnancy test result (25 microg/ml sensitivity) • OC Exclusion criteria of the trial • Included history of acute vestibular adverse events, such as vertigo, light-headedness, nausea, or vomiting within 30 days prior to enrolment; history or current risk of hepatic dysfunction; history or current risk of renal dysfunction, systemic lupus erythematosus, or - in the phase 3 study only - a positive test result for antinuclear antibodies at screening; history of alcohol or drug dependency; baseline safety laboratory values outside of the reference range for liver function tests that were determined to be clinically significant • SENS; PREG; men with facial hair; use of supplements containing aluminium, calcium, iron, magnesium, or vitamin A; or a prior history of complicating illnesses or medications • Use of oral isotretinoin within 6 months, oral antibiotics (e.g. tetracyclines or erythromycin) within 4 weeks, systemic corticosteroids within 4 weeks, topical retinoids or retinol-containing products for facial acne within 2 weeks, topical antibiotics for facial acne within 2 weeks, topical corticosteroids applied to the face within 2 weeks, topical benzoyl peroxide for facial acne within 2 weeks, or topical over-the-counter remedies (e.g. salicylic acid) for facial acne within 2 weeks prior to the baseline visit
Interventions	• 1 mg/kg minocycline (n = 300) • Placebo (n = 151) "Each subject's study drug supply was determined by body weight and available tablet strength." Concomitant therapy: none Appearance: not specified Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified

Outcomes	**Outcomes of the trial** 1. Grade: not stated (EGSA scale and grade described in table 1, page 23) 2. Primary efficacy assessments for the phase 3 studies included the investigator-conducted inflammatory lesion count at each study visit as well as EGSA (which was based on inflammatory lesions only and defined as the proportion of participants who had achieved success (score of 0 [clear] or 1 [almost clear]) (primary outcome) 3. Secondary efficacy assessments included non-inflammatory and total (inflammatory and non-inflammatory) lesion counts 4. Adverse drug reactions: Safety was assessed in the phase 2 and phase 3 studies at each visit by the results of physical examinations, vital sign assessments, chemistry and haematology panels, urinalysis, and review of adverse drug events. In the phase 3 studies, thyroid function tests and systemic evaluations (e.g. antinuclear antibodies)
Notes	Country: United States Language: English Review version: 2012 The blinding was potentially negated: "Each subject's study drug supply was determined by body weight and available tablet strength."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	For the phase 3 study, participants were randomised in a 2:1 ratio to 2 treatment groups stratified by severity of acne (moderate or severe) (page 22). Comment: This was probably done.
Allocation concealment (selection bias)	Unclear risk	No details were given. "Each subject's study drug supply was determined by body weight and available tablet strength." This suggests that the blinding may have been potentially negated; it was not stated how this was dealt with.
Blinding (performance bias and detection bias)	Low risk	It was stated to be double-blind. "Each subject's study drug supply was determined by body weight and available tablet strength." This suggests that the blinding may have been potentially negated; it was not stated how this was dealt with.
Incomplete outcome data (attrition bias)	High risk	451 participants were recruited (Table 3, page 25). The table on page 26 stated that the number for a pooled analysis was 674 for the treatment group and 364 for the placebo group at all time points, suggesting that there were no dropouts. Quote (page 24): "89% of subjects completed the 84-day treatment phase. The most frequent reasons for premature withdrawal in the extended-release minocycline group were loss to follow up (3.3%) and adverse experiences (3.0%); the most frequent reasons for premature withdrawal in the placebo group were loss to follow-up (4.1%) and withdrawal of consent (4.9%)." Comment: 89% completed treatment, but dropouts and withdrawals totaled 15.3%.
Selective reporting (reporting bias)	Low risk	All outcomes were reported at each time point.

Fleisch 2006b (MP010405)

Methods	• This was a prospective, double-blind, placebo-controlled RCT in a multicentre setting. • The duration of the trial was 12 weeks. • Randomisation details were not given, but a participant's assignment to a treatment group was stratified by severity of acne. • Industrial support came from Medicis Pharmaceutical Corporation who produce Solodyn®, the extended-release minocycline preparation. • The use of UV control was not stated. • Prior to the start of the trial and the baseline visit, all acne treatments were stopped at the following time-frames: oral isotretinoin (6 months); oral antibiotics, for example, tetracyclines, erythromycin, (4 weeks); systemic corticosteroids (4 weeks); topical retinoid or retinol-containing products for facial acne (2 weeks); topical antibiotics (2 weeks); topical corticosteroids applied to the face (2 weeks); topical benzoyl peroxide (2 weeks); topical over-the-counter remedies, for example, salicylic acid (2 weeks). • Evaluation was at days 28, 56, and 84. • The area evaluated was the face. • The assessor was not stated. • An intention-to-treat analysis was possibly used, as data using last observation carried forward were imputed.
Participants	The mean age was 20.0 years in the minocycline group and 19.6 years in the placebo group. After screening and baseline evaluations in the phase 3 studies, participants were randomised in a 2:1 ratio to 2 treatment groups (ER-minocycline 1 mg/kg [n = 615] or placebo [n = 309). Each participant's study drug supply was determined by body weight and available tablet strength (Table 2). Assignment to treatment groups was stratified by the severity of acne (moderate or severe). The number of dropouts was not given by group (21% in both phase RCTs). The mean age was 19.2 years in the minocycline group and 21.3 years in the placebo group. It was not stated where participants were recruited from. **Inclusion criteria of the trial** • 12 to 30 years of age • 39.1 kg to 102.3 kg (86 to 225 lb) • Moderate to severe facial acne vulgaris - they were required to have >/= 25 and < 75 facial IL; < 2 facial nodules or cysts • Women of childbearing potential had to have a negative urine pregnancy test result (25 microg/ml sensitivity) • OC **Exclusion criteria of the trial** • Included history of acute vestibular adverse events, such as vertigo, light-headedness, nausea, or vomiting within 30 days prior to enrolment; history or current risk of hepatic dysfunction; history or current risk of renal dysfunction, systemic lupus erythematosus, or - in the phase 3 study only - a positive test result for antinuclear antibodies at screening; history of alcohol or drug dependency; baseline safety laboratory values outside of the reference range for liver function tests that were determined to be clinically significant • SENS; PREG; men with facial hair; use of supplements containing aluminium, calcium, iron, magnesium, or vitamin A; or a prior history of complicating illnesses or medications • Use of oral isotretinoin within 6 months, oral antibiotics (e.g. tetracyclines or erythromycin) within 4 weeks, systemic corticosteroids within 4 weeks, topical retinoids or retinol-containing products for facial acne within 2 weeks, topical antibiotics for facial acne within 2 weeks, topical corticosteroids applied to the face within 2 weeks, topical benzoyl peroxide for facial acne within 2 weeks, or topical over-the-counter remedies (e.g. salicylic acid) for facial acne within 2 weeks prior to the baseline visit

Interventions	• 1 mg/kg minocycline (n = 315) • Placebo (n = 158) "Each subject's study drug supply was determined by body weight and available tablet strength." Concomitant therapy: none Appearance: not specified Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	Outcomes of the trial 1. Grade: not stated (EGSA scale and grade described in table 1, page 23) 2. Primary efficacy assessments for the phase 3 studies included the investigator-conducted inflammatory lesion count at each study visit as well as EGSA (which was based on inflammatory lesions only and defined as the proportion of participants who had achieved success (score of 0 [clear] or 1 [almost clear])) (primary outcome) 3. Secondary efficacy assessments included non-inflammatory and total (inflammatory and non-inflammatory) lesion counts 4. Adverse drug reactions: Safety was assessed in the phase 2 and phase 3 studies at each visit by the results of physical examinations, vital sign assessments, chemistry and haematology panels, urinalysis, and review of adverse drug events. In the phase 3 studies, thyroid function tests and systemic evaluations (e.g. antinuclear antibodies) were carried out
Notes	Review version: 2012

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	For the phase 3 study, participants were randomised in a 2:1 ratio to 2 treatment groups stratified by severity of acne (moderate or severe) (page 22).
Allocation concealment (selection bias)	Unclear risk	No details were given. "Each subject's study drug supply was determined by body weight and available tablet strength." This suggests that the blinding may have been potentially negated; it was not stated how this was dealt with.
Blinding (performance bias and detection bias)	Low risk	It was stated to be double-blind. "Each subject's study drug supply was determined by body weight and available tablet strength." This suggests that the blinding may have been potentially negated; it was not stated how this was dealt with.
Incomplete outcome data (attrition bias)	High risk	451 participants were recruited (Table 3, page 25). The table on page 26 states that the number for a pooled analysis was 674 for the treatment group and 364 for the placebo group at all time points, suggesting that there were no dropouts. Quote (page 24): "89% of subjects completed the 84-day treatment phase. The most frequent reasons for premature withdrawal in the extended-release minocycline group were loss to follow up (3.3%) and adverse experiences (3.0%); the most frequent reasons for premature withdrawal in the placebo group were loss to follow-up (4.1%) and withdrawal of consent (4.9%)." Comment: 89% completed treatment, but dropouts and withdrawals totaled 15.3%.
Selective reporting (reporting bias)	Low risk	All outcomes were reported at each time point.

Gollnick 1997

Methods	• This was an open-label RCT in a multicentre (10)/multicountry setting. • The duration of the trial was 6 months. • The method of randomisation was not specified: "50 participants assigned at random to the AA/Mino group and 35 to the Iso group." • Schering Health Care Ltd sponsored the trial. • Participants could not have received isotretinoin in the previous 12 months. Oral acne treatments were stopped 4 weeks prior to the start of the trial and all topicals were stopped 2 weeks before. • The face and trunk were evaluated separately. • The study was invalidated as individuals who achieved a very good clinical response were transferred over to AA maintenance prior to the end of the 6-month study period. • The use of UV control was not stated. • Evaluation was at 0, 4, 8, 12, 16, 20, and 24 weeks. • Clinical assessment was of the chest and back. • The assessor was not specified. • The data were analysed using the following statistical methods: differences in lesion counts using the Mann-Whitney U test (Wilcoxon 2-samples test), and Fisher's test on global assessments and for determining the percentage reduction in lesion counts. All participants attending at least 1 examination after baseline were included in the statistical evaluation.

Participants	85 men were enrolled. The number of randomised participants was not specified, but it was unequal as 50 were assigned to minocycline/azelaic acid and 35 were assigned to isotretinoin. 50 participants were randomised to the minocycline/azelaic acid group and 35 to the isotretinoin group. There were 8 (9%) dropouts. The mean age was 19 (range = 15 to 31). Recruitment was fulfilled by hospital out-patients. At baseline the 2 groups were comparable for age. There were however differences between the groups in the duration of acne, the numbers of individuals who had received pre-treatment, those who had acne on their face and trunk, and those who had papulopustular acne. It was not reported whether these differences had been subjected to statistical analyses. **Inclusion criteria of the trial** • Severe inflammatory forms of facial acne (acne conglobata, acne papulopustulosa nodosa), men > 16 years of age, severity greater than grade 4 Leeds (Burke 1984), at least 2 deep inflammatory lesions on the face, or no systemic therapy at least 4 weeks prior to the trial (12 months for isotretinoin) or topical treatment for 2 weeks **Exclusion criteria of the trial** • Women • Participants with milder (comedonal or papulopustular acne) or more severe (acne fulminans, acne tetrade) forms of acne, photosensitive participants, participants with contradictions to isotretinoin or minocycline, or those hypersensitive to the excipients in AA cream
Interventions	• Minocycline 50 mg twice daily plus azelaic acid 20% cream twice daily • Isotretinoin - initial dose = 0.8 mg/kg/day, month 2 = 0.7 mg/kg, month 3 = 0.5 to 0.7 mg/kg, month 4 = 6 0.5 mg/kg Instructions: use 1 inch of cream If there was pronounced local irritation, the frequency of applications reduced temporarily to once-daily. It was stopped where necessary until symptoms had disappeared. The isotretinoin group had regular liver function test monitoring. Concomitant therapy: not specified Appearance: standard-open trial Instructions: not specified Skin hygiene: vehicle of AA cream for individuals in isotretinoin group as a moisturiser. Otherwise, not stated Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Facial lesion count of the following: Cc, Co, PA, PU, NOD, nodes, cysts 2. Optional assessment of the trunk (chest/back) 3. Global overall result (5-point scale) as reported by the assessor 4. Global overall result (5-point scale) as reported by the participants 5. Change in inflamed lesion counts (PA, PU, and deep IL) from baseline (primary outcome) 6. Adverse drug reactions as reported by the participants and investigator (nature, duration, severity, and causal association) at each visit 7. Degree of seborrhoea

Notes	Country: Germany, Austria, and Switzerland Lanugage: English Review version: 2002 abstract, 2012 full This was open necessarily due to the adverse effect profile of isotretinoin. In the initial version of this review, the only information that could be obtained was a brief summary of the study that was published in a review article. The 2006 update included the information included in the full publication published in 2001. Primary outcomes were presented graphically and a median was given. "Participants who during study phase 1 had achieved a very good therapeutic improvement were eligible for admission to the second, 3 month study phase (maintenance treatment). Participants in whom a very good clinical improvement was achieved prematurely, i.e. before completing the 6 months of study phase 1, were transferred early to phase 2. The participants of the initial AAMino group admitted to the second study phase used AA cream twice daily as maintenance therapy over a period of 3 months. Participants in the Iso group did not receive any further maintenance therapy." This trial was a 2-phase trial: 6 months of treatment and then 3 months of maintenance. Participants in whom a very good clinical improvement was achieved prematurely, i.e. before completing the 6 months of study phase 1, were transferred early to study phase 2. The paper stated that all 85 participants were included in the analysis of efficacy. The therapy was regarded as completed before the end of the 6 months in 10% of the participants in the minocycline/azelaic group, while 78% of the participants of this group finished the first study phase as per the schedule after 6 months. The corresponding figures in the isotretinoin group were 14.3% and 77.1%.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was randomised and open-label. No details were given. There were unequal numbers of participants, which suggested a problem with the randomisation as did the differences reported at baseline.
Allocation concealment (selection bias)	High risk	This was not used.
Blinding (performance bias and detection bias)	High risk	This was open-label. It was not possible to blind due to the side-effect profile of isotretinoin.
Incomplete outcome data (attrition bias)	Low risk	Quote (page 541): "All 85 participants were included in the analysis of efficacy." Comment: All participants were accounted for: 85 were recruited and 77 completed.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were reported at each time point. Secondary outcomes were investigator and participant global assessments of the therapeutic result. It was unclear if participant-rated global outcomes were reported; Figure 3 gave global outcomes, but it was unclear if this included participant-reported outcomes.

Harrison 1988

Methods	• This was an observer-blinded RCT in a hospital setting. • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • Industrial support came from Pfizer. • The use of UV control was not stated. • All antibiotics were stopped prior to the start of the trial. It was not specified whether topical treatments were stopped. • Evaluation was at 0, 4, 8, and 12 weeks. • The area evaluated was the whole face/chin anterior to the sternomastoid muscles but excluding the nose/hairline. • There was a single assessor. • A per-protocol analysis was used: analysis of covariance and Chi² test.
Participants	43 participants were enrolled. 22 participants were randomised in the minocycline group, and 21 participants were randomised in the doxycycline group. There were 3 (14%) dropouts in the minocycline group, and 6 (29%) in the doxycycline group. The mean age was 20 (range = 16 to 35). Recruitment was fulfilled by hospital out-patients. The groups were equivalent at baseline for gender and duration of acne. **Inclusion criteria of the trial** • Not specified **Exclusion criteria of the trial** • PREG, BF, OC, or facial hair. No participant received antibiotics for at least 4 weeks prior to the study
Interventions	• Minocycline 50 mg twice daily • Doxycycline 50 mg once daily • Plus topical 4% chlorhexidine/5% benzoyl peroxide Concomitant therapy: recorded, but no details were given Appearance: standard Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Cyst count, NO count, PA count, PU count (subdivided into active/less active), TLC, and MAC count (weighted according to severity) 2. Percentage change in lesion counts from baseline (primary outcome) 3. Score: Each lesion was given the following score: PA = 2; PU = 4; NOD = 10; Cysts = 15 4. Overall efficacy (4-point scale) as reported by the participants 5. Severity (10 cm VAS) as reported by the participants 6. Adverse drug reactions as reported by the participants (reported to direct questioning)
Notes	Country: UK Language: English Review version: 2002 Additional data were provided by Pfizer. We cannot attribute any changes/alterations to oral therapy as benzoyl peroxide is highly active, particularly against non-inflamed lesions. Division of lesions into active and less active was likely to be highly subjective. Lesion counts and scores were adjusted to account for different baseline values; no further details were given.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 242): "The participants were randomised." Comment: No details were given.
Allocation concealment (selection bias)	Unclear risk	No information was provided.
Blinding (performance bias and detection bias)	Unclear risk	This was observer-blinded; there were no further details.
Incomplete outcome data (attrition bias)	Low risk	43 participants entered the study: 21 received doxycycline and 22 received minocycline. 15 in the doxycycline group completed and were analysed; 19 in the minocycline group completed and were analysed. Analysis was per-protocol.
Selective reporting (reporting bias)	Low risk	All the lesion count data were presented. The participants' assessment of severity on the visual analogue scale and score 0 to 100 was found to be inconsistent, and it was felt that these types of data were insufficiently accurate to compare the effects of the 2 drugs.

Hayashi 2011

Methods	• This was an open-label, parallel-group RCT in a multicentre setting (21 centres - primarily dermatology clinics). • The duration of the trial was 4 weeks treatment plus 4 weeks follow up. • Randomisation was by use of "the envelope method". • There was no mention of industrial support. • The use of UV control was not stated. • All oral antibiotic treatment was stopped 1 month prior to the start of the trial. It was not stated whether topical treatment was also withdrawn. Topical treatment was permitted during the second 4-week observation period. • Evaluation was at 0, 2, and 4 (plus 6, 8) weeks. • The area evaluated was the face. • The assessor was not specified. • A per-protocol analysis was used.
Participants	50 participants were enrolled. 49 participants were randomised in the minocycline group, 50 participants were randomised in the roxithromycin group, and 51 participants were randomised in the faropenem group. There were 9, 7, and 8 dropouts, respectively. All were accounted for. The mean age was 26.5 (26.1, 26.2, 27,1). Recruitment was not specified. There were no baseline differences in age, gender, duration of disease or severity. Inclusion criteria of the trial • Moderate to severe inflammatory acne (Japanese Acne study group criteria = 6 to 50 ILC per half face) • > 16 years of age Exclusion criteria of the trial • Oral antibiotics for acne in the last month; hypersensitivity to ß-lactam, macrolide, or tetracyclines; participants taking medications containing ergotamine; participants continuously using non-steroidal anti-inflammatory drugs (NSAIDs); pregnancy, nursing, or participants who may be pregnant; other participants judged as ineligible by the attending physician (but no details were given)

Interventions	• Minocycline 100 mg once daily or 50 mg twice-daily • Roxithromycin 150 mg twice-daily • Faropenem 200 mg 3 times per day Concomitant therapy: those with indication for acne or influence on acne prohibited. Permitted: treatment for complications that did not affect acne temporary use of antibiotics to treat incidental infections except azithromycin, external non-comedogenic moisturisers, and vitamin B2, B6, C and E preparations permitted. Hormone therapy and physical treatments prohibited. Topical medication permitted during the second 4-week 'observation' period: 34 participants used nadifloxacin or clindamycin "when participants were treated with any concomitant drugs or therapies, the name of the drug or therapy, route of administration, daily dose, treatment duration and reason for concomitant use were recorded in the case report form." Appearance: standard-open trial Instructions: not specified Skin hygiene: external non-comedogenic moisturisers permitted Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Grade 2. Percentage change from baseline (primary outcome) of the ILC (PA and PU) 3. Changes in ILC and NILC, QOL (Japanese Skindex), 0 and 4 week microbiology 4. Adverse drug reactions (ascertainment was not described)
Notes	Country: Japan Language: English Review version: 2012 The first 4 weeks only were eligible for inclusion because oral therapy stopped and topical clindamycin or nadifloxacin was given. Many variables affecting acne treatment were not controlled. Physicians were permitted to exclude patients.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was described as 'randomised'.
Allocation concealment (selection bias)	Low risk	The envelope method was stated, but no details were provided. Comment: This was probably done.
Blinding (performance bias and detection bias)	High risk	This was an open-label study; there was no blinding.
Incomplete outcome data (attrition bias)	Low risk	All participants were accounted for, even with regard to distribution of dropouts between groups.
Selective reporting (reporting bias)	Low risk	All outcomes were included, but no data were provided. The results were presented in graphical form only.

Hersle 1976

Methods	• This was a double-blind, cross-over RCT in a hospital setting (2 centres). • The duration of the trial was 5 weeks/5 weeks. • The method of randomisation was not stated. • Industrial support came from Lederle. • The use of UV control was not stated. • No tetracyclines (presumed to be oral) were permitted within the "last months" before the start of the trial. • Evaluation was at 0, 5, and 10 weeks. • The area evaluated was unspecified. • The assessor was not specified, but there was an adverse event self-report by participants. • A per-protocol analysis was used.
Participants	50 participants were enrolled. 25 participants were randomised in the minocycline group, and 25 participants were randomised in the placebo group. There were 9 (24%) dropouts (all in the minocycline group). The age range was 14 to 34. Recruitment was fulfilled by hospital out-patients. **Inclusion criteria of the trial** • Not specified **Exclusion criteria of the trial** • Not specified
Interventions	• Minocycline 200 mg od for 7 days then 100 mg od for 4 weeks • Placebo od Concomitant therapy: not permitted Appearance: identical Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Grade: Witowski (I to III), modified for this study 2. Number of lesions of each grade 3. Score: grade I = 1, grade II = 2, and grade III = 4 4. Percentage reduction from baseline of acne lesion score (primary outcome) 5. Adverse drug reactions as reported through the participants' self-reporting
Notes	Country: Sweden Language: English Review version: 2002 The report was too inadequate to permit accurate validity assessment. There was no wash-out period between the study arms. The outcome measures were inappropriate.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details were given; it was stated to be randomised.
Allocation concealment (selection bias)	Unclear risk	This was unclear.
Blinding (performance bias and detection bias)	Low risk	It was stated to be double-blind. The tablets were identical and filled in coded bottles.
Incomplete outcome data (attrition bias)	High risk	All dropouts were accounted for, but all were in the minocycline group (7/50).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported, but there was insufficient data to calculate the effect size.

Hubbell 1982

Methods	• This was a double-blind RCT. • The duration of the trial was 24 weeks. • The method of randomisation was not stated. • Any industrial support was not specified. • UV control was used. • All previous "systemic" (oral) treatment was stopped prior to the start of the trial. • Evaluation was at 0, 3, 6, 9, 12, 15, 18, 21, and 24 weeks. • The area evaluated was 4 cm² of the most involved cheek. • It was not stated whether the same assessor was used for each participant at each visit. • A per-protocol analysis was used.
Participants	104 participants were enrolled. 52 participants were randomised in the minocycline group, and 52 participants were randomised in the tetracycline group. There were 27 (52%) dropouts in the minocycline group and 28 (54)* in the tetracycline group. The mean age was 17.4 (range = 14 to 35). Recruitment was fulfilled through the Airforce. **Inclusion criteria of the trial** • Moderate pustular acne (Pilsbury grade II to III) **Exclusion criteria of the trial** • ILL, SENS, PREG, BF, ACID, OC if started less than 6 months prior to trial, or vertigo
Interventions	• Minocycline 50 mg bd • Tetracycline 250 mg bd Concomitant therapy: not permitted Appearance: identical Instructions: take on empty stomach Skin hygiene: wash bd with common soap Empty stomach: yes Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Grade: Pillsbury (I to III) 2. Number of participants converting to grade I acne and mean time to conversion (primary outcome) 3. Adverse drug reactions as reported by the participants 4. Laboratory tests
Notes	Country: United States Language: English Review version: 2002 *25 minocycline participants and 26 tetracycline participants did not attend a minimum of 6 visits, although no reasons were given for this.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised, but no details were given about generation of the sequence.
Allocation concealment (selection bias)	Unclear risk	It was unclear if the allocation was concealed. It stated that each participant "was randomly assigned a numbered medication." (page 989)
Blinding (performance bias and detection bias)	Low risk	It was stated to be double-blind, but no details were given. Appearance of the capsules was identical.
Incomplete outcome data (attrition bias)	High risk	Yes - all participants were accounted for, although no reasons were given for the 55 who dropped out. There were contradictory report numbers regarding dropouts and side-effects. There was a very high dropout rate: 104 commenced, 55 dropped out, and 51 did not fulfil the visit requirements. 4 dropped out as follows: In the tetracycline group, 1 dropped out due to side-effects, and 1 due to worsening of acne. In the minocycline group, 1 participant dropped out because of unsatisfactory results, and 1 because of a severe flare of acne.
Selective reporting (reporting bias)	Unclear risk	Yes - all outcomes were reported at each time point.

Khanna 1993

Methods	• This was an open-label RCT in a hospital setting. • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • Any industrial support was not specified. • The use of UV control was not stated. • All oral antibiotics were stopped 1 month prior to the start of the trial. • Evaluation was at 0, 6, and 12 weeks. • The area evaluated was the face only. • There was a single assessor. • A per-protocol analysis was used.
Participants	44 participants were enrolled. 23 participants were randomised in the minocycline group, and 21 participants were randomised in the tetracycline group. There were 4 (17%) dropouts in the minocycline group and 6 (29%) in the tetracycline group. The mean age was 20.7 (range = 14 to 24). Recruitment was fulfilled by hospital out-patients. **Inclusion criteria of the trial** • Moderately-severe and severe acne vulgaris **Exclusion criteria of the trial** • Acne conglobata, PREG, OC, or endocrinopathy
Interventions	• Minocycline 50 mg bd • Tetracycline 500 mg bd Concomitant therapy: not permitted Appearance: standard Instructions: empty stomach for tetracycline Skin hygiene: normal soap and water Compliance: not specified
Outcomes	**Outcomes of the trial** 1. NIL count, small IL count, and large IL count 2. Score = (NIL x1) and (small IL x3) and (large IL x5) 3. Grade: derived from percentage reduction in score 4. Change in score from baseline (primary outcome) 5. Adverse drug reactions as reported by the participants through direct questions
Notes	Country: India Language: English Review version: 2002 It was not clear whether large IL referred to nodules.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated "participants were randomly allocated."
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding (performance bias and detection bias)	High risk	The trial was an open trial (confirmed by the author).
Incomplete outcome data (attrition bias)	Low risk	All dropouts were accounted for, but the analysis was per-protocol. 19/23 participants completed in the minocycline group; 15/21 participants completed in the tetracycline group (completed at 12 weeks).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Laux 1989

Methods	• This was an open-label RCT in a hospital setting. • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • Any industrial support was not specified. • UV control was used. • Information regarding previous treatment withdrawal was not specified. • Evaluation was at 0, 4, 8, and 12 weeks. • The area evaluated was the face. • The assessor was not specified. • A per-protocol analysis was used.
Participants	100 participants were enrolled. 50 participants were randomised in the minocycline group, and 50 participants were randomised in the doxycyline group. The number of dropouts was not specified. The mean age was 21 (range = 15 to 36). Recruitment was fulfilled by hospital out-patients. **Inclusion criteria of the trial** • Inflammatory facial acne **Exclusion criteria of the trial** • PREG, BF, SENS, OC > 20 mg, facial hair, hepatic and renal dysfunction, or secondary acne
Interventions	• Minocycline 50 mg bd • Doxycycline 50 mg od Concomitant therapy: not specified Appearance: standard Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Grade: NIL, PA, PU, NOD, and Cyst (severity 4-point scale) 2. Overall improvement (3-point scale) as reported by the assessor 3. Distribution of lesion grades (primary outcome) 4. Adverse drug reactions as reported by the participants 5. Laboratory assessment
Notes	Country: Germany Language: German Review version: 2002 Translation was only available for interim analysis. No denominators were given for the results. There was no information on dropouts.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was not specified. It was described as a "randomised comparative clinical study".
Allocation concealment (selection bias)	High risk	This was not used.
Blinding (performance bias and detection bias)	High risk	This was an open trial.
Incomplete outcome data (attrition bias)	High risk	There was no information on dropouts. No denominators were given for the results, and it was unclear how many participants were in each group at each time point.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Leyden 2004

Methods	• This was a double-blind, placebo-controlled RCT in a multicentre setting. • The duration of the trial was 12 weeks (designed to be 24 weeks) plus a 2-week placebo run-in. • There were no details of the randomisation process. • Industrial support came from Merck Research Laboratories. • The use of UV control was not stated. • It was not specified whether oral and topical treatment was stopped prior to the start of the trial, but there was a 2-week single-blind placebo run-in. • Evaluation was at weeks 1 and 12. • The area evaluated was unspecified. • The assessor was not stated. • Analysis of variance was used.
Participants	Only men were enrolled. The number of participants enrolled was not specified: "182 evaluable", but 269 had safety data suggesting the number randomised was > 182. The randomisation of participants was not specified. The number of dropouts was not specified. Recruitment was fulfilled through hospitals and medical centres. There was no difference between the groups in lesion counts at baseline. **Inclusion criteria of the trial** • Moderately-severe acne: >/= 20 IL **Exclusion criteria of the trial** • Not specified
Interventions	• Minocycline 100 mg bd (0 to 6 months) • Compound A 25 mg daily (selective and potent type 1 5-alpha reductase inhibitor) (0 to 6 months) • Minocycline 100 mg bd plus compound A 25 mg daily (0 to 3 months) then compound A 25 mg daily (4 to 6 months) • Minocycline 100 mg bd plus compound A 25 mg daily (0 to 3 months) then placebo (4 to 6 months) • Placebo (0 to 3 months) then minocycline 100 mg bd plus compound A 25 mg daily (4 to 6 months) Concomitant therapy: not specified Appearance: double-dummy Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. ILC, TLC, and investigator and participant assessment through photographs 2. Grade: not specified 3. Adverse drug reactions: not specified
Notes	Country: United States Language: English Review version: 2012 The publication provided a brief summary of the trial and insufficient information for proper analysis. There were inconsistencies in the trial report about duration and the numbers of participants included. We suspect that the trial was stopped early due to lack of efficacy. No demographic data were reported.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details were given.
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding (performance bias and detection bias)	Low risk	Quote (page 444): "Treatment groups were blinded by adding placebo tablets in a double-dummy design."
Incomplete outcome data (attrition bias)	High risk	The number of participants assigned to each group was not reported. The number of dropouts or participants lost to follow up were not reported. Data reported on 182 "evaluable " participants, yet 269 were available for safety data.
Selective reporting (reporting bias)	High risk	The specified outcomes were ILC, TLC, investigator and participant assessment, and photographs. Only inflammatory lesions were reported. Adverse drug reactions were briefly summarised: Only serious adverse drug reactions were reported.

Leyden 2006 (Part 2)

Methods	• RCT: This had a multicenter, open-label, treatment phase (Part 1) followed by a double-blind randomised, parallel-group maintenance phase (Part 2). Participants were then eligible to enter the double-blind phase if they showed a 75% or greater global improvement at the end of the initial open-label phase. Only the results of Part 2 have been included in this review because Part 1 was not randomised. • The duration of the trial was 12 weeks (randomised phase). • The method of randomisation was as follows: Participants were assigned a unique number obtained from a computer-generated randomisation schedule. • The trial was funded by Allergan Inc. • There was no UV control. • It was not stated whether all previous oral and topical treatment was stopped prior to the start of the trial, but all participants had received topical tazarotene gel and minocycline 100 mg daily during Part 1 of the study. • Evaluation was at 12 weeks. • The area evaluated was the face. • The assessor was not specified. • ITT results were given for all participants in the study and those randomised in the maintenance phase (Table 3, page 608).

Participants	*The following are taken from page 606 of the trial.* "189 participants enrolled, 137 completed open label phase, 110 [were] randomised to [the] maintenance phase." Randomised: 0.1% tazarotene gel each evening plus a placebo capsule twice-daily, vehicle gel each evening plus minocycline capsule twice-daily, or 0.1% tazarotene gel each evening plus a minocycline capsule twice-daily. 20 participants did not complete the randomised phase of the study. The mean age was 22 years. Participants "enrolled from 5 investigational sites in the United States. The sites were referral or research centres, and enrolment was generally performed by investigators who recruited their existing participants or participants who responded to an advertisement." There were comparable demographics at baseline. **Inclusion criteria of the trial** • "Participants were eligible for enrolment in the study if they were at least 12 years of age and had moderately-severe to severe facial acne vulgaris, 10 to 100 facial non-inflammatory acne lesions, 25 to 60 facial inflammatory acne lesions, and no more than 2 facial nodular cystic lesions" • Participants were eligible to enter the double-blind phase if they showed a 75% or greater global improvement at the end of the initial open-label phase **Exclusion criteria of the trial** • Antibiotic-resistant acne vulgaris; PREG, BF, or planning pregnancy; uncontrolled systemic disease; participating in any other study in the preceding 30 days
Interventions	• 0.1% tazarotene gel each evening plus a placebo capsule twice-daily • Vehicle gel each evening plus a 100 mg minocycline hydrochloride capsule twice-daily • 0.1% tazarotene gel each evening plus a 100 mg minocycline capsule twice-daily Concomitant therapy: none permitted Appearance: standard (open-label) Instructions: pea-sized amount to the face in a thin film 15 to 20 minutes after washing with a mild, non-medicated cleanser and drying with a soft towel Skin hygiene: Quote (page 606): "Washing with a mild non-medicated cleanser and drying with a soft towel. Participants were supplied with a noncomedogenic moisturiser to use if facial dryness developed. No other lotions, creams, medicated powders, or solutions were allowed on the treatment area." Empty stomach: no Compliance: measured as reported in Figure 1, page 607, but method of assessment was not specified Wash-out periods: 14 days topical acne medications, 30 days oral antibiotics and investigational drugs, 12 weeks oestrogens or birth control pills if used for less than 12 weeks, 2 years for oral retinoids
Outcomes	**Outcomes of the trial** 1. OC count, Cc count, PA count, PU count, TIL count, and NIL count 2. Global improvement (7-point scale), severity (0 to 6) 3. TIL count, NIL count (overall disease severity, global response to treatment, mean percentage change in open - plus closed - comedone count, mean percentage change in papule plus pustule count - overall disease severity was rated on a 7-point scale, with 0 indicating none; 2, mild; 4, moderate; and 6, severe, with 1, 3, and 5 as intermediate grades. Global response to treatment was rated as 100% improvement, approximately 90% improvement, approximately 75% improvement, approximately 50% improvement, approximately 25% improvement, no change, or worsening) (primary outcome) 4. Adverse drug reactions: Peeling, erythema, dryness, burning, and pruritus were assessed as a primary outcome measure. Both investigator or participant classified as none, trace, mild, moderate, marked, or severe

Notes	Country: United States Language: English Review version: 2012 The trial was financially sponsored, but disclosure was made. Quote (page 612): "The initial draft of the manuscript was reviewed by Allergan Inc, but the company did not prepare the manuscript or have the opportunity to approve the final version."

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 606): "Participants who achieved at least 75% global improvement at week 12 were assigned a unique participant number obtained from a computer-generated randomisation schedule (using a block size of 6) provided by the sponsor. The assignment of numbers was not necessarily continuous (because 1 investigator may have received noncontiguous blocks of numbers) but was always in blocks of 6." Comment: Yes, this was randomised.
Allocation concealment (selection bias)	Low risk	Small block randomisation was employed. Comment: It was possible to predict sequence in small block randomisation, but this was judged as probably low risk.
Blinding (performance bias and detection bias)	Low risk	Quote (page 606): "The labels on the medication containers were concealed." It was stated as double-blind, but it was unclear if the appearance of products was identical.
Incomplete outcome data (attrition bias)	Low risk	All participants were accounted for at each time point (please see Figure 1, page 607).
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Lorette 1994

Methods	• This was a double-blind RCT in a hospital setting (4 centres). • The duration of the trial was 17 weeks. • The method of randomisation was not stated. • Industrial support came from Biorga, France. • The use of UV control was not stated. • All previous oral acne treatment was stopped 6 weeks prior to the start of the trial, and all topical treatment was stopped 2 weeks previously. • Evaluation was at days 0, 15, 30, 60, 90, and 120. • The area evaluated was 4.5 cm² of the most affected region of the face. • The assessor was not specified. • A per-protocol analysis was used.
Participants	71 participants were enrolled. 35 participants were randomised in the minocycline group, and 36 participants were randomised in the doxycycline group. There were 12 dropouts (34%) in the minocycline group and 5 dropouts (14%) in the doxycycline group. Plus, 1 was unspecified. The mean age was 18.6. Recruitment was fulfilled by hospital out-patients. **Inclusion criteria of the trial** • Juvenile polymorphic inflammatory acne (Michaelson grade 4 to 6), localised predominantly on face, > 13 years old, and on a contraceptive pill if a woman **Exclusion criteria of the trial** • SENS or nodulo-cystic acne
Interventions	• Minocycline 100 mg od • Doxycycline 50 mg od Concomitant therapy: not permitted Appearance: not specified Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Cc count, Co count, PA count, and PU count 2. Score: Each lesion type was given the following score (Cc = 1, Co = 1, PA = 3, PU = 4) 3. Percentage change in lesion counts and score from baseline (primary outcome) 4. Adverse drug reactions as reported by the participants who were questioned
Notes	Country: France Language: French Review version: 2002 The baseline mean Cc count was significantly different (at 5%): doxycycline 8.5, minocycline 4.1. Side-effects were not documented. Results were expressed as percentages only with no dispersion.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was not described in detail; it was only stated that it was a multicentre (4 centres), phase IV, double-blind, 2 parallel-group study
Allocation concealment (selection bias)	Unclear risk	This was unclear. No details were given.
Blinding (performance bias and detection bias)	Low risk	This was described as double-blind, but no details were given.
Incomplete outcome data (attrition bias)	Unclear risk	From the 71 participants recruited, 1 was excluded due to taking a vitamin A therapy concurrently, 7 were lost to follow up (2 in the doxycyline group and 5 in the minocycline group), and 10 dropped out (3 in the doxycycline group and 7 in the minocycline group). Howver, results were expressed as percentages only with no participant numbers; therefore, this was unclear.
Selective reporting (reporting bias)	High risk	Adverse effects were reported in that clinical tolerability was described as "satisfactory". Adverse effects included gastro-intestinal disturbances, headaches, and dizziness, but the numbers of each participants reporting adverse events were not given for each time point or for each group (minocycline or doxycycline).

Monk 1987

Methods	• This was an open-label RCT in a hospital setting (6 centres). • The duration of the trial was 24 weeks. • The method of randomisation was not stated. • Industrial support came from Schering Health Care Ltd. • The use of UV control was not stated. • It was not stated whether all oral and topical treatment was stopped prior to the start of the trial. All hormonal steroid contraceptives were stopped 1 month before. • Evaluation was at 0, 8, 16, and 24 weeks. • The area evaluated was the separate face, neck, shoulders, and back. • There was a single assessor. • A per-protocol analysis was used.
Participants	98 women were enrolled. 49 participants were randomised in the minocycline group, and 49 participants were randomised in the cyproterone group. There were 10 (20%) dropouts in the minocycline group and 10 (20%) in the cyproterone group. The mean age was 23.5. Recruitment was fulfilled through hospitals. With regard to baseline characteristics, there was no difference between groups in terms of age, weight, blood pressure, cycle length, or face lesions, but the minocycline group at baseline had a larger number of comedones. **Inclusion criteria of the trial** • Women with acne of sufficient severity to merit systemic antibiotic therapy **Exclusion criteria of the trial** • SENS, PREG, severe nodular/cystic acne, or contraindications to oral contraceptives
Interventions	• Minocycline 50 mg bd • Cyproterone acetate 2 mg/ethinyloestradiol 0.05 mg on days 5 to 26 of menstrual cycle Concomitant therapy: not specified but no other oral contraceptive or steroid during study period Appearance: standard Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. NIL count, PA count, and PU count 2. Reduction in lesion counts from baseline (primary outcome) 3. Participant response (6-point scale) 4. Adverse drug reactions
Notes	Country: United Kingdom Language: English Review version: 2002 The study results were quoted as median and range. No further details were available from the manufacturers.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was unclear; no details were given.
Allocation concealment (selection bias)	High risk	This was not used.
Blinding (performance bias and detection bias)	High risk	This was intentionally not blinded due to a difference in the dose regime and contraceptive advice.
Incomplete outcome data (attrition bias)	High risk	The reasons for dropout were recorded (Table 3, page 320). 78 completed 24 weeks of treatment: 39 from each group. 10 from each group failed to complete the study. However, most data were presented graphically or as percentages of participants. There was tabulated total lesion count data for 36 and 35 participants in the Diane™ and minocycline groups, respectively.
Selective reporting (reporting bias)	Unclear risk	All acne outcomes (lesion counts and subjective assessments, side-effects) were reported at each time point. Weight and blood pressure were recorded at each visit, but these measurements did not appear in the published report of the trial.

Olafsson 1989

Methods	• This was a double-blind, double-dummy RCT in a hospital setting. • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • Industrial support came from Delta, Iceland. • UV control was used. • Information about previous treatment withdrawal was not specified. • Evaluation was at 0, 4, 8, and 12 weeks. • The area evaluated was the face, including the neck/chest/back. • There was a single assessor. • A per-protocol analysis was used.
Participants	79 participants were enrolled. 39 participants were randomised in the minocycline group, and 40 participants were randomised in the doxycycline group. There were 8 (21%) dropouts in the minocycline group and 7 (18%) in the doxycycline group. The mean age was 20.5 (range = 14 to 37). Recruitment was fulfilled by hospital out-patients. Compliance was not specified, but publication notes that 1 dropped out due to poor compliance (doxycycline). **Inclusion criteria of the trial** • Moderate/moderately-severe acne • Age > 14 **Exclusion criteria of the trial** • PREG • BF
Interventions	• Minocycline 50 mg bd for 4 weeks then 50 mg od • Doxycycline 50 mg bd for 4 weeks then 50 mg od Concomitant therapy: not specified Appearance: double-dummy Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Co count, Cc count, PA count, and PU count 2. Participants' and doctors' assessment of overall effectiveness (4-point scale) 3. Change in lesion counts from baseline (primary outcome) 4. Adverse drug reactions as reported by the participants
Notes	Country: Iceland Language: English Review version: 2002 The results were given in graphical form - there were no data. Overall effectiveness: number of participants given as per cent with no indication of denominator (i.e. the total numbers of participants). There was no indication of participant numbers overall. The minocycline group had more lesions at baseline, but this was not significant. The manufacturers were unable to supply further information.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 15): "The participants were randomly allocated to two groups." No further details about the method of randomisation were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear. No details were given in the published report.
Blinding (performance bias and detection bias)	Low risk	This was described as double-blind and double-dummy. Matching placebos were supplied for both the doxycycline and the minocycline tablets (see page 17 "Acknowledgements").
Incomplete outcome data (attrition bias)	Low risk	15 participants dropped out, with reasons given in the published report. 8 did not complete the study from the minocycline group, 7 did not complete the study from the doxycycline group, but the number of participants was given as per cent with no indication of denominator, and there is no indication of participant numbers for the overall dropout.
Selective reporting (reporting bias)	Low risk	All outcomes were reported at each time point.

Ozolins 2005

Methods	• This was an observer-blinded RCT of pragmatic design using 97 general practices. • The duration of the trial was 18 weeks. • Randomisation was generated using a statistical computer program called "SAS PROC PLAN" with block size of 11. • In order to conceal which treatments participants had been allocated to, the treatments were supplied by pharmacy in identical opaque cardboard boxes, labelled with participant numbers. • The topical vehicle was donated by Stiefel. • The use of UV control was unclear. • All oral and topical acne treatment was stopped 4 weeks prior to the start of the trial. • Evaluation was at 0, 6, 12, and 18 weeks. • The area evaluated was the face. • The assessor was trained, and each participant was seen by the same assessor throughout. Photographic standards were provided. • The method of statistical analysis used was an intention-to-treat analysis in which covariates were investigated. The technique of least squared means was used and logistic regression for the assessor global assessments. The acne grades, severity scores, and quality of life were analysed using the analysis of covariance (ANCOVA) technique. • In order to calculate whether sufficient numbers of participants had been included to exclude the possibility that the results had occurred by chance, a "power calculation" was undertaken. This estimated that 132 participants per group would be needed to have an 80% possibility that the results had not occurred by chance. The following assumptions were made in the calculations: There would be a 20% difference in the participant's own assessment of their acne severity between the groups who received the experimental treatment and those receiving 5% benzoyl peroxide; there would be a 75% response rate, alpha = 0.05 (2-sided); and 23% of participants would not finish the trial. The calculation was revised after the number of treatments included in the trial was reduced from 1 to 5.

Participants	649 participants were enrolled. • In the oxytetracycline 500 mg bd group, 37/131 dropped out. • In the minocycline 100 mg od group, 40/130 dropped out. • In the erythromycin 3% and benzoyl peroxide (BP) 5% bd group, 38/130 dropped out. • In the erythromycin 2% od and BP 5% od group, 25/127 dropped out. • In the BP 5% od group, 38/131 dropped out. The mean age was 19.7 (SD 6.07) (range = 11 to 42). Recruitment was fulfilled from GP surgeries in Leeds and Nottingham, United Kingdom, and colleges in the United Kingdom. A letter was sent from GPs to patients requesting participation. There was baseline equivalence between the groups, except that participants in the erythromycin + BP group had more tetracycline-resistant propionibacteria. Inclusion criteria of the trial • Mild to moderate acne (grades 0.25 to 3.0 on Burke and Cunliffe scale) • Age 12 to 39 • At least 15 inflamed and 15 non-inflamed lesions • No acne treatment in the 4 weeks preceding the trial Exclusion criteria of the trial • Primarily comedonal or nodular acne, exclusively truncal acne, rosacea, late onset acne, acne secondary to endocrine disorders or drugs, pregnancy or breast feeding, significant systemic disease, current therapy with interacting medication, known hypersensitivity to 1 of the test medications, dysmorphophobia, facial dermatological disease, previous oral isotretinoin treatment, Dianette™ therapy within the last 3 months, current acne care and treatment from hospital dermatologist, participation in another clinical trial within the past 3 months
Interventions	• Oxytetracycline 500 mg bd and topical vehicle control bd • Minocycline 100 mg od and topical vehicle control bd • Combination erythromycin 3%, benzoyl peroxide (BP) 5% bd, and oral placebo daily (low-dose vitamin C) • Erythromycin 2% in the morning, BP 5% at night, and oral placebo daily (low-dose vitamin C) • BP 5% twice daily and oral placebo daily 7 treatment comparisons were made. Concomitant therapy: not permitted Appearance: vehicle control plus low-dose vitamin C, not matching Instructions: thorough and adequate Skin hygiene: controlled-unperfumed soap and E45 cream or own unmedicated products Empty stomach: clear instructions for proper use (and storage) of medication given Compliance: return of unused mediation and diary cards
Outcomes	Outcomes of the trial 1. Grade: participant global assessment; lesion counts; assessor global assessment; Likert scale for improvement at 6, 12, and 18 weeks. Grade (Burke and Cunliffe method), combined acne severity score, and 'willingness to pay' assessment. Bacterial counts were undertaken 2. Quality of life scores (SF-36, Dermatology Life quality Index (DLQI), Children's Dermatology Life quality Index (CDLQI), and Diabetes Quality of Life (DQoL)), local irritation (participant and assessor), use of moisturiser, worst aspect of having acne, re-referral rates and adverse events recorded 3. Photographic standards used and lighting conditions stabilised 4. Participant self-assessment of overall improvement (6-point Likert scale) and inflamed lesions (primary outcome) (non-inflamed lesions not counted because of poor repeatability during piloting) 5. Antibiotic resistance 6. Cost-effectiveness

Notes	Country: United Kingdom Language: English Review version: 2012 The HTA report was available. Due to poor recruitment, 6 treatment groups were discontinued (112 randomised): • erythromycin 500 mg bd; • erythromycin topical 2% bd; • clindamycin topical 1% bd; • erythromycin 4%/zinc acetate 1.2% bd; • tetracycline 0.22% bd plus oral oxytetracycline 500 mg bd; and • benzoyl peroxide 5% plus oral oxytetracycline 500 mg bd. The trial was independent of industry sponsorship.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2189) (Lancet 2004;364:2188-95): "Participants were randomly allocated to one of five antimicrobial treatment groups by use of a computer-generated randomisation code, generated using SAS PROC PLAN (HTA report)."
Allocation concealment (selection bias)	Low risk	Quote (page 2189) (Lancet 2004;364:2188-95): "...randomly allocated to one of five antimicrobial treatment groups by use of a computer-generated randomisation code known only to the trial coordinator and pharmacy staff at Queen's Medical Centre, Nottingham, United Kingdom. The randomisation was in blocks of 11, without stratification." "Each participant received from the assessor a sealed opaque box labelled with his or her unique identification number. Each box contained both oral and topical formulations with detailed instructions for their proper use and storage." Comment: Particpants were enrolled and allocated treatment numbers by the clinical assessors, who had no knowledge of which treatment they were allocating to the participant (HTA report).
Blinding (performance bias and detection bias)	Low risk	Observer-masked participants received medications in their original packaging, so participants could have been aware of their treatment assignment. Quote (page 2189) (Lancet 2004;364:2188-95): "Participants were given specific written and spoken instructions not to discuss the nature of their medication with assessors. Instances of treatment unmasking to assessors during the study were recorded." GPs of participants were not involved in the assessment of the trial, but they were still kept blind to the treatment as they could withdraw participants from the trial (HTA report).
Incomplete outcome data (attrition bias)	Low risk	All participants were accounted for at each time point with reasons (please see Figure, page 2190) (Lancet 2004;364:2188-95). In the oxytetracycline 500 mg bd group, 37/131 dropped out. In the minocycline 100 mg od group, 40/130 dropped out. In the erythromycin 3% and BP 5% bd group, 38/130 dropped out. In the erythromycin 2% od and BP 5% od group, 25/127 dropped out. In the BP 5% od group, 38/131 dropped out.
Selective reporting (reporting bias)	Unclear risk	The 2 primary outcomes for efficacy were both reported at the 18-week end point only. The 2 grading methods reported as secondary outcomes were reported at 18 weeks (internet version only: Lancet 2004;364:2188-95). Quality of life estimates were reported elsewhere (HTA report), using the Dermatology Life quality Index (DLQI) or the children's version (CDQLI). All participants and dropouts were accounted for. Reductions in bacterial growth score and proportion of participants with viable Proprionibacteria were reported at weeks 6, 12, and 18 for all treatment arms. Skin colonisation by antibiotic-resistant propionibacteria was monitored at weeks 6, 12, and 18. Features of local irritate and adverse events were recorded at weeks 6, 12, and 18. Cost effectiveness and 'willingness to pay' measures were reported at the 18-week end point. Numbers were analysed as intention-to-treat (HTA report).

Peacock 1990

Methods	• This was an observer-blinded RCT based in student health centres (4 centres). • The duration of the trial was 12 weeks. • Randomisation was by blocks of 10 allocated to each centre. • Industrial support came from Upjohn. • UV control was used. • All previous systemic antibiotic and prescribed acne therapy was stopped 14 days prior to the start of the trial. • Evaluation was at 0, 2, 4, 8, and 12 weeks. • The area evaluated was the face. • There was a single, trained assessor. • A per-protocol analysis was used: analysis of variance. • In order to calculate whether sufficient numbers of participants had been included to exclude the possibility that the results had occurred by chance, a "power calculation" was undertaken. In order to have an 80% possibility that the results had not occurred by chance using statistical tests set at alpha = 0.05, the following assumption was made: The study was capable of detecting a clinical difference of 17 between the 2 treatments in respect of the change from baseline in inflamed lesion counts utilising the distribution variances actually recorded.
Participants	80 participants were enrolled. 38 participants were randomised in the minocycline group, and 42 participants were randomised in the clindamycin group. There were 9 (24%) dropouts in the minocycline group and 8 (14%) in the clindamycin group. The mean age was 21 (range = 18 to 34). Recruitment was fulfilled though students at 3 university health centres. There was baseline comparability between the groups in terms of demographics, severity, duration, and previous medication. **Inclusion criteria of the trial** • Moderate to severe acne: 12-100 IL with < 6 NOD/cysts above the jawline • 16 to 35 years of age **Exclusion criteria of the trial** • SENS, PREG, BF, ILL, OC stopped/started within 1 month, history of chronic bowel disease, diarrhoea, or colitis • Women not using contraceptives, participation in other trials, or participants receiving corticosteroids or androgens within 14 days of commencing study
Interventions	• Minocycline 50 mg bd • 1% clindamycin phosphate solution applied bd Concomitant therapy: not permitted Appearance: standard Instructions: women were not to use new cosmetics Skin hygiene: wash bd with non-medicated soap Empty stomach: not specified Compliance: count/measure of unused medication
Outcomes	**Outcomes of the trial** 1. Cc count, Co count, PA count, PU count, NO count, MAC count, ILC, and NILC 2. Change in ILC count from baseline (primary outcome) 3. Global severity as reported by the assessor (-10 cm VAS) (no lesions to face covered) and participant 4. Participant response (5-point scale) 5. Participant assessment of well-being/self-image 6. Adverse drug reactions

Notes	Country: United Kingdom Language: English Review version: 2002 All participants were included in the analysis if they received a minimum of 4 weeks treatment and attended week 4 and final assessments.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation was used. No details were given about the randomisation method. Comment: This was probably done.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding (performance bias and detection bias)	Unclear risk	Observer nurses were blind to allocation; dispenser nurses were aware of allocation. It was unclear if the outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	8/42 clindamycin participants did not complete, and 9/38 minocycline participants did not complete (reasons were given).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.

Pelfini 1989

Methods	• This was an open-label RCT in 3 centres. • The duration of the trial was 8 weeks. • The method of randomisation was not stated. • Industrial support came from Schering. • There was no information regarding the use of UV control. • No details were provided regarding oral and topical treatment withdrawal. • Evaluation was at 0, 2, 4, 6, and 8 weeks. • The area evaluated was 1 side of the face (Plewig and Kligman (P&K) scale). • There were no details of the assessor. • A per-protocol analysis was used.
Participants	122 participants were enrolled. 61 participants were randomised in the minocycline group, and 61 participants were randomised in the josamycin group. There was 1 dropout (minocycline participant). The mean age was 21.3 in the minocycline group (range = 14 to 34) and 20.3 in the josamycin group (range = 14 to 33). Participants were recruited from the university dermatology departments. **Inclusion criteria of the trial** • severe or refractory papulopustular acne **Exclusion criteria of the trial** • No details
Interventions	• For micropapulopustular variant IIa: minocycline 100 mg orally once-daily for 2 months (n = 39) • For micropapulopustular variant Ia: josamycin 500 mg once-daily for 2 months (n = 39) • For micropapulopustular variant IIb: minocycline 200 mg orally once-daily for 2 months (n = 22) • For micropapulopustular variant Ib: josamycin 1000 mg once-daily for 2 months (n = 22) Concomitant therapy: "In 69 patients, 35 in the josamycin group, 34 in the minocycline group, the clinical presentation suggested the association of a topical medication 5% benzoyl peroxide ointment to the oral treatment." Appearance: standard Instructions: orally once-daily for 2 months Skin hygiene: no details Empty stomach: no details Compliance: no details
Outcomes	**Outcomes of the trial** 1. Grade: Plewig and Kligman grades I to IV based on lesion counts, pustules, nodulo-cysts erythema, and seborrhoea 2. Reduction in number and severity of lesions (primary outcome) 3. Adverse drug reactions
Notes	Country: Italy Language: English Review version: 2012 35/61 josamycin participants and 34/61 minocycline participants suggested concomitant use of 5% benzoyl peroxide treatment at presentation. There was concomitant use of benzoyl peroxide in some participants. There were 2 different regimens, and it was unclear how participants were allocated to each. This was a very poor trial write-up due to the English not being the first language of the authors.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "...randomly allocated." Comment: The report suggests that a number of participants were also given 5% benzoyl peroxide, which is very active. These were not randomised. Also, there were 2 different treatments schedules, and it was unclear how they were randomised (possibly based on severity).
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding (performance bias and detection bias)	High risk	'Previous open studies...' was stated, implying that this was also open.
Incomplete outcome data (attrition bias)	Low risk	1/61 participants discontinued in the minocycline group due to severe gastric intolerance. It appears all other participants provided data.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported. The results were presented graphically only.

Pierard 2002

Methods	• This was a double-blind, double-dummy RCT. • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • This trial received industrial support. • There was no UV control. • It was not stated whether all previous oral and topical treatment was stopped prior to the start of the trial. • Evaluation was at 0, 1, 2, 4, 8, and 12 weeks. • The area evaluated was the forehead. • The assessor was not stated. • The statistical analysis used was an intention-to-treat analysis using the technique of last observation carry forward. The lesion counts were analysed using the Wilcoxon rank sum test, and Chi² tests were used for global assessments.
Participants	86 participants were enrolled. The following were randomised: 31 minocycline 100 mg then 50 mg/28 minocycline 50 mg/27 lymecycline 300 mg. There were 7, 4, and 7 dropouts, respectively (18 in total). Age was 24 +/- 3 years; the mean was not stated, but the range was 17 to 35. Recruitment was fulfilled by hospital out-patients. **Inclusion criteria of the trial** • Moderate to severe acne **Exclusion criteria of the trial** • Not stated ("designed to avoid previous treatment effects, pregnancy and drug interferences")
Interventions	• Minocycline 50 mg once-daily and placebo once-daily • Minocycline 50 mg twice-daily for 4 weeks then minocycline 50 mg once-daily/placebo once-daily • Lymecycline 300 mg once-daily and placebo once-daily Concomitant therapy: not stated Appearance: identical, double-dummy Instructions: to be taken with meals and water in the morning and evening Skin hygiene: not stated Empty stomach: no Compliance: not stated
Outcomes	**Outcomes of the trial** 1. Cc count, Co count, PA count, and PU count on the forehead 2. Grade: not stated 3. Global severity as reported by the investigators and participants: change in counts and grade from week 0 to week 12 (primary outcome) 4. Adverse drug reactions 5. Participant and Investigator global assessments of acne severity
Notes	Sponsorship: Wyeth Lederle Country: Belgium Review version: 2012 Bacterial viability assessments were undertaken using cyanoacrylate skin surface stripping. Dual flow cytometry was used to obtain fluorescence data.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated to be randomised, but no details were given.
Allocation concealment (selection bias)	Unclear risk	No details were given.
Blinding (performance bias and detection bias)	Low risk	It was stated to be double-blind and double-dummy. No details were given.
Incomplete outcome data (attrition bias)	Low risk	The number of participants in each treatment group was reported at the start and the end (after 12 weeks) of the study, but the reasons for dropouts were not given.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.

Pigatto 1986

Methods	• This was an open-label RCT in a hospital setting. • The duration of the trial was 20 weeks. • The method of randomisation was not stated. • Any industrial support was not specified. • The use of UV control was not stated. • Information regarding previous treatment withdrawal was not specified. • Evaluation was at 2-week intervals. • The area evaluated was the face. • The assessor was not specified. • An intention-to-treat analysis was used.
Participants	24 men were enrolled. 12 participants were randomised in the minocycline group, and 12 participants were randomised in the isotretinoin group. There were no dropouts. The mean age was 23 +/- 3 (range = 20 to 29). Recruitment was fulfilled though a university hospital. **Inclusion criteria of the trial** • Severe cystic acne • Normal liver function tests (LFTs) & glucose tolerance tests **Exclusion criteria of the trial** • Overweight • Drugs interfering with lipid metabolism • > 5 g alcohol per day • > 15 cigarettes per day
Interventions	• Minocycline 100 mg/day for 10 weeks then 50 mg od for 10 weeks • Isotretinoin 1 mg/kg/day for 10 weeks then 0.5 mg/kg/day for 10 weeks Concomitant therapy: not specified Appearance: standard Instructions: not specified Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Change in cyst number and diameter from baseline (primary outcome) 2. Liver Function tests: haematology, blood chemistry, urinanalysis, cholesterol, triglycerides, lipases 3. Adverse drug reactions as reported by the participants (and events)
Notes	Country: Italy Language: English Review version: 2002 There was insufficient information in report to permit adequate validity assessment.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Randomly divided' was stated. No details were given.
Allocation concealment (selection bias)	High risk	This was not used.
Blinding (performance bias and detection bias)	High risk	This was not possible due to the side-effect profile of isotretinoin.
Incomplete outcome data (attrition bias)	Low risk	All 24 participants completed the study.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported. Data were presented in graphical form only.

Revuz 1985

Methods	• This was a double-blind RCT in a hospital setting. • The duration of the trial was 60 days. • The method of randomisation was not stated. • Industrial support came from Lederle. • The randomisation method was not specified. • The use of UV control was not stated. • All oral antibiotic treatment was stopped 48 hours prior to the start of the trial. • Evaluation was at days 0, 15, 30, 45, and 60. • The area evaluated was the forehead or cheeks or chin: a prespecified area that was assessed throughout the trial. • There was a single assessor. • The following statistical analyses were used, and all participants who had completed the trial protocol were included in the analyses: Non-parametric data were analysed using a Chi² test, a paired Wilcoxon test, or a Mann-Whitney U test. Parametric data were analysed using a student's t-test.
Participants	91 participants were enrolled. 43 participants were randomised in the minocycline group, and 47 participants were randomised in the placebo group. There were 4 (9%) dropouts in the minocycline group and 13 (28%) in the placebo group. The mean age was 22.4 +/- 4.7 (range = 14 to 37). Recruitment was fulfilled by hospital out-patients. There was baseline comparability in terms of type of acne, number of features, severity, assessment site, gender, and age of the participants. **Inclusion criteria of the trial** • Polymorphous, microcystic, nodulo-cystic, or papular acne - predominantly facial **Exclusion criteria of the trial** • SENS, PREG, BF, and receiving antibiotics for any other disorder 48 hours before the trial
Interventions	• Minocycline 100 mg daily • Placebo daily • Plus topical tretinoin/erythromycin gel (strength not given) Concomitant therapy: not specified Appearance: identical Instructions: take in the evening Skin hygiene: "washing and drying" Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. NIL count, PA count, PU count, and cyst count 2. Change in lesion counts from baseline (primary outcome) 3. Assessor and participant global response (4-point scale) 4. Adverse drug reactions as reported by the participants (spontaneous and observed reporting)
Notes	Country: France Language: English Review version: 2002 The concomitant therapy was very active; no strength was given. There was confusion in terms of the participant numbers. No further information was obtained after requests to the author/manufacturer.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was unclear; it was stated to be randomised, but no details were given. It was noted that a "code" was used.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding (performance bias and detection bias)	Low risk	This was unclear; it was stated to be double-blind, but no details were given.
Incomplete outcome data (attrition bias)	Unclear risk	91 participants were included in the trial, but 1 was excluded from the analysis as the acne was located solely on the back. Demographic details were given for 90 participants in table 1, page 105 of the published report; however, on page 103, it was unclear whether 89 or 90 participants started the trial.
Selective reporting (reporting bias)	Low risk	All outcomes were reported at each time point.

Ruping 1985

Methods	• This was an open-label RCT in a multicentre setting (15 centres). • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • Industrial support came from Lederle. • The use of UV control was not stated. • All previous systemic (oral) and topical treatment was stopped 14 days before the start of the trial. • Evaluation was at 0, 2, 4, 6, 8, 10, and 12 weeks. • The area evaluated was the left or right side of the face or chest or back. • There was a single assessor. • A per-protocol analysis was used.
Participants	The number of enrolled participants was unclear: 283 participants were available for evaluation at the end of the study (15 therapeutic centres). 127 participants were randomised in the minocycline group, and 120 participants were randomised in the tetracycline group. For 36 participants, randomisation was unspecified. The number of dropouts was not specified. The age of the participants was not specified. It was not stated where participants were recruited from. **Inclusion criteria of the trial** • Papulo-pustular and conglobata acne **Exclusion criteria of the trial** • PREG, BF, SENS, or taking zinc supplements
Interventions	• Minocycline 50 mg bd • Tetracycline: 'routine' Concomitant therapy: not specified Appearance: standard Instructions: minocycline to be taken 30 minutes before meals Skin hygiene: not specified Empty stomach: minocycline = yes, tetracycline = no Compliance: 'largely satisfactory'
Outcomes	**Outcomes of the trial** 1. NIL count and IL (PA, PU) count 2. Change in lesion count from baseline (primary outcome) 3. Participant satisfaction (10 cm VAS) 4. Doctor's and participant's tolerance (6-point scale) 5. Adverse drug reactions
Notes	Country: Germany Language: English Review version: 2002

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated to be 'randomised', and participants were divided in to 2 groups. No details were given.
Allocation concealment (selection bias)	High risk	This was not used.
Blinding (performance bias and detection bias)	High risk	This was an open study.
Incomplete outcome data (attrition bias)	High risk	It reported only the participants available at the end of the study; the number randomised was not given. There was no information on 36 participants whose 'information was inadequate or faulty'. There were no details on dropouts or indication of denominator in outcome measures.
Selective reporting (reporting bias)	Unclear risk	The results were presented graphically; all outcomes were reported. The adverse event data were very sparse. There were non-standardised follow-up periods.

Samuelson 1985

Methods	• This was a double-blind RCT in a private practice setting. • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • Any industrial support was not specified. • The use of UV control was not stated. • All previous oral and topical treatment was stopped 2 months before the start of the trial. • Evaluation was at 0, 2, 4, 6, 8, and 12 weeks. • The area evaluated was the face/chest/back. • There was a single assessor. • A per-protocol analysis was used.
Participants	62 participants were enrolled. 30 participants were randomised in the minocycline group, and 32 participants were randomised in the tetracycline group. The number of dropouts was 4 (14%) in the minocycline group and 6 (19%) in the tetracycline group. The mean age was 19 (range = 17 to 30). Recruitment was fulfilled through students attending a private clinic. **Inclusion criteria of the trial** • Moderate to severe inflammatory acne > 4 Samuelson grade **Exclusion criteria of the trial** • ILL, SENS, PREG, BF, ACID, IRON, OC, or vertigo
Interventions	• Minocycline 50 mg bd • Tetracycline 250 mg bd Concomitant therapy: not specified Appearance: identical Skin hygiene: not specified Empty stomach: not specified Compliance: taken under nurse supervision
Outcomes	**Outcomes of the trial** 1. Grade: Samuelson (0 to 9) with photographic references 2. Mean acne grade (primary outcome) 3. Overall Response as reported by the assessor (5-point scale derived from grade reduction) 4. Adverse drug reactions as reported by the participants
Notes	Country: United States Language: English Review version: 2002 62 participants were randomised, but only 55 were included in the efficacy analysis as the others had grade 3 acne.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 463): "...fully randomised double blind format."
Allocation concealment (selection bias)	Unclear risk	This was not specified.
Blinding (performance bias and detection bias)	Low risk	This was described as double-blind; it was unclear who was blinded - whether it was the investigator, participants, or an independent dermatologist.
Incomplete outcome data (attrition bias)	Unclear risk	Dropouts were accounted for at each time point. 2/30 minocycline participants dropped out due to attendance or psychiatric problems; 2/32 tetracycline participants dropped out due to adverse events.
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported at the specified time points.

Schollhammer 1994

Methods	• This was an open-label RCT in a hospital setting (3 centres). • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • Industrial support came from Galderma. • UV control was used. • Previous acne treatment was stopped before the start of the trial for the following time periods: topical treatments (14 days); oral antibiotics and anti-inflammatories (28 days); systemic retinoids (6 months); topical anti-inflammatories (14 days). • Evaluation was at weeks 0 and 12. • The area evaluated was the face. • The assessor was not specified. • A per-protocol analysis was used.
Participants	77 participants were enrolled. 22 participants were randomised in the minocycline group, 33 participants were randomised in the lymecycline group, and 22 participants were randomised in the doxycycline group. There were 2 (9%) dropouts in the minocycline group, 4 (12%) dropouts in the lymecycline group, and 6 (27%) in the doxycycline group. The age range was 9 to 30. Recruitment was fulfilled by hospital out-patients. Baseline severity was equivalent between the groups. **Inclusion criteria of the trial** • Leeds grade 2 to 5 (Burke 1984), 10 to 60 NIL, 20 to 120 IL, and a maximum of 6 NOD/cyst **Exclusion criteria of the trial** • Acne conglobata/fulminans/secondary, interacting medications, renal/hepatic insufficiency, SENS, women not using effective contraception
Interventions	• Minocycline 100 mg/day for 2 weeks then 100 mg/alternate days • Lymecycline 300 mg/day for 2 weeks then 150 mg/day • Doxycyline 100 mg/day for 2 weeks then 50 mg/day Concomitant therapy: not permitted Appearance: standard Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. IL count 2. Percentage of participants attaining a 50% lesion reduction (primary outcome) 3. Overall change as reported by the participants and the assessor (5-point scale) 4. Adverse drug reactions as reported by the participants
Notes	Country: France Language: French Review version: 2002

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was described as randomised (3-arm). There were no details of the randomisation method.
Allocation concealment (selection bias)	High risk	This was not used.
Blinding (performance bias and detection bias)	High risk	This was not specified (not apparently blinded).
Incomplete outcome data (attrition bias)	Unclear risk	This was unclear. The dropouts and reasons for dropout in each group were not given. And for the analyses in this review, the number of participants at each time point were estimated by calculating from the percentages of the numbers in each group (Table 3, page 25).
Selective reporting (reporting bias)	Unclear risk	This was unclear. The outcomes were reported at time point 0 and at 12 weeks for the average number of lesions (week 0), % reduction of lesions by week 12, and percentage of participants with more than 50% reduction in lesions at week 12. No denominators were given for the number of participants with 50% lesion reduction.

Sheehan-Dare 1989

Methods	• This was a double-blind, double-dummy RCT in a hospital setting. • The duration of the trial was 12 weeks. • Randomisation was stated to be by matched pairs on the basis of age, sex, acne grade, and numbers of both inflamed and non-inflamed lesions, but no details were given about the method of sequence generation. • Industrial support came from Upjohn. • UV control was used in the winter months. • Previous acne treatment was stopped 30 days before the start of the trial, which included all acne therapy, antibiotics, corticosteroids, and antiandrogens. • Evaluation was at 0, 4, 8, and 12 weeks. • The area evaluated was the face. • The assessor was not stated. • All participants who completed the trial according to the protocol were included in the analysis. The following statistical tests were used: student's t-test for differences from baseline, and the second trial publication also reported that analysis of variance and Newman-Keuls techniques were used, and an analysis of variance for between group differences was undertaken.
Participants	66 participants were enrolled. 33 participants were randomised to the minocycline group; 33 participants were randomised to the clindamycin group. There was 1 (6%) dropout in the minocycline group and 6 (18%) in the clindamycin group. The age range was 14 to 35. Recruitment was fulfilled by hospital out-patients. There was baseline comparability (age, sex, grade, and count). Inclusion criteria of the trial • Moderate to severe facial acne, 10 to 120 IL with a maximum of 6 NOD/cyst on the face Exclusion criteria of the trial • PREG, BF, SENS, started or stopped OC within 90 days of the study, history of chronic bowel disease or diarrhoea

Interventions	• Minocycline 50 mg bd • Clindamycin phosphate 1% topical solution bd Appearance: standard but double-dummy used Concomitant therapy: not specified Instructions: capsules to be taken before meals, apply lotion to whole face Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. NIL (Cc, Co) and IL count (PA, PU, NOD, MAC) 2. Grade: Leeds (0 to 10) (Burke 1984) 3. Mean changes in NILC and ILC, and grade from baseline (primary outcome) 4. Adverse drug reactions as reported by the participants
Notes	Country: United Kingdom Language: English Review version: 2002 Data were presented in graphical form only. Macules were included in the ILC. Grades and counts were log transformed prior to analysis. The manufacturers or authors couldn't supply further information. The numbers of participants in each group were not reported. There were differences between the 2 reports of the same trial, including whether or not there was a statistically significant reduction in non-inflamed lesion counts, and in the type of statistical tests used. There were differences between 2 publications of this trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stated to be by matched pairs on the basis of age, sex, acne grade, and numbers of both inflamed and non-inflamed lesions, but no details were given about the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no details were given.
Blinding (performance bias and detection bias)	Low risk	It was stated to be "double blind, double dummy" (page 25 of the published report). No further details were given.
Incomplete outcome data (attrition bias)	Unclear risk	66 participants were enrolled, but there were no details on how many participants were randomised to each group: It was assumed to be 33 due to matched pairs. 6 dropped out from the clindamycin arm and 1 from the minocycline arm, but it was unclear at which time point these dropouts occurred.
Selective reporting (reporting bias)	Low risk	All outcomes, including adverse events, were reported at each time point. No data were reported (graphical only).

Smit 1978

Methods	• This was a double-blind RCT in a hospital setting. • The duration of the trial was 12 weeks. • Randomisation was by a 'pre-arranged system'. • Any industrial support was not specified. • The use of UV control was not stated. • Information regarding previous treatment withdrawal was not specified. • Evaluation was at 0, 4, 8, and 12 weeks. • The area evaluated was unspecified. • There was a single assessor. • A per-protocol analysis was used.
Participants	18 participants were enrolled. 9 participants were randomised in the minocycline group, and 9 participants were randomised in the doxycycline group. There was 1 (11%) dropout in the minocycline group and 1 (11%) in the doxycycline group. The age of the participants was not specified. Recruitment was fulfilled through a hospital. Baseline comparability was not specified. **Inclusion criteria of the trial** • Severe acne vulgaris **Exclusion criteria of the trial** • Not specified
Interventions	• Minocycline 100 mg od • Doxycycline 100 mg od • Plus 5% salicylic acid/5% resorcinol applied topically bd Concomitant therapy: not specified Appearance: not specified Instructions: capsules to be taken after dinner Skin hygiene: not specified Empty stomach: no Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Score = E x (S + C + P + I + A) E = Extent of symptoms (1 to 5) S = Seborrohea (0 to 4) C = Comedones (0 to 4) P = Papules/pustules (0 to 4) I = Infiltration (0 to 4) A = Abscess (0 to 4) 2. Change in score from baseline (primary outcome) 3. Laboratory tests 4. Adverse drug reactions as reported by the participants
Notes	Country: Netherlands Language: English Review version: 2002 There were very small numbers of participants. Concommitant therapy was likely to mask treatment effect. The trial report was very brief; it was inadequate for validity assessment. Individual participant results were given.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 187): "The participant was given either doxycycline or minocycline according to a prearranged system of allocation."
Allocation concealment (selection bias)	Unclear risk	This was unclear. No details were given in the published report.
Blinding (performance bias and detection bias)	Low risk	This was described as "double blind", but no details were given.
Incomplete outcome data (attrition bias)	Low risk	Of 18 participants who entered the trial, "2 were lost to follow up due to non-medical reasons." (page 187)
Selective reporting (reporting bias)	Low risk	All outcomes were recorded at each time point, only the before and after (at 3 months) scores were reported in Table 3 of the published report.

Stainforth 1993

Methods	• This was an observer-blinded RCT in a hospital setting (4 centres). • The duration of the trial was 12 weeks. • Randomisation was without stratification. • Industrial support came from Yamanouchi. • UV control was used. • All previous acne therapy was stopped 1 month before the start of the trial. • Evaluation was at 0, 2, 4, 8, and 12 weeks. • The area evaluated was the whole face. • The assessor was the same for each participant at all times. • 2 types of analysis were undertaken and compared; all those that actually completed the trial according to the protocol and all those who had taken 1 dose of the medicine. The following statistical methods were used: Wilcoxon matched pairs signed rank test and Wilcoxon 2-group test for unpaired data. The acne-graded data were analysed using the Mann-Whitney U test. The percentage change from baseline was analysed using the Mantel-Haenszel Chi² test.
Participants	109 participants were enrolled. 54 participants were randomised in the minocycline group, and 55 participants were randomised in the erythromycin group. There were 9 (17%) dropouts in the minocycline group and 7 (13%) in the erythromycin group. The mean age was 20.2 (range = 14 to 47). Recruitment was fulfilled through a hospital. There was baseline comparability for age, sex, extent of disease, NILC, superficial ILC, and ILC. The mean acne grade was slightly greater in minocycline participants: 1.18 (range 0.5 to 2.5) versus 0.89 (0.5 to 2.0). **Inclusion criteria of the trial** • Facial grade of 0.5 to 5 (Leeds) (Burke 1984) • > 12 years of age **Exclusion criteria of the trial** • Retinoids and hormonal preparations taken during the preceding 3 months, drug-induced/secondary acne, other dermatoses, women at risk of pregnancy, PREG, or BF

Interventions	• Minocycline 50 mg bd • 4% erythromycin /1.2% zinc acetate lotion topically bd Concomitant therapy: not specified Appearance: standard Instructions: lotion to be applied after washing morning and evening, 2 tablets to be taken 12 hours apart Skin hygiene: not specified Empty stomach: not specified Compliance: not specified
Outcomes	**Outcomes of the trial** 1. NIL count (Co, Cc), superficial IL count (PA, PU), and TILC (NOD, MAC, PA, PU) 2. Grade: Leeds (0 to 10) - overall response (0 to 5) derived from per cent reduction in lesion counts (Burke 1984) 3. Absolute and percentage change in lesion counts (primary outcome) 4. Participant-rated severity (10 cm VAS), diary card of severity 5. Adverse drug reactions as reported by the participants
Notes	Country: United Kingdom Language: English Review version: 2002 The minocycline counts were static after 2 weeks of therapy. The total inflamed lesion count were not valid as it included macules. The assessor guessed the therapy allocation in 7 cases. The results were presented in graphical form only, but additional information was supplied by the manufacturer.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 119): "Patients were allocated randomly, without stratification." No further details were given.
Allocation concealment (selection bias)	Unclear risk	This was unclear; no further details were given.
Blinding (performance bias and detection bias)	Unclear risk	This was single-blind. Quote: "The investigator clinically assessing a patent was not informed of which treatment that participant was on." But it was observed that the participant notes indicated that in 7 cases the assignment was guessed.
Incomplete outcome data (attrition bias)	Low risk	Yes, all participants, dropouts, and losses to follow up were accounted for.
Selective reporting (reporting bias)	Low risk	Yes, all outcomes were reported at each time point (assessments not planned at week 8 of study).

Stewart 2006 (MP010401)

Methods	• This was a double-blind RCT in a multicentre setting (phase 2 dose ranging). • The duration of the trial was 12 weeks (84 days). • The method of randomisation was not stated (stratified by weight of participant). • Industrial support came from Medicis Pharmaceutical Corporation who produce Solodyn®, the extended-release minocycline use in this trial. This conflict of interest was declared. • The use of UV control was not stated. • The inclusion criteria permitted the use of dietary supplements • It was not stated whether all previous oral or topical treatment was stopped prior to the start of the trial. • Evaluation was at baseline and days 28, 54, and 84. There were also safety assessments on these dates plus at days 7 and 91. • The area evaluated was the face. • The assessor was not stated. • An intention-to-treat analysis was used, which included all randomised participants who received the study drug. Where data were missing, the last observation carried forward technique was employed. The statistical analysis was undertaken using a 2-way analysis of variance (based on the treatment taken and which trial centre the participant was from) for lesion counts. A Cochrane Mantel-Haenszel analysis was used for the global grade outcomes and the percentage of individuals who had improved.
Participants	241 participants were enrolled, and 233 received study medication. Randomised was as follows: Minocycline 1 mg/kg n = 59, 2 mg/kg n = 59, 3 mg/kg n = 60; placebo n = 55. It was stratified based on participant weight. There were 49 dropouts: 8 participants were randomised but not given medication, 16 discontinued due to adverse events, 9 withdrew consent, 8 were lost to follow up, and for 16 no reasons were given (described as "other" on page 13). The dropouts were not stated by group. A total of 57 failed to complete trials to follow up, leaving 184 evaluable out of 241 randomised, or n = 231 who received medication. The mean age was 17.7 years (range = 17 to 19 year). It was not stated where participants were recruited from. The groups were comparable at baseline in terms of demographics and baseline lesion counts. Participants had moderate to severe acne. **Inclusion criteria of the trial** • 12 to 30 years of age • 39.1 kg to 102.3 kg (86 to 225 lb) • Moderate to severe facial acne vulgaris - they were required to have >/= 20 and < 100 facial IL, < 5 facial nodules or cysts • Women of childbearing potential had to have a negative urine pregnancy test result (25 microg/ml sensitivity) • OC **Exclusion criteria of the trial** • SENS; PREG; men with facial hair; use of supplements containing aluminium, calcium, iron, or magnesium, or vitamin A • A prior history of complicating illnesses or medications
Interventions	• Minocycline - extended-release daily: n = 59 1 mg/kg, n = 59 2 mg/kg, n = 60 3 mg/kg; placebo n = 55 Concomitant therapy: not stated Appearance: not stated Instructions: to be taken in the morning Skin hygiene: not stated Empty stomach: not stated Compliance: not stated

Outcomes	**Outcomes of the trial** 1. TLC, IL count, and NIL count 2. Investigator static global evaluation of acne severity (6-point scale) 3. Reduction in the number and percentage of inflammatory lesions (papules, pustules, nodules, and cysts) from baseline (day 1) to day 84, i.e. MIL (primary outcome) 4. Secondary efficacy end points: reduction in inflammatory lesions at interim visits (days 28 and 56); changes in non-inflammatory (open and closed comedones) and total (inflammatory and non-inflammatory) lesion counts, i.e. TIL; and changes in the Investigator's static global evaluation of acne severity 5. Adverse drug reactions: adverse events reported at each post-baseline visit (days 28, 54, and 84) and at telephone contacts on days 7 and 91 as well as ADEs recorded in each participant's daily diary during the first 5 days of treatment 6. Complete blood counts and serum chemistries were monitored at baseline and at the end of the study for evidence of clinically significant changes
Notes	Country: United States multicentre Language: English Review version: 2012

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was described as in the following quote (page 12): "Subjects randomly were assigned to 1 of 3 active treatments (1, 2 or 3 mg/kg daily) or placebo). No further details given about method of randomisation. Randomisation was stratified by participant's weight." Comment: This was probably done.
Allocation concealment (selection bias)	Unclear risk	No details were given. Comment: This was probably done.
Blinding (performance bias and detection bias)	Low risk	It was stated to be double-blind. Comment: This was probably done.
Incomplete outcome data (attrition bias)	Low risk	241 participants were randomised; 233 received treatment. 49 dropped out or were lost to follow up with reasons given in the Results (page 13). Analsyses were performed as ITT (on participants who received the study drug). "Last observation carried forward" was used to impute missing data.
Selective reporting (reporting bias)	Low risk	Primary outcomes: There was a reduction in the number of inflammatory lesions from day 1 to day 84. Secondary outcomes: There was a reduction in the number of inflammatory lesions at interim visits, changes in non-inflammatory (open and closed comedones) and total inflammatory and non-inflammatory lesion counts and changes in the investigator's static global evaluation of acne severity. Safety assessments. All outcomes were reported at given time points.

Waskiewicz 1992

Methods	• This was an open-label RCT in a hospital setting. • The duration of the trial was 12 weeks. • The method of randomisation was not stated. • Industrial support came from Biorga, France. • The use of UV control was not stated. • All previous acne therapy was withdrawn 6 weeks prior to the start of the trial. • Evaluation was at days 0, 15, 30, 60, and 90. • The area evaluated was 20 cm² of the face. • There was a single assessor. • A per-protocol analysis was used.
Participants	74 participants were enrolled. 38 participants were randomised in the minocycline group, and 36 participants were randomised in the doxycycline group. There were 8 (21%) dropouts in the minocycline group and 6 (17%) in the doxycycline group. The age of the participants was over 15 years. Recruitment was fulfilled by hospital out-patients. At baseline, the groups were compared to find differences between their TLC and acne score. **Inclusion criteria of the trial** • Acne vulgaris with inflammatory component • > 15 years **Exclusion criteria of the trial** • SENS, OC, comedonal acne, or previous isotretinoin therapy
Interventions	• Minocycline 100 mg od • Doxycycline 50 mg od Concomitant therapy: not permitted Appearance: standard Instructions: with main meal Skin hygiene: not specified Empty stomach: no Compliance: not specified
Outcomes	**Outcomes of the trial** 1. Score: Michaelson (Oc = 1, Cc = 2, PA = 3, PU = 4) 2. Cc count, Co count, PA count, PU count, and TLC (lesions counted by same clinician throughout study) 3. Percentage reduction in TLC and score from baseline (primary outcome) 4. Adverse drug reactions as reported by the participants through open questioning
Notes	Country: France Language: French Review version: 2002

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The investigators stated that the trial "was performed on 74 participants, randomly divided into 2 groups. In the course of the study 14 participants gave up and each of them was replaced by a new participant to maintain finally the number of 30 in each group. 3 participants dropped out and were re-included in the trial, 3 to 6 months after their dropout. In the meantime their acne did not improve spontaneously or with other treatments." Comment: It was unclear if the randomisation was adequate, but it was probably high risk of bias due to unusual randomisation method.
Allocation concealment (selection bias)	High risk	This was not used.
Blinding (performance bias and detection bias)	High risk	This was an open study.
Incomplete outcome data (attrition bias)	High risk	This was deemed high risk due to the re-inclusion of dropouts. 60/74 competed, three who withdrew were re-included after 3 to 6 months.
Selective reporting (reporting bias)	High risk	Results were given as percentage improvement and acne counts. No standard deviations were given.

Footnotes

Abbreviations: AA = azelaic acid; ACID = concomitant antacids; ADR = adverse drug reactions; BF = lactating/breast feeding; Cc = closed comedone; Co = open comedone; Dr-assessed = doctor (physician)-assessed; ECLA = Echelle de Cotation des Lésions d'Acné or Acne Lesion Score Scale; ER= extended-release; IL = inflammatory lesion; ILC = inflammatory lesion count; ILL = significant systemic illness; IRON = concomitant iron supplements; ITT = intention-to-treat analysis; LOCF = last observation carried forward; MAC = macule; MDR = history of multiple drug reactions; n = number; NA = not applicable; NIL = non-inflammatory lesion; NILC = non-inflammatory lesion count; NOD = nodule; OC = taking oral contraceptives; PA = papule; PREG = pregnancy; PU = pustule; RCT = Randomised controlled trial; SENS = history of sensitivity to tetracyclines; TLC = total lesion count; VAS = visual analogue scale; VERT = vertigo

Characteristics of excluded studies

Alberto 1990

Reason for exclusion	This was an uncontrolled clinical study.

Altieri 1989

Reason for exclusion	This was an uncontrolled clinical study.

Anonymous 2006

Reason for exclusion	This was a summary paper.

Arata 1969

Reason for exclusion	This undertook bacteriological evaluation, and there was no clinical data.

Arrese 1998

Reason for exclusion	This undertook bacterial viability evaluation, comparing minocycline and lymecycline. There was no clinical data.

Barba 1989

Reason for exclusion	This was an uncontrolled clinical study.

Barba Gomez 1990

Reason for exclusion	This was an uncontrolled clinical study.

Becker 1974

Reason for exclusion	This was an uncontrolled clinical study in participants with tetracycline-recalcitrant acne.

Bodokh 1997

Reason for exclusion	This was an RCT on the evaluation of impact of minocycline on pilosebaceous follicles.

Bok 1985

Reason for exclusion	This was an uncontrolled, retrospective clinical study.

Clerico 1984

Reason for exclusion	This was an uncontrolled clinical study.

Cohen1985

Reason for exclusion	This was an uncontrolled clinical study in participants with antibiotic-recalcitrant acne.

Coskey 1976

Reason for exclusion	This was an uncontrolled clinical study in participants with antibiotic-recalcitrant acne.

Cullen 1978

Reason for exclusion	This was an uncontrolled clinical study in participants with tetracycline-recalcitrant acne.

Degitz 2008

Reason for exclusion	This was a review.

Degreef 1983

Reason for exclusion	This was an uncontrolled clinical study in participants with antibiotic-recalcitrant acne.

Del Rosso 2004

Reason for exclusion	This was a review.

Donadini 1989

Reason for exclusion	All participants were given minocycline then they were randomised to topical treatment with either meclocycline or placebo.

Eady 1990

Reason for exclusion	This was a bacteriological investigation with additional clinical data.

Eady 1993

Reason for exclusion	This was a bacteriological investigation with additional clinical data.

Fernandez-Obregon 2000

Reason for exclusion	This was a retrospective study.

Funt 1985

Reason for exclusion	This was an uncontrolled clinical investigation of combination therapy with minocycline and ibuprofen.

Goto 1969

Reason for exclusion	This was a bacteriological investigation.

Goulden 1996

Reason for exclusion	This was a non-randomised uncontrolled study.

Gruber 1998

Reason for exclusion	This was a non-randomised controlled clinical trial.

Hughes 1989

Reason for exclusion	This was a non-randomised study in participants with acne recalcitrant to erythromycin/benzoyl peroxide combination therapy.

Jeanmougin 1987

Reason for exclusion	This was an uncontrolled clinical evaluation of combination therapy with minocycline and benzoyl peroxide.

Ketelbey 1988

Reason for exclusion	This was an uncontrolled clinical study.

Kircik 2010

Reason for exclusion	This was a review.

Kircik 2011

Reason for exclusion	This was a commentary of minocycline therapy for acne.

Kligman 1998

Reason for exclusion	This was a RCT of microbiological evaluation.

Knaggs 1993

Reason for exclusion	This was a retrospective study in participants with tetracycline-recalcitrant acne.

Kurka 1976

Reason for exclusion	This was an uncontrolled clinical study.

Laux 1987

Reason for exclusion	This was an interim analysis of Laux 1989.

Layton 1992

Reason for exclusion	This was an abstract of Knaggs 1993.

Leyden 1982

Reason for exclusion	This was a cross-over study with all participants receiving tetracycline 500 mg bd followed by minocycline 100 mg bd. This was a bacteriological investigation with additional clinical data.

Leyden 1996

Reason for exclusion	There were no clinical outcomes.

Leyden 1997a

Reason for exclusion	There were microbial outcomes only.

Leyden 2006(Part 1)

Reason for exclusion	The randomisation was broken.

Lowy 1982

Reason for exclusion	This was an uncontrolled clinical study.

Luderschimidt 1985

Reason for exclusion	There were no clinical outcomes; they were microbiological only.

Millar 1987

Reason for exclusion	This was an uncontrolled clinical study.

Minami 1969

Reason for exclusion	This was a bacteriological investigation.

Miura 1969

Reason for exclusion	This was a bacteriological investigation.

Mizuno 1980

Reason for exclusion	This was an uncontrolled clinical study.

Mobacken 1993

Reason for exclusion	This assessed lymecycline, not minocycline.

Monk 2011

Reason for exclusion	This was a review.

Montero 1972

Reason for exclusion	This was an uncontrolled clinical study.

Ng 2002

Reason for exclusion	This was a non-randomised prospective cohort looking at depressive symptoms in people treated with isotretinoin compared to antibiotics and topical.

Nishijima 1996

Reason for exclusion	This was a controlled clinical study with microbiological outcomes.

Ochsendorf 2010a

Reason for exclusion	This was a review.

Pablo 1975

Reason for exclusion	This was a RCT, but it analysed sebum by spectroscopy.

Pavone 1994

Reason for exclusion	This was a non-randomised, controlled, open-label study.

Randazzo 1981

Reason for exclusion	There was no control group for minocycline as all participants were allocated to minocycline then randomly assigned Varidase or placebo.

Reisner 1983

Reason for exclusion	This was a review.

Rocco 1998

Reason for exclusion	This trial entailed non-randomised microbiological evaluation with additional clinical data.

Rossman 1981

Reason for exclusion	This was an open-label, controlled, cross-over trial with no wash-out period. Participants were assigned to tetracycline 250 mg 4 times a day for 6 weeks followed by minocycline 50 mg tds for 6 weeks.

Sanchez 2006

Reason for exclusion	This was an uncontrolled trial.

Savage 2010

Reason for exclusion	This was a review.

Schulz 1984

Reason for exclusion	This was an uncontrolled clinical study.

Shalita 2011

Reason for exclusion	This was a review.

Sloan 2008

Reason for exclusion	This was a review of safety.

Takeuchi 1980

Reason for exclusion	This was an uncontrolled clinical study.

Thiboutot 2011

Reason for exclusion	This was a review.

Thielitz 2009

Reason for exclusion	This was a review.

Unna 1989

Reason for exclusion	This was an uncontrolled clinical study.

Villano 1984

Reason for exclusion	This was an uncontrolled clinical study.

Zaenglein 2006

Reason for exclusion	This was a review.

Footnotes

Characteristics of studies awaiting classification

Kawana 2007

Methods	We are not able to complete this cell; please see the 'Notes' cell.
Participants	Acne
Interventions	• Roxithromycin • Minocycline
Outcomes	• Efficacy
Notes	This paper could not be supplied by the British Library.

Revuz 1990

Methods	We are not able to complete this cell; please see the 'Notes' cell.
Participants	Acne
Interventions	• Minocycline • Zinc gluconate
Outcomes	• Efficacy
Notes	This paper could not be ordered. The authors were contacted, but they could not supply data.

Revuz 1993 [pers comm]

Methods	This was an double-blind RCT in a hospital setting (17 centres). The duration of the trial was 28 weeks. Industrial support came from Lederle.
Participants	300 participants were enrolled. 98, 96, and 100 participants were randomised, respectively. Recruitment was fulfilled by hospital out-patients.
Interventions	• Minocycline 100 mg od plus benzoyl peroxide (BP) (4 weeks) then placebo plus BP (24 weeks) • Minocycline 100 mg od plus BP (12 weeks) then placebo plus BP (16 weeks) • Minocycline 100 mg od plus BP (20 weeks) then placebo plus BP (8 weeks) The appearance of the capsules were identical.
Outcomes	These were not known.
Notes	Country: France Language: English Review version: 2002 The strength of the benzoyl peroxide was not known. The authors and sponsors were contacted for additional information. The author could not supply additional data.

Yoon 2005

Methods	We are not able to complete this cell; please see the 'Notes' cell.
Participants	Acne
Interventions	• Isotretinoin • Minocycline
Outcomes	• Cost of drug • Medical management of disease and any adverse reactions • Average total cost and cure rate • Cumulative reduction rates of grade • Recurrence rate • Total cost to final cumulative reduction rate and grade and relative cost-effectiveness ratio
Notes	This trial was written in Japanese, and it is awaiting translation. It was not clear if it was randomised.

Footnotes

Characteristics of ongoing studies

EUCTR2008-002642-32-GB

Study name	A Placebo Controlled, Single-Blind, Pilot Clinical Evaluation of the Effect of a Novel Antibiotic Preparation on the Cutaneous Microflora and Clinical Signs in Acne Patients
Methods	This is a randomised, single-blind trial.
Participants	Mild to moderate facial acne vulgaris: grade = 4
Interventions	• 2% minocycline gel • Placebo
Outcomes	• Cutaneous microflora • Lesion counts • Quality of life (Leeds scale) (Burke 1984)
Starting date	June 2009
Contact information	Warner Chilcott United Kingdom
Notes	It is not clear whether this trial has completed.

NCT00240513

Study name	A Randomized Study to Compare the Acne Relapse Rate After a 3-mo Course of Oral Minocycline, to a 3-mo Course of Oral Minocycline in Combination With a Daily Dose of Topical Tretinoin 0.01% Followed by 3 mo of Topical Tretinoin Alone [sic]
Methods	This is a RCT.
Participants	Diagnosis of acne vulgaris with a minimum of 20 IL on the face
Interventions	• Minocycline • Minocycline plus topical tretinoin 0.01%
Outcomes	• Long-term efficacy • Relapse rate at 4 years
Starting date	2004
Contact information	Richard Thomas (Principal Investigator) DermResearch @888 Inc Canada
Notes	The Clinical trials register states that this has been terminated.

NCT00392223

Study name	A Phase III, Multicenter, Randomized, Double Blind-Double Dummy Study, To Evaluate Efficacy And Safety Of Treatment With Azithromycin, Microspheres, Oral Powder For Suspension, 2 G, In One Administration A Week, For 8 Weeks, Compared With Treatment With Minocycline Capsules, 100 Mg Die For 8 Weeks, In Outpatients With Moderate To Severe Inflammatory Acne
Methods	This is a randomised, double-blind, phase III trial in a multicentre setting (8 weeks).
Participants	Moderate to severe acne vulgaris
Interventions	• Minocycline 100 mg per day • Azithromycin microspheres oral powder for suspension 2 g - 1 administration per week
Outcomes	• Global acne grading system • Leeds score (Burke 1984)
Starting date	October 2007
Contact information	Pfizer Italy
Notes	This was terminated.

NCT00988026

Study name	Safety and Efficacy Comparison of Minocycline Microgranules vs Lymecycline in the Treatment of Mild to Moderate Acne. Randomized, Double Blind, Parallel and Prospective Clinical Trial for 8 Weeks
Methods	This is a randomised, parallel-assignment, double-blind, phase IV trial (8 weeks).
Participants	Mild to moderate acne: > 20 NIL and > 15 IL
Interventions	• Minocycline microgranules • Lymecycline
Outcomes	• Lesion counts • Adverse events
Starting date	June 2009
Contact information	Luis Leobardo Velazequez-Arenas leovel2002@yahoo.com.mx
Notes	-

NCT01206348

Study name	A Phase IV, Open-Label Study Evaluating the Use of Solodyn® (Minocycline HCL Extended-Release Tablets), Ziana, and Triaz Foaming Cloths as Combination Acne Therapy Prior to Treatment With Isotretinoin
Methods	This is a phase IV, open-label RCT (12 weeks).
Participants	Moderate to severe acne
Interventions	• Minocycline • Clindamycin • Tretinoin • Benzoyl peroxide
Outcomes	• Proportion of participants showing improvement from baseline
Starting date	September 2010
Contact information	Medicis Global Service Corporation
Notes	This has been completed.

NCT01362010

Study name	Pilot, Multicenter, Randomized, Double Blind, Placebo Controlled, Parallel Group, Dose Range Finding Study, to Evaluate the Tolerability and Safety of FXFM244 Antibiotic Foam and to Monitor Its Clinical Effect in Acne Vulgaris Patients
Methods	This is a pilot, randomised, double-blind, placebo-controlled, parallel-group, dose-range-finding trial in a multicentre setting.
Participants	Acne vulgaris: minimum of 20, but not more than 50, inflammatory lesions, and 20 to 100 non-inflammatory lesions
Interventions	• Topical minocycline foam • Placebo
Outcomes	• Vital signs • Adverse events • Lesion counts • Global assessments (investigator) • Percentage change in lesion count • Global assessment by photograph • Subjective assessment by the participant
Starting date	July 2011 (but stated as not yet recruiting)
Contact information	Avner Shemer Tel-Nordau Clalit health services
Notes	-

Footnotes

NA = not applicable

Summary of findings tables

Additional tables

1 Glossary of terms

Medical term	Explanation/description
Antineutrophil antibody (ANA) positivity	Antineutrophil antibodies are a group of autoantibodies. They are detected in a blood test in a number of autoimmune disorders
Autoimmune hepatitis	A disease of the liver that occurs when the body's immune system attacks cells of the liver
Benign intracranial hypertension	Also known as 'pseudotumour cerebri', this is a syndrome that shows increased pressure in the brain that is not caused by tumours. Symptoms are the same as those that result from brain tumours and other types of intracranial hypertension. They include headaches, nausea, double vision, and loss of vision. There is some controversy between different groups about the causes, but there are some known causes, including several prescription medications
Dual-flow cytometry analysis	An analytical method that is laser-based and used to count cells and detect biomarkers
Eosinophilia	An increase in the number of a type of white blood cells known as eosinophils
Matrix metalloproteinase inhibitors	A drug that stops the action of zinc-dependent proteases (enzymes that break down proteins)
Nephritis	Nephritis is inflammation of the nephrons in the kidneys
Pneumonitis	Inflammation of lung tissue
Polyarteritis nodosa	A disease of unknown cause that affects arteries
Proteolytic tissue damage	Tissue damage caused by proteolysis (the breakdown of proteins into smaller polypeptides or amino acids)
Serological marker	Serology is the science that deals with the characterisation of serum, the non-cellular component of blood. Serological markers are used to distinguish specific diseases in individuals. These markers are invaluable in the detection of some cancers, especially due to their potential in identifying the early stages of the disease, prior to the onset of symptoms
Serum-sickness-like syndrome	Serum-sickness-like reactions are specific drug reactions that cause a range of symptoms, including fever, skin rash, swelling of the mouth and lymph nodes, joint and muscle pain and protein in the urine
Systemic lupus erythematosus-like syndrome	Systemic lupus erythematosus often abbreviated to 'SLE' or 'lupus', is a systemic autoimmune disease (or autoimmune connective tissue disease) that can affect any part of the body. As occurs in other autoimmune diseases, the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage

Footnotes

2 Relative costs of oral antibiotics for acne (BNF April 2012)

Antibiotic	Dose unit	Number of capsules/tablets	Cost per pack (£)	7-day cost (1 g or 100 mg)
Tetracycline	250 mg	28	13.35	13.35
Oxytetracycline generic	250 mg	*28*	1.19	1.19
Lymecycline (Tetralysal)	300 mg	28	7.77	7.77
-	300 mg	56	14.97	7.49
Doxycycline generic	50 mg	28	1.70	1.70
-	100 mg	*8*	1.03	0.90
Doxycycline (Vibramycin)	100 mg	8	4.91	4.30
Doxycycline ER (Efracea)	40 mg	56	29.78	Not acne
Minocycline generic	50 mg	56 capsules	15.27	3.82
-	100 mg	28 capsules	13.09	3.27
-	50 mg	28 tablets	4.76	2.38
-	100 mg	28 tablets	10.97	2.74
Minocycline ER generic	100 mg	56 capsules	20.08	2.51
Erythromycin generic	-	-	-	-
Erythrocin	250 mg	100 tablets	18.20	5.10
-	500 mg	100 tablets	36.40	5.10
Erymax	250 mg	28 capsules	5.61	5.61
-	-	112 capsules	22.44	5.61
Erythroped A	500 mg	28	10.78	5.39
Trimethoprim generic	100 mg	28	0.88	0.44
-	200 mg	14	0.82	n/a

Footnotes

3 Minocyline adverse events

Author	Adverse event	Methods	Population	Case Definition	Number of cases	Interventions	Outcom
Angulo 1998	Coexisting systemic lupus erythematosus (SLE) and autoimmune hepatitis	A systematic review of MEDLINE - 1966 to April 1998. Not all search terms were stated. Bibliographies were searched	Any patients treated with tetracycline	SLE, Autoimmune hepatitis, arthritis, lupus, chronic hepatitis, antimyeloperoxidase, vasculitis, and toxicity	There were 60 cases of systematic lupus erythematosus, and 24 cases of minocycline-induced autoimmune hepatitis. 13/84 had both conditions	Minocycline 'long-term' therapy	Clincial sympto laborat for liver involve and autoant

Fay 2008	Hyperpigmentation	Retrospective medical record review of patients with rheumatoid arthritis (RA) visiting 2 centres (1992 to 2005)	Rheumatoid arthritis	4/7 had American College of Rheumatologists criteria for RA or diagnosis from a board-certified rheumatologist. Hyperpigmentiation when the rheumatologist, physical exam, or both consistent with this finding	44/121 (36%) participants receiving at least 1 course of minocycline of 30 days or more	Minocycline	Bluish-g muddy-discolou non-bla non-tra
Goulden 1996	All adverse events	Cohort study to estimate the absolute incidence of common ADRs	Acne	-	95/700 patients (13.6%) experienced a side-effect attributable to minocycline.The mean duration of treatment was 10.5 months (range 2 weeks to 4 years)	Minocycline	-
Grasset 2003	All - systemic disease, drug-induced lupus, hepatitis, autoimmune vasculitis, hypersensitivity reactions (DRESS: drug reaction with eosinophilia and systemic symptoms), pseudodisease serum, intracranial hypertension, abnormal pigmentation, and various other side-effects	Comprehensive systematic literature review (search methods reported): MEDLINE, IPA (International Pharmaceutical Abstracts), EMBASE (current contents, 1997-2001). The search resulted in 96 papers, of which 70 were eligible for review	Acne	-	-	All tetracyclines	Clinical sympto laborato for auto disease markers

Ten Holder 2002	Cutaneous and systemic manifestations of drug-induced vasculitis	MEDLINE 1965 to December 1999. Not all search terms were stated (English-language only). The results were not systematically stated. Bibliography review	All	Included drug-induced vasculitis, Churg-Strauss syndrome, Good pastures syndrome, Henoch-Schonlein purpura, polyarteritis nodosa, Wegeners granulomatosus, hypersensitivity vasculitis, microscopic polyangiitis, serum-sickness, and cryoglobulinaemia	13 cases of vasculitis in a second course of therapy following an uneventful first course	All drugs	Death, laborat measur autoimr disease markers
Lawrenson 2000	Liver damage	Systematic review. MEDLINE CINAHL Cochrane EMBASE Current Contents TOXLINE (earliest available to December 1998). The search terms were stated. English, French, German, Swedish and Spanish Bibliographic databases Grey literature A Citation search was undertaken using the BIDS database. Data on the number of adverse events reported was taken from the Uppssala Monitoring Center for the time period 1968 - October 1998. Sales data were obtained from the company 'Intercontinental Medical Statistics'. All references of the retrieved articles were searched for further relevant publications.	Literature review: acne WHO: all reactions	Liver damage: 1) liver disease (fatty liver, liver failure, liver function tests, liver transplantation, hepatic dysfunction); 2) Hepatitis (hepatitis, autoimmune hepatitis, chronic hepatitis, chronic drug-induced hepatitis, toxic hepatitis); and 3) jaundice	65 case reports in the literature review WHO: 493/8025 (6%) reactions recorded as involving the liver	Minocycline	Altered enzyme positive histolog evidenc chronic hepatiti Autoimr hepatiti mortalit minocyc related hepatot

Lebrun-Vignes 2012 (AFSSAPS 2009)	All	Review of spontaneous reports to the French National Pharmacovigilence Committee. Data from Marketing Authorisation Holders. Sales figures taken into account	All patients receiving tetracycline therapy	Any adverse event reported	924	Minocycline, doxycycline, metacycline and lymecycline	Adverse Serious adverse

Margolis 2007	Lupus erythematosus	Retrospective cohort study. United Kingdom Health Improvement Network database	Acne	History of acne; at least one year of follow-up; between age of 15 to 35. Diagnosis of LE; systemic or cutaneous as determined by the GP.	97 694 individuals with acne. 24 282 exposed to minocycline 5% random sample of age-matched individuals from entire database used to provide estimate of incidence in general population.	Tetracyclines	Diagnos LE; sys cutaneo determi the GP.
Margolis 2010	Inflammatory bowel disease (IBD)	Retrospective cohort study United Kingdom Health Improvement Nework database	Acne	History of acne; at least one year of follow-up; between age of 15 to 35. Diagnosis of LE; systemic or cutaneous as determined by the GP.	94,487 individuals with acne. 24,085 individuals with a minocycline prescription, 41 of whom developed IBD.	Tetracyclines	Diagnos IBD as determi GP.
Marzo-Ortega 2007	Antineutorophil antibody (ANA) and Antineutrophil cytoplasmic antibody (ANCA) positivity.	Cross sectional study of consecutive patients attending United Kingdom acne clinic June 1998 and Oct 1999.	Acne	Acne patients who agreed to participate in study. Retrospective review of experience	252 consecutive patients with acne who agreed to participate. 174 (69%) exposed to minocycline	Mnocycline	Blood te ANA, A liver fur tests ar analysis

Schlienger 2000	Lupus	Systematic review. MEDLINE 1966 to October 1999 EMBASE Search terms stated: minocycline, arthritis, arthralgia, lupus, SLE. English and non-English Bibliographies searched Cases screened,	All	1) No history of SLE before minocycline started. 2) positive ANA along with at least one clinical feature of SLE 3) recovery after minocycline withdrawal.	57 cases (27 publications)	Minocycline	Clinical manifes time to exposu laborat manifes
Schoonen 2010	Lupus	Matched case-control study using the general practice research database (GPRD) between 1987 and 2001.	All	SLE or drug-induced lupus.	875 cases with no comorbid autoimmune condition and 3632 controls matched for age, gender and the medical practice attended.	A number of drugs, including minocycline	Diagnos lupus.
Seaman 2001	Liver damage	Cohort analysis and case-control study using the United Kingdom General Practice Research database which contains the anonymous records of approximately 8 million people.	All	Cohort: new users of minocycline compared with new users of oxytetracycline, tetracycline Case-control study assessing antibiotic exposure in new cases of liver dysfunction in those exposed to minocycline	Cohort: 153,530 with a diagnosis of acne. 29,332 (19.1%) exposed to minocycline - who had not previously been exposed. 13 new users with liver-dysfunction. Case-control: 250 cases of liver dysfunction.	Minocycline oxytetracycline tetracycline	Liver dysfunc Raised enzyme jaundic dysfunc hepatiti failure.

Shapiro 1997	Hypersensitivity syndrome reaction (HSR), serum-sickness like reaction (SSLR), single organ dysfunction (SOD) and drug induced lupus (DIL)	Case series. MEDLINE (1966 to October 1996): search terms not all stated. Ontario drug safety clinic database Adverse Drug Reaction Monitoring Division of the Canadian Heath Protection Branch. Utilisation data from IMS to identify prescribing patterns.	All	Separate definitions provided for each condition.	19 reports of HSR, 11 reports of SSLR, 40 reports of SOD, 33 reports of DIL attributable to minocycline.	Tetracycline Minocycline Doxycycline	Autoimr drug-inc reactior hyperse
Smith 2005	All	Systematic review, of safety of doxycycline and minocycline. MEDLINE Embase Biosis 1966 and August 2003 Search terms stated FDA MedWatch data. English language only number of new prescriptions Jan 1998 to Aug 2003.	All	Adverse event, adverse reaction, side-effect.	333 AEs with minocycline and 130 with doxycycline MEDWATCH: 628 with doxycyline and 1099 minocycline Approx 47.63 million doxycycline prescriptions and 15.235 million minocycline prescriptions	Doxycycline Minocycline	n/a

Sturkenboom 1999	Drug-induced SLE	Case-control study. Cohort of participants identified by the General Practice Research Database	Acne	Cases were included if they had negative findings in a rheumatoid arthritis test or latex agglutination test, positive or unmeasured anti-nuclear antibodies, elevated or unmeasured ESR or absent or unmeasured anti-DNA antibodies	27688 acne patients aged 15 to 29. Each case identified matched with 8 controls. 29 participants with lupus like syndrome matched with 152 controls. 27 of whom were women	Minocycline or other tetracyclines.	-

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Data and analyses

1 Minocycline 100 mg bd versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Inflamed lesion count - percentage change from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.1.1 Week 12 - per-protocol - inflamed lesions	1		Mean Difference(IV, Fixed, 95% CI)	No totals

2 Minocycline ER versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Percentage change in inflamed lesion counts	3	1038	Mean Difference(IV, Fixed, 95% CI)	13.43[7.10, 19.76]
2.2 Percentage change in total lesion counts	3	1038	Mean Difference(IV, Fixed, 95% CI)	9.84[4.84, 14.84]
2.3 Investigator global severity - successful treatment	2	924	Risk Ratio(M-H, Fixed, 95% CI)	1.90[1.27, 2.84]
2.4 Clear or almost clear 12 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
2.4.1 3 mg versus placebo	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
2.4.2 2 mg versus placebo	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
2.4.3 1 mg versus placebo	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
2.4.4 Pooled	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

3 Minocycline ER dose response

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Clear or almost clear 12 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
3.1.1 3 mg/kg versus 2 mg	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
3.1.2 3 mg versus 1 mg	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
3.1.3 2 mg versus 1 mg	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

4 Minocycline 100 mg od versus 100 mg/50 mg od

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Lesion counts - reduction from baseline after 60 days therapy	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.1.1 Non-inflamed: intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.1.2 Non-inflamed lesions: per-protocol analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.1.3 Inflamed lesions: intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.1.4 Inflamed lesions: per-protocol analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.1.5 Total lesions: intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.1.6 Total lesions: per-protocol analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals

4.2 Overall clinical improvement - dr-assessed	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
4.2.1 Any improvement: intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
4.2.2 Any improvement: per-protocol analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
4.2.3 Any improvement: worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
4.2.4 Moderate or excellent improvement: intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
4.2.5 Moderate or excellent improvement: per-protocol analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
4.2.6 Moderate or excellent improvement: worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
4.3 Participant evaluations - 10 cm visual analogue scales	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.1 Overall efficacy: intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.2 Overall efficacy: per-protocol analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.3 Importance of acne - change from baseline: intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.4 Importance of acne - change from baseline: per-protocol analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.5 Impact on relationships - change from baseline: intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.6 Impact on relationships - change from baseline: per-protocol analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.7 Impact on sexual relationships - change from baseline: intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.8 Impact on sexual relationships - change from baseline: per-protocol analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.9 Impact on physical appearance - change from baseline: intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
4.3.10 Impact on physical appearance - change from baseline: per-protocol analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals

5 Minocycline 50 mg bd/100 mg od versus (oxy)tetracycline 250 mg qd/bd

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Cook grading scale - number of participants improved by at least two grades	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.1.1 Week 2	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.1.2 Week 4	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.1.3 Week 8	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.1.4 Week 12	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.2 Decrease in inflamed lesion count from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.2.1 Week 6	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.2.2 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.2.3 Week 18	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.2.4 Week 18: least squares mean adjusted	1		Mean Difference(IV, Fixed, 95% CI)	No totals

5.3 At least moderate improvement according to participant	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.3.1 6 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.3.2 12 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.3.3 18 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.4 At least moderate improvement according to assessor	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.4.1 6 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.4.2 12 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.4.3 18 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.5 Samuelson lesion grade as assessed by physician	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.5.1 Baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.5.2 Week 2	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.5.3 Week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.5.4 Week 6	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.5.5 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.5.6 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.6 Samuelson lesion grade as assessed by participant	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.6.1 Baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.6.2 Week 2	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.6.3 Week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.6.4 Week 6	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.6.5 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.6.6 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.7 Number of participants converting to Pillsbury grade I	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.7.1 Week 6: intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.7.2 Week 6: per-protocol analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.7.3 Week 24: intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.7.4 Week 24: per-protocol analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
5.8 Overall improvement	4		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
5.8.1 Week 6: investigator-assessed	2	148	Risk Ratio(M-H, Fixed, 95% CI)	1.43[1.04, 1.96]
5.8.2 Week 12: investigator-assessed	3	199	Risk Ratio(M-H, Fixed, 95% CI)	0.97[0.83, 1.13]
5.8.3 Week 24: investigator-assessed	1	104	Risk Ratio(M-H, Fixed, 95% CI)	1.28[0.79, 2.07]
5.8.4 Week 12: participant-assessed	1	100	Risk Ratio(M-H, Fixed, 95% CI)	0.97[0.72, 1.31]
5.8.5 Week 18: satisfactory overall clinical response: participant-assessed	1	100	Risk Ratio(M-H, Fixed, 95% CI)	0.89[0.68, 1.16]
5.8.6 Week 18: participant-assessed	1	100	Risk Ratio(M-H, Fixed, 95% CI)	0.97[0.72, 1.31]
5.8.7 Week 18: investigator-assessed	1	100	Risk Ratio(M-H, Fixed, 95% CI)	0.97[0.72, 1.31]
5.9 Khanna acne lesion score: absolute reduction from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.9.1 Week 6	1		Mean Difference(IV, Fixed, 95% CI)	No totals
5.9.2 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals

6 Minocycline versus lymecycline

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

6.1 Lesion count - absolute change from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.1 Inflamed lesions (including nodules) - week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.2 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.3 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.4 End point - intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.5 Non-inflamed lesions - week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.6 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.7 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.8 End point - intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.9 Total lesions - week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.10 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.11 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.1.12 End point - intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2 Lesion count - percentage change from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.1 Inflamed lesions (including nodules) - week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.2 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.3 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.4 End point - intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.5 Non-inflamed lesions - week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.6 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.7 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.8 End point - intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.9 Total lesions - week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.10 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.11 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.2.12 End point - intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals

6.3 Lesion count - number of participants achieving > 25% reduction	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.1 TLC: Week 4 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.2 TLC: Week 8 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.3 TLC: Week 12 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.4 TLC: Week 4 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.5 TLC: Week 8 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.6 TLC: Week 12 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.7 TLC: End point - intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.8 IL : Week 4 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.9 IL: Week 8 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.10 IL: Week 12 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.11 IL: Week 4 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.12 IL: Week 8 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.13 IL: Week 12 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.14 IL: End point - intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.15 NIL: Week 4 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.16 NIL: Week 8 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.17 NIL: Week 12 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.18 NIL: Week 4 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.19 NIL: Week 8 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.20 NIL: Week 12 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.3.21 NIL: End point - intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

6.4 Lesion count - number of participants achieving > 50% reduction	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.1 TLC: Week 4 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.2 TLC: Week 8 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.3 TLC: Week 12 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.4 TLC: Week 4 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.5 TLC: Week 8 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.6 TLC: Week 12 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.7 TLC: End point - intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.8 IL: Week 4 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.9 IL: Week 8 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.10 IL: Week 12 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.11 IL: Week 4 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.12 IL: Week 8 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.13 IL: Week 12 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.14 IL: End point - intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.15 NIL: Week 4 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.16 NIL: Week 8 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.17 NIL: Week 12 - per-protocol	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.18 NIL: Week 4 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.19 NIL: Week 8 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.20 NIL: Week 12 - worse-case analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.4.21 NIL: End point - intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
6.5 Leeds grade	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.5.1 Absolute change from baseline - week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.5.2 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.5.3 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.5.4 End point - intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.5.5 Percentage change from baseline - week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.5.6 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.5.7 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
6.5.8 End point - intention-to-treat analysis	1		Mean Difference(IV, Fixed, 95% CI)	No totals

6.6 Global assessment - number of participants with overall improvement	2		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
6.6.1 Participant - per-protocol analysis	1	144	Risk Ratio(M-H, Fixed, 95% CI)	1.10[0.93, 1.30]
6.6.2 Participant - intention-to-treat analysis	2	270	Risk Ratio(M-H, Fixed, 95% CI)	0.95[0.85, 1.06]
6.6.3 Participant - assigned worse outcome analysis	1	144	Risk Ratio(M-H, Fixed, 95% CI)	1.06[0.91, 1.24]
6.6.4 Doctor - per-protocol analysis	1	114	Risk Ratio(M-H, Fixed, 95% CI)	1.03[0.91, 1.17]
6.6.5 Doctor - intention-to-treat analysis	2	270	Risk Ratio(M-H, Fixed, 95% CI)	0.94[0.85, 1.04]
6.6.6 Doctor - assigned worse outcome analysis	1	144	Risk Ratio(M-H, Fixed, 95% CI)	1.06[0.91, 1.24]

7 Minocycline versus doxycycline

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Number of participants with > 50% reduction in IL count	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
7.2 Global efficacy rating	3		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
7.2.1 Overal efficacy: participant-assessed	1	64	Risk Ratio(M-H, Fixed, 95% CI)	1.06[0.89, 1.28]
7.2.2 Overal efficacy: investigator-assessed	3	150	Risk Ratio(M-H, Fixed, 95% CI)	0.99[0.88, 1.12]
7.3 Cure	1	50	Risk Ratio(M-H, Fixed, 95% CI)	0.50[0.10, 2.49]
7.4 Other outcome	3		Other data	No numeric data

8 Minocycline 100 mg/200 mg per day versus josamycin 500 mg/1000 mg

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Pustules change in P&K severity grade 8 weeks	1	122	Mean Difference(IV, Fixed, 95% CI)	0.30[0.07, 0.53]
8.2 Nodulo-cysts change in P&K severity grade 8 weeks	1	122	Mean Difference(IV, Fixed, 95% CI)	0.40[0.20, 0.60]
8.3 Erythema change in severity score 8 weeks	1	122	Mean Difference(IV, Fixed, 95% CI)	0.30[0.12, 0.48]
8.4 Seborrhea change in severity score 8 weeks	1	122	Mean Difference(IV, Fixed, 95% CI)	0.40[0.22, 0.58]
8.5 Evaluation of clinical efficacy 8 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
8.5.1 Markedly effective	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
8.5.2 Effective	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
8.5.3 Moderately effective	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
8.5.4 Combined effective or markedly effective	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
8.5.5 Ineffective	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

9 Minocycline 50 mg bd versus Diane™ (cyproterone acetate 2 mg/ethinyloestradiol 50 mcg)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
9.1 Participant-subjective evaluation	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
9.1.1 Improved - intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
9.1.2 Improved - per-protocol analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
9.1.3 Cleared - intention-to-treat analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
9.1.4 Cleared - per-protocol analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

10 Minocycline100 mg bd versus compound A

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

10.1 Inflamed lesion count - percentage change from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
10.1.1 Week 12 - per-protocol - inflamed lesions	1		Mean Difference(IV, Fixed, 95% CI)	No totals

11 Minocycline 100 mg daily versus zinc gluconate 30 mg bd

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
11.1 Lesion count - percentage change from baseline 90 days	1	318	Mean Difference(IV, Fixed, 95% CI)	-16.42[-25.10, -7.74]
11.1.1 Inflamed lesion counts - papules pustules	1	318	Mean Difference(IV, Fixed, 95% CI)	-16.42[-25.10, -7.74]
11.2 Investigator global severity - successful treatment (2/3 reduction in IL)	1	318	Risk Ratio(M-H, Fixed, 95% CI)	2.03[1.56, 2.63]
11.3 Overall opinion on efficacy (100 mm VAS)	1		Mean Difference(IV, Fixed, 95% CI)	Subtotals only
11.3.1 Clinician-assessed	1	307	Mean Difference(IV, Fixed, 95% CI)	13.70[7.67, 19.73]
11.3.2 Participant-assessed	1	296	Mean Difference(IV, Fixed, 95% CI)	16.70[10.68, 22.72]

12 Minocycline 50 mg bd versus clindamycin 1% lotion bd

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
12.1 Overall improvement - participant-assessed	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

13 Minocycline 50 mg bd versus fusidic acid 2% lotion bd

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
13.1 Participants achieving > 40% reduction in lesion counts	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.1.1 Total lesion counts	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.1.2 Inflammatory lesions	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.1.3 Non-inflammatory lesions	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.1.4 Any lesion count	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.2 Lesion count changes from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.1 Inflamed lesions - week 2	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.2 Week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.3 Week 6	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.4 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.5 End of treatment	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.6 Non-inflamed lesions - week 2	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.7 Week 4	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.8 Week 6	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.9 Week 8	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.2.10 End of treatment	1		Mean Difference(IV, Fixed, 95% CI)	No totals
13.3 Overall clinical response	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.1 Participants with average or greater response - week 2	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.2 Week 4	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.3 Week 6	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.4 Week 8	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.5 End of treatment	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.6 Participants with good or very good response - week 2	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.7 Week 4	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.8 Week 6	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.9 Week 8	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
13.3.10 End of treatment	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

14 Minocycline 50 mg bd versus zineryt bd (erythromycin 4%/zinc 1.2% lotion)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
14.1 12-week lesion count - change from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
14.1.1 Non-inflamed week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
14.1.2 Inflamed lesions week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals
14.2 12-week percentage of baseline lesion counts	1		Mean Difference(IV, Fixed, 95% CI)	No totals
14.2.1 Non-inflamed lesions	1		Mean Difference(IV, Fixed, 95% CI)	No totals
14.2.2 Superficial inflamed lesions	1		Mean Difference(IV, Fixed, 95% CI)	No totals
14.2.3 Total inflamed lesions	1		Mean Difference(IV, Fixed, 95% CI)	No totals
14.3 Number of participants attaining > 45% reduction in lesion counts from baseline	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
14.3.1 Inflamed week 12	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
14.3.2 Non-inflamed week 12	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
14.4 Leeds grade - change from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
14.4.1 Week 12	1		Mean Difference(IV, Fixed, 95% CI)	No totals

15 Minocycline 100 mg ER od versus benzoyl peroxide bd

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
15.1 Overall improvement - participant assessed at least moderate improvement at 18 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
15.2 Overall improvement - assessor at least moderate improvement at 18 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
15.3 Lesion count - change from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
15.3.1 Inflamed lesions	1		Mean Difference(IV, Fixed, 95% CI)	No totals

16 Minocycline 100 mg ER od versus erythromycin/benzoyl peroxide (ery/BP) bd

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
16.1 Overall improvement - participant assessed at least moderate improvement at 18 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
16.2 Overall improvement - assessor at least moderate improvement at 18 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
16.3 Lesion count - change from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
16.3.1 Inflamed lesions	1		Mean Difference(IV, Fixed, 95% CI)	No totals

17 Minocycline 100 mg ER od versus erythromycin od/benzoyl peroxide (ery/BP) od

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
17.1 Overall improvement - participant assessed at least moderate improvement at 18 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
17.2 Overall improvement - assessor at least moderate improvement at 18 weeks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
17.3 Lesion count - change from baseline	1		Mean Difference(IV, Fixed, 95% CI)	No totals
17.3.1 Inflamed lesions	1		Mean Difference(IV, Fixed, 95% CI)	No totals

18 Combination with 5% benzoyl peroxide/4% chlorhexidine

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate

18.1 Lesion count	1		Mean Difference(IV, Fixed, 95% CI)	No totals
18.1.1 Pustules (active) - actual values	1		Mean Difference(IV, Fixed, 95% CI)	No totals
18.1.2 Pustules (active) - adjusted values	1		Mean Difference(IV, Fixed, 95% CI)	No totals
18.1.3 Papules (active) - actual values	1		Mean Difference(IV, Fixed, 95% CI)	No totals
18.1.4 Papules (active) - adjusted values	1		Mean Difference(IV, Fixed, 95% CI)	No totals
18.1.5 Total lesion count - actual values	1		Mean Difference(IV, Fixed, 95% CI)	No totals
18.1.6 Total lesion count - adjusted values	1		Mean Difference(IV, Fixed, 95% CI)	No totals
18.1.7 Lesion score - actual values	1		Mean Difference(IV, Fixed, 95% CI)	No totals
18.1.8 Lesion score - adjusted values	1		Mean Difference(IV, Fixed, 95% CI)	No totals

19 Minocycline versus placebo plus combination erythromycin/tretinoin gel (strength unspecified)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
19.1 Global grade - good/very good response	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
19.1.1 Dr-assessed: 'worse-case' analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
19.1.2 Dr-assessed: per-protocol analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
19.1.3 Participant-assessed: 'worse-case' analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
19.1.4 Participant-assessed: per-protocol analysis	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

20 Minocycline/azelaic acid (min/AA) versus isotretinoin

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
20.1 Number of participants with good or very good response after 6 months	1	85	Risk Ratio(M-H, Random, 95% CI)	0.93[0.83, 1.03]
20.2 Reduction in NIL: percentage change from baseline	1	85	Mean Difference(IV, Fixed, 95% CI)	-14.00[-27.80, -0.20]
20.3 Reduction in IL: percentage change from baseline	1	85	Mean Difference(IV, Fixed, 95% CI)	-8.90[-17.67, -0.13]

21 Minocycline 100 mg od maintenance

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
21.1 Lesion count - percentage change from baseline versus tazarotene	1		Mean Difference(IV, Fixed, 95% CI)	No totals
21.1.1 NIL	1		Mean Difference(IV, Fixed, 95% CI)	No totals
21.1.2 IL	1		Mean Difference(IV, Fixed, 95% CI)	No totals
21.2 Overall disease severity score versus tazarotene	1		Mean Difference(IV, Fixed, 95% CI)	Subtotals only
21.3 Overall clinical improvement - Dr-assessed versus tazarotene	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
21.3.1 < = 50%	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
21.3.2 > = 75%	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
21.4 Lesion count - percentage change from baseline versus tazarotene/minocycline combination	1		Mean Difference(IV, Fixed, 95% CI)	No totals
21.4.1 IL	1		Mean Difference(IV, Fixed, 95% CI)	No totals
21.4.2 NIL	1		Mean Difference(IV, Fixed, 95% CI)	No totals
21.5 Overall disease severity score versus tazarotene/minocycline combination	1		Mean Difference(IV, Fixed, 95% CI)	Subtotals only

21.6 Overall clinical improvement - Dr-assessed versus tazarotene/minocycline combination	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
21.6.1 < = 50%	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
21.6.2 > = 75%	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

22 Adverse drug reactions

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
22.1 All reactions	24		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
22.1.1 Placebo	2	262	Risk Ratio(M-H, Fixed, 95% CI)	1.25[0.95, 1.65]
22.1.2 100 mg od versus 100 mg/50 mg od	1	325	Risk Ratio(M-H, Fixed, 95% CI)	1.15[0.62, 2.15]
22.1.3 Dose response 3 mg/kg vs 2 mg/kg	1	119	Risk Ratio(M-H, Fixed, 95% CI)	1.16[0.87, 1.56]
22.1.4 Dose response 3 mg/kg vs 1 mg/kg	1	119	Risk Ratio(M-H, Fixed, 95% CI)	1.24[0.91, 1.68]
22.1.5 (Oxy)tetracycline	7	806	Risk Ratio(M-H, Fixed, 95% CI)	0.73[0.53, 1.01]
22.1.6 (Oxy)tetracycline (Bleschmidt removed)	4	321	Risk Ratio(M-H, Fixed, 95% CI)	1.07[0.59, 1.95]
22.1.7 Dose response 2 mg/kg vs 1 mg/kg	1	118	Risk Ratio(M-H, Fixed, 95% CI)	1.06[0.76, 1.48]
22.1.8 Tetracycline 500 mg/day	4	321	Risk Ratio(M-H, Fixed, 95% CI)	1.07[0.59, 1.95]
22.1.9 Tetracycline 1 g/day	2	291	Risk Ratio(M-H, Fixed, 95% CI)	0.70[0.39, 1.25]
22.1.10 Doxycycline	2	179	Risk Ratio(M-H, Fixed, 95% CI)	1.10[0.52, 2.33]
22.1.11 Lymecycline	3	364	Risk Ratio(M-H, Fixed, 95% CI)	0.95[0.66, 1.37]
22.1.12 Faropenem	1	100	Risk Ratio(M-H, Fixed, 95% CI)	0.69[0.12, 3.98]
22.1.13 Roxithromycin	1	99	Risk Ratio(M-H, Fixed, 95% CI)	5.10[0.25, 103.59]
22.1.14 2 mg cyproterone acetate/50 mcg ethinyloestradiol	1	98	Risk Ratio(M-H, Fixed, 95% CI)	0.78[0.44, 1.38]
22.1.15 Zinc	1	332	Risk Ratio(M-H, Fixed, 95% CI)	0.63[0.44, 0.91]
22.1.16 1% clindamycin lotion/gel	1	66	Risk Ratio(M-H, Fixed, 95% CI)	1.00[0.15, 6.68]
22.1.17 2 % fusidic acid lotion	1	174	Risk Ratio(M-H, Fixed, 95% CI)	0.48[0.22, 1.04]
22.1.18 4% erythromycin/1.2% zinc lotion	1	105	Risk Ratio(M-H, Fixed, 95% CI)	0.79[0.30, 2.13]
22.1.19 Doxycycline plus topical 4% chlorhexidine/5% benzoyl peroxide	1	43	Risk Ratio(M-H, Fixed, 95% CI)	0.72[0.18, 2.82]
22.1.20 Minocycline/azelaic acid vs isotretinoin	1	85	Risk Ratio(M-H, Fixed, 95% CI)	0.55[0.35, 0.85]
22.1.21 Isotretinoin	1	24	Risk Ratio(M-H, Fixed, 95% CI)	0.60[0.37, 0.97]
22.1.22 Josamycin	1	122	Risk Ratio(M-H, Fixed, 95% CI)	2.00[0.19, 21.48]

22.2 Requiring therapy cessation	30		Risk Difference(M-H, Fixed, 95% CI)	Subtotals only
22.2.1 Placebo	2	313	Risk Difference(M-H, Fixed, 95% CI)	0.08[0.03, 0.13]
22.2.2 100 mg od versus 100/50 mg od	1	325	Risk Difference(M-H, Fixed, 95% CI)	0.00[-0.03, 0.04]
22.2.3 Dose response 3 mg/kg vs 2 mg/kg	1	119	Risk Difference(M-H, Fixed, 95% CI)	0.03[-0.08, 0.14]
22.2.4 Dose response 3 mg/kg vs 1 mg/kg	1	119	Risk Difference(M-H, Fixed, 95% CI)	0.07[-0.03, 0.16]
22.2.5 Dose response 2 mg/kg vs 1 mg/kg	1	118	Risk Difference(M-H, Fixed, 95% CI)	0.03[-0.06, 0.12]
22.2.6 Tetracycline 1 g/day	2	144	Risk Difference(M-H, Fixed, 95% CI)	0.03[-0.04, 0.09]
22.2.7 Oxytetracycline	2	455	Risk Difference(M-H, Fixed, 95% CI)	-0.06[-0.11, -0.02]
22.2.8 (Oxy)tetracycline	8	920	Risk Difference(M-H, Fixed, 95% CI)	-0.03[-0.06, NaN]
22.2.9 Tetracycline 500 mg/day	3	266	Risk Difference(M-H, Fixed, 95% CI)	-0.01[-0.05, 0.04]
22.2.10 Doxycycline	3	223	Risk Difference(M-H, Fixed, 95% CI)	NaN[-0.07, 0.07]
22.2.11 Lymecycline	4	419	Risk Difference(M-H, Fixed, 95% CI)	0.01[-0.03, 0.05]
22.2.12 Roxithromycin	1	99	Risk Difference(M-H, Fixed, 95% CI)	0.04[-0.03, 0.11]
22.2.13 Faropenem	1	100	Risk Difference(M-H, Fixed, 95% CI)	0.00[-0.08, 0.08]
22.2.14 Zinc	1	332	Risk Difference(M-H, Fixed, 95% CI)	-0.01[-0.04, 0.03]
22.2.15 2 mg cyproterone acetate/50 mcg ethinyloestradiol	1	98	Risk Difference(M-H, Fixed, 95% CI)	-0.02[-0.12, 0.08]
22.2.16 1% clindamycin lotion/gel	3	220	Risk Difference(M-H, Fixed, 95% CI)	NaN[-0.05, 0.05]
22.2.17 4% erythromycin/zinc 1.2% lotion	1	105	Risk Difference(M-H, Fixed, 95% CI)	0.02[-0.03, 0.07]
22.2.18 Tazarotene	1	73	Risk Difference(M-H, Fixed, 95% CI)	0.03[-0.05, 0.10]
22.2.19 2% fusidic acid lotion	1	174	Risk Difference(M-H, Fixed, 95% CI)	-0.02[-0.07, 0.02]
22.2.20 Benzoyl peroxide 5% twice-daily	1	260	Risk Difference(M-H, Fixed, 95% CI)	-0.02[-0.08, 0.03]
22.2.21 Benzoyl peroxide 5% plus 3% erythromycin twice-daily	1	257	Risk Difference(M-H, Fixed, 95% CI)	0.02[-0.02, 0.07]
22.2.22 Benzoyl peroxide 5% evening plus 2% erythromycin morning	1	261	Risk Difference(M-H, Fixed, 95% CI)	-0.02[-0.08, 0.03]
22.2.23 Placebo plus topical erythromycin/tretinoin gel	0	0	Risk Difference(M-H, Fixed, 95% CI)	Not estimable
22.2.24 Minocycline/azelaic acid versus isotretinoin	1	85	Risk Difference(M-H, Fixed, 95% CI)	0.04[-0.03, 0.11]
22.2.25 Tazorotene/minocycline combination	1	74	Risk Difference(M-H, Fixed, 95% CI)	0.00[-0.07, 0.07]
22.2.26 Doxycycline plus topical 4% chlorhexidine/5% benzoyl peroxide	1	43	Risk Difference(M-H, Fixed, 95% CI)	0.00[-0.09, 0.09]
22.2.27 Isotretinoin	1	24	Risk Difference(M-H, Fixed, 95% CI)	0.00[-0.15, 0.15]
22.2.28 Josamycin	1	122	Risk Difference(M-H, Fixed, 95% CI)	0.02[-0.03, 0.06]

22.3 Gastro-intestinal disturbances	19		Risk Difference(M-H, Fixed, 95% CI)	Subtotals only
22.3.1 Placebo	2	262	Risk Difference(M-H, Fixed, 95% CI)	-0.05[-0.16, 0.06]
22.3.2 100 mg od versus 100 mg/50 mg od	1	325	Risk Difference(M-H, Fixed, 95% CI)	0.00[-0.04, 0.05]
22.3.3 50 mg bd for 4 weeks then 50 mg od for 8 weeks versus 50 mg od for 8 weeks	1	59	Risk Difference(M-H, Fixed, 95% CI)	-0.04[-0.13, 0.06]
22.3.4 Dose response 3 mg/kg vs 2 mg/kg	1	119	Risk Difference(M-H, Fixed, 95% CI)	0.10[-0.07, 0.26]
22.3.5 Dose response 3 mg/kg vs 1 mg/kg	1	119	Risk Difference(M-H, Fixed, 95% CI)	0.18[0.03, 0.33]
22.3.6 Dose response 2 mg/kg vs 1 mg/kg	1	118	Risk Difference(M-H, Fixed, 95% CI)	0.08[-0.06, 0.23]
22.3.7 Tetracycline 500 mg/day	4	319	Risk Difference(M-H, Fixed, 95% CI)	-0.01[-0.05, 0.04]
22.3.8 Tetracycline 1 g/day	2	144	Risk Difference(M-H, Fixed, 95% CI)	0.00[-0.05, 0.05]
22.3.9 (Oxy)tetracycline	5	365	Risk Difference(M-H, Fixed, 95% CI)	-0.00[-0.05, 0.04]
22.3.10 Doxycycline	2	179	Risk Difference(M-H, Fixed, 95% CI)	0.01[-0.08, 0.10]
22.3.11 Lymecycline	2	230	Risk Difference(M-H, Fixed, 95% CI)	-0.04[-0.12, 0.04]
22.3.12 Faropenem	1	100	Risk Difference(M-H, Fixed, 95% CI)	-0.06[-0.13, 0.01]
22.3.13 Roxithromycin	1	99	Risk Difference(M-H, Fixed, 95% CI)	0.00[-0.04, 0.04]
22.3.14 Josamycin	1	122	Risk Difference(M-H, Fixed, 95% CI)	0.00[-0.05, 0.05]
22.3.15 Zinc	0	0	Risk Difference(M-H, Fixed, 95% CI)	Not estimable
22.3.16 2 mg cyproterone acetate/50 mcg ethinyloestradiol	1	98	Risk Difference(M-H, Fixed, 95% CI)	0.18[0.05, 0.31]
22.3.17 1% clindamycin lotion/gel	1	66	Risk Difference(M-H, Fixed, 95% CI)	0.03[-0.05, 0.11]
22.3.18 4% erythromycin/1.2% zinc lotion	1	105	Risk Difference(M-H, Fixed, 95% CI)	0.02[-0.03, 0.07]
22.3.19 2% fusidic acid lotion	1	174	Risk Difference(M-H, Fixed, 95% CI)	0.04[-0.01, 0.09]
22.3.20 Doxycycline plus topical 4% chlorhexidine/ 5% benzoyl peroxide	1	43	Risk Difference(M-H, Fixed, 95% CI)	-0.05[-0.17, 0.07]
22.4 Acute vestibular disturbances	1	699	Risk Ratio(M-H, Fixed, 95% CI)	1.37[1.09, 1.72]
22.4.1 Dose response 3 mg/kg vs placebo	1	115	Risk Ratio(M-H, Fixed, 95% CI)	1.64[0.95, 2.82]
22.4.2 Dose response 2 mg/kg vs placebo	1	114	Risk Ratio(M-H, Fixed, 95% CI)	1.27[0.71, 2.27]
22.4.3 Dose response 1 mg/kg vs placebo	1	114	Risk Ratio(M-H, Fixed, 95% CI)	0.93[0.49, 1.77]
22.4.4 Dose response 3 mg/kg vs 2 mg/kg	1	119	Risk Ratio(M-H, Fixed, 95% CI)	1.29[0.80, 2.08]
22.4.5 Dose response 3 mg/kg vs 1 mg/kg	1	119	Risk Ratio(M-H, Fixed, 95% CI)	1.76[1.02, 3.03]
22.4.6 Dose response 2 mg/kg vs 1 mg/kg	1	118	Risk Ratio(M-H, Fixed, 95% CI)	1.36[0.75, 2.44]

Other data tables

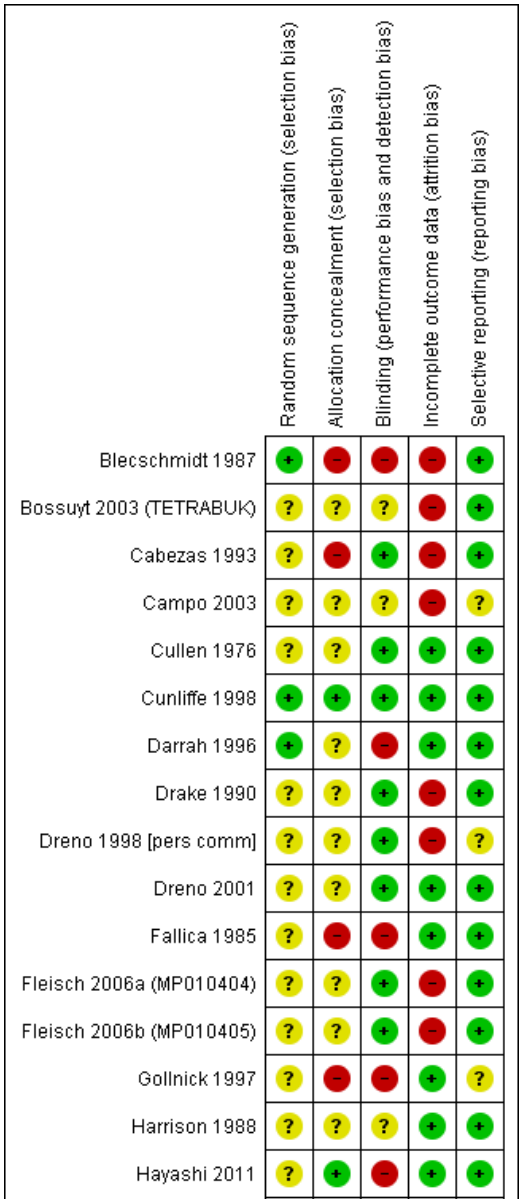
7 Minocycline versus doxycycline

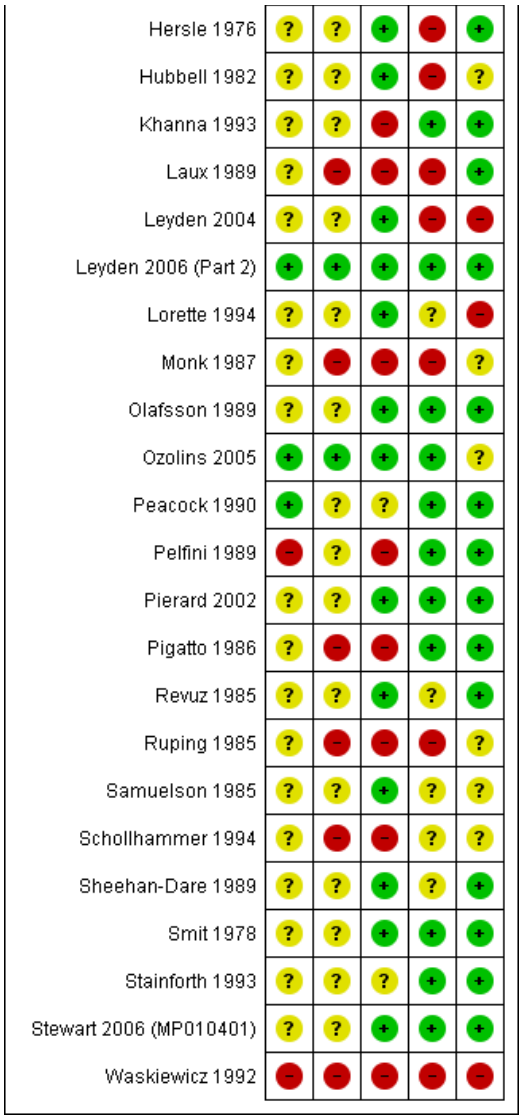
7.4 Other outcome

Study ID	Outcome	Minocycline	Doxycycline	Inter-group analysis
Lorette 1994	Per cent reduction in lesion counts from baseline - day 120	N = 23 Comedones: 77.4% Papules: 69.6% Pustules: 65.5% Score: 68.4%	N = 31 Comedones: 69.3% Papules: 84.7% Pustules: 86.9% Score: 79.4%	Comedones: P = 0.516 (Chi² test); Effect Size = 0.156 Pustules: P = 0.187 (Chi² test); Effect Size = 0.313 Papules: P = 0.064 (Chi² test); Effect Size = 0.44 Score: P = 0.36 (Chi² test); Effect Size = 0.253
Schollhammer 1994	Week 12 per cent reduction in inflamed lesion count	N = 13 68.4%	N = 11 62.4%	P > 0.05 (test unknown)
Waskiewicz 1992	Per cent reduction in lesion counts from baseline	N = 30 Closed comedones: 67.7% Open comedones: 59.2% Papules: 64.2% Pustules: 76.1% Total lesion count: 66.3% SCORE: 67.1%	N = 30 Closed comedones: 66.7% Open comedones: 67.0% Papules: 65.4% Pustules: 76.8% Total lesion count: 67.7% SCORE: 68.8%	No statistical analysis performed

Figures

Figure 1





Caption

Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Sources of support

Internal sources

- Leeds Foundation for Dermatological Research, UK
- National Institute for Health and Clinical Excellence, UK

External sources

- National Institute for Health Research Cochrane Review Incentive Scheme 2011, UK
  Grant to enable the update to be undertaken

Feedback

Appendices

1 Skin Group Specialised Register search strategy

(Minomycin or Akamin or Minocin or Minoderm or Cyclimycin or Aknemin or Solodyn or Dynacin or Sebomin or Acnamino or Minopen or Maracyn or minocycline or cyclomin or mynocine or mestacine or arestin or minakne or minox or lederderm or minoplus or blemix or dentomycin or minotab or minolis or Cyclops or aknosan or minoclir or klinomycin or Minocyclin or Minocyclinum or Minocyklin or Minocyklina or Minosiklin or Minosykliini or Minociclina or borymycin or cynomycin or lederderm or logryx or menocycline or mestacine or micromycin or minaxen or Minoclin or minoclir or minocyn or minogalen or minoline or minomax or mirosin or mynocine or romin or skinocyclin or spicline or vectran or vectrin or “Mino-Tabs” or “aknin-mino” or “akne-puren” or “mino wolff” or “mino-wolff” or “icht oral” or “akne puren” or “icht-oral” or “aknin mino” or “7 dimethylamino 6 demethyl 6 deoxytetracycline” or “mino-50”) AND acne

2 CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor Acne Vulgaris explode all trees
#2 (acne):ti,ab,kw
#3 (#1 OR #2)
#4 MeSH descriptor Minocycline explode all trees
#5 (Minomycin or Akamin or Minocin or Minoderm or Cyclimycin or Aknemin or Solodyn or Dynacin or Sebomin or Acnamino or Minopen or Maracyn or minocycline or cyclomin or mynocine or mestacine or arestin or minakne or minox or lederderm or minoplus or blemix or dentomycin or minotab or minolis or Cyclops or aknosan or minoclir or klinomycin or Minocyclin or Minocyclinum or Minocyklin or Minocyklina or Minosiklin or Minosykliini or Minociclina or borymycin or cynomycin or lederderm or logryx or menocycline or mestacine or micromycin or minaxen or Minoclin or minoclir or minocyn or minogalen or minoline or minomax or mirosin or mynocine or romin or skinocyclin or spicline or vectran or vectrin or "Mino-Tabs" or "aknin-mino" or "akne-puren" or "mino wolff" or "mino-wolff" or "icht oral" or "akne puren" or "icht-oral" or "aknin mino" or "7 dimethylamino 6 demethyl 6 deoxytetracycline" or "mino-50")
#6 (#4 OR #5)
#7 (#3 AND #6)

3 MEDLINE (OVID) search strategy

1. exp Minocycline/
2. (Minomycin or Akamin or Minocin or Minoderm or Cyclimycin or Aknemin or Solodyn or Dynacin or Sebomin or Acnamino or Minopen or Maracyn or minocycline or cyclomin or mynocine or mestacine or arestin or minakne or minox or lederderm or minoplus or blemix or dentomycin or minotab or minolis or Cyclops or aknosan or minoclir or klinomycin or Minocyclin or Minocyclinum or Minocyklin or Minocyklina or Minosiklin or Minosykliini or Minociclina or borymycin or cynomycin or lederderm or logryx or menocycline or mestacine or micromycin or minaxen or Minoclin or minoclir or minocyn or minogalen or minoline or minomax or mirosin or mynocine or romin or skinocyclin or spicline or vectran or vectrin).mp.
3. (Mino-Tabs or aknin-mino or akne-puren or mino wolff or mino-wolff or icht oral or akne puren or icht-oral or aknin mino or mino-50).mp.
4. "7 dimethylamino 6 demethyl 6 deoxytetracycline".mp.
5. 10118-90-8.rn.
6. 1 or 2 or 3 or 4 or 5
7. acne.mp. or exp Acne Vulgaris/
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.ab.
12. clinical trials as topic.sh.
13. randomly.ab.
14. trial.ti.
15. 8 or 9 or 10 or 11 or 12 or 13 or 14
16. (animals not (human and animals)).sh.
17. 15 not 16
18. 6 and 7 and 17

4 EMBASE (OVID) search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp acne vulgaris/
15. acne.ti,ab.
16. 14 or 15
17. exp minocycline/
18. 10118-90-8.rn.
19. "7 dimethylamino 6 demethyl 6 deoxytetracycline".mp.
20. (Minomycin or Akamin or Minocin or Minoderm or Cyclimycin or Aknemin or Solodyn or Dynacin or Sebomin or Acnamino or Minopen or Maracyn or minocycline or cyclomin or mynocine or mestacine or arestin or minakne or minox or lederderm or minoplus or blemix or dentomycin or minotab or minolis or Cyclops or aknosan or minoclir or klinomycin or Minocyclin or Minocyclinum or Minocyklin or Minocyklina or Minosiklin or Minosykliini or Minociclina or borymycin or cynomycin or

lederderm or logryx or menocycline or mestacine or micromycin or minaxen or Minoclin or minoclir or minocyn or minogalen or minoline or minomax or mirosin or mynocine or romin or skinocyclin or spicline or vectran or vectrin).mp.
21. (Mino-Tabs or aknin-mino or akne-puren or mino wolff or mino-wolff or icht oral or akne puren or icht-oral or aknin mino or mino-50).mp.
22. 17 or 18 or 19 or 20 or 21
23. 13 and 16 and 22

5 LILACS search strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Words] and acne [Words] and “Mino-Tabs” or “aknin-mino” or “akne-puren” or “mino wolff” or “mino-wolff” or “icht oral” or “akne puren” or “icht-oral” or “aknin mino” or “7 dimethylamino 6 demethyl 6 deoxytetracycline” or “mino-50” or Minomycin or Akamin or Minocin or Minoderm or Cyclimycin or Aknemin or Solodyn or Dynacin or Sebomin or Acnamino or Minopen or Maracyn or minocycline or cyclomin or mynocine or mestacine or arestin or minakne or minox or lederderm or minoplus or blemix or dentomycin or minotab or minolis or Cyclops or aknosan or minoclir or klinomycin or Minocyclin or Minocyclinum or Minocyklin or Minocyklina or Minosiklin or Minosykliini or Minociclina or borymycin or cynomycin or lederderm or logryx or menocycline or mestacine or micromycin or minaxen or Minoclin or minoclir or minocyn or minogalen or minoline or minomax or mirosin or mynocine or romin or skinocyclin or spicline or vectran or vectrin [Words]

6 Adverse effects search strategy EMBASE (OVID)

1. side effect$.ti,ab.
2. metabolite$.ti,ab.
3. photoallergic reaction$.ti,ab.
4. phototoxicit$.ti,ab.
5. (sensitization or sensitisation).ti,ab.
6. stinging.ti,ab.
7. burning.ti,ab.
8. fetal abnormalit$.ti,ab.
9. (toxic effect$ or drug effect$).ti,ab.
10. (safe or safety).ti,ab.
11. toxicity.ti,ab.
12. noxious.ti,ab.
13. complication$.ti,ab.
14. tolerability.ti,ab.
15. treatment emergent.ti,ab.
16. tolerability.ti,ab.
17. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
18. rebound.ti,ab.
19. skin thinning.ti,ab.
20. lupus induced hepatitis.ti,ab.
21. exp postmarketing surveillance/
22. exp drug surveillance program/
23. exp drug hypersensitivity/ or exp hypersensitivity reaction/ or exp delayed hypersensitivity/ or exp hypersensitivity/ or exp immediate type hypersensitivity/
24. exp drug eruption/
25. exp anaphylaxis/
26. exp allergic conjunctivitis/
27. exp atopic dermatitis/
28. exp food allergy/
29. exp respiratory tract allergy/
30. exp urticaria/
31. exp intoxication/
32. exp toxic hepatitis/
33. exp addiction/
34. exp drug toxicity/
35. exp teratogenic agent/
36. exp mutagenic agent/
37. exp carcinogen/
38. exp contact dermatitis/
39. exp skin allergy/
40. exp irritant dermatitis/
41. exp phototoxicity/

42. exp photodermatosis/ or exp photoallergy/
43. exp burning mouth syndrome/
44. exp drug monitoring/
45. exp sleep apnea syndrome/
46. exp heart arrhythmia/
47. hypercalcemia/
48. urolithiasis/
49. tachyphylaxis/
50. withdrawal syndrome/
51. atrophy/
52. telangiectasia/
53. liver disease/
54. kidney disease/
55. disseminated intravascular clotting/
56. multiple organ failure/
57. Stevens Johnson syndrome/
58. toxic epidermal necrolysis/
59. heart block/
60. coma/
61. paralysis/
62. nausea/
63. vomiting/
64. benign intracranial hypertension.ti,ab. or exp brain pseudotumor/
65. exp pigment disorder/
66. exp pigmentation/
67. pigmentation.ti,ab.
68. exp adverse drug reaction/
69. exp drug safety/
70. exp phase 4 clinical trial/
71. (ae or to).fs.
72. exp minocycline/
73. 10118-90-8.ti,ab.
74. "7 dimethylamino 6 demethyl 6 deoxytetracycline".ti,ab.
75. (Minomycin or Akamin or Minocin or Minoderm or Cyclimycin or Aknemin or Solodyn or Dynacin or Sebomin or Acnamino or Minopen or Maracyn or minocycline or cyclomin or mynocine or mestacine or arestin or minakne or minox or lederderm or minoplus or blemix or dentomycin or minotab or minolis or Cyclops or aknosan or minoclir or klinomycin or Minocyclin or Minocyclinum or Minocyklin or Minocyklina or Minosiklin or Minosykliini or Minociclina or borymycin or cynomycin or lederderm or logryx or menocycline or mestacine or micromycin or minaxen or Minoclin or minoclir or minocyn or minogalen or minoline or minomax or mirosin or mynocine or romin or skinocyclin or spicline or vectran or vectrin).ti,ab.
76. (Mino-Tabs or aknin-mino or akne-puren or mino wolff or mino-wolff or icht oral or akne puren or icht-oral or aknin mino or mino-50).ti,ab.
77. or/72-76
78. 71 and 77
79. or/1-70
80. 77 and 79
81. 78 or 80
82. limit 81 to human

7 Adverse effects search strategy MEDLINE (OVID)

1. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp clinical trials, phase iv/
2. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
3. exp hypersensitivity/ or exp drug hypersensitivity/ or exp drug eruptions/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
4. exp anaphylaxis/ or exp conjunctivitis, allergic/ or exp dermatitis, atopic/ or exp food hypersensitivity/ or exp respiratory hypersensitivity/ or exp urticaria/
5. side effect$.ti,ab.
6. exp Poisoning/
7. exp hepatitis, toxic/ or exp hepatitis, chronic, drug-induced/
8. exp Substance-Related Disorders/
9. exp Drug Toxicity/
10. exp Abnormalities, Drug-Induced/
11. exp Teratogens/
12. exp Mutagens/
13. exp Carcinogens/
14. metabolite$.ti,ab.
15. exp dermatitis, contact/ or exp dermatitis, allergic contact/ or exp dermatitis, irritant/ or exp dermatitis, phototoxic/
16. photoallergic reaction$.ti,ab.

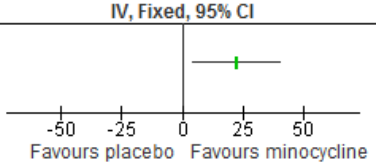
17. exp dermatitis, allergic contact/ or exp dermatitis, photoallergic/
18. phototoxicit$.ti,ab.
19. (sensitization or sensitisation).ti,ab.
20. exp Burning Mouth Syndrome/
21. stinging.ti,ab.
22. burning.ti,ab.
23. fetal abnormalit$.ti,ab.
24. exp Drug Monitoring/
25. drug effect$.ti,ab.
26. Sleep Apnea, Obstructive/
27. ARRHYTHMIA/
28. (safe or safety).ti,ab.
29. toxicity.ti,ab.
30. noxious.ti,ab.
31. complication$.ti,ab.
32. treatment emergent.ti,ab.
33. tolerability.ti,ab.
34. rebound.ti,ab.
35. Hypercalcemia/ci [Chemically Induced]
36. Urinary Calculi/ci [Chemically Induced]
37. Tachyphylaxis/ci, de [Chemically Induced, Drug Effects]
38. Substance Withdrawal Syndrome/ci, de [Chemically Induced, Drug Effects]
39. ATROPHY/ci [Chemically Induced]
40. TELANGIECTASIS/ci [Chemically Induced]
41. skin thinning.ti,ab.
42. Liver Diseases/ci [Chemically Induced]
43. Kidney Diseases/ci [Chemically Induced]
44. Disseminated Intravascular Coagulation/ci [Chemically Induced]
45. Multiple Organ Failure/ci [Chemically Induced]
46. Stevens-Johnson Syndrome/ci [Chemically Induced]
47. Epidermal Necrolysis, Toxic/ci [Chemically Induced]
48. Heart Block/ci [Chemically Induced]
49. COMA/ci [Chemically Induced]
50. PARALYSIS/ci [Chemically Induced]
51. exp Nausea/
52. exp Vomiting/
53. benign intracranial hypertension.ti,ab. or exp Pseudotumor Cerebri/
54. exp Pigmentation Disorders/ or pigmentation.ti,ab. or exp Pigmentation/
55. lupus induced hepatitis.ti,ab.
56. or/1-55
57. (Minomycin or Akamin or Minocin or Minoderm or Cyclimycin or Aknemin or Solodyn or Dynacin or Sebomin or Acnamino or Minopen or Maracyn or minocycline or cyclomin or mynocine or mestacine or arestin or minakne or minox or lederderm or minoplus or blemix or dentomycin or minotab or minolis or Cyclops or aknosan or minoclir or klinomycin or Minocyclin or Minocyclinum or Minocyklin or Minocyklina or Minosiklin or Minosykliini or Minociclina or borymycin or cynomycin or lederderm or logryx or menocycline or mestacine or micromycin or minaxen or Minoclin or minoclir or minocyn or minogalen or minoline or minomax or mirosin or mynocine or romin or skinocyclin or spicline or vectran or vectrin).ti,ab.
58. exp Minocycline/
59. (Mino-Tabs or aknin-mino or akne-puren or mino wolff or mino-wolff or icht oral or akne puren or icht-oral or aknin mino or mino-50).ti,ab.
60. "7 dimethylamino 6 demethyl 6 deoxytetracycline".ti,ab.
61. 10118-90-8.rn.
62. or/57-61
63. 56 and 62
64. ae.fs.
65. to.fs.
66. co.fs.
67. po.fs.
68. or/64-67
69. 62 and 68
70. 63 or 69
71. limit 70 to humans

Graphs

1 - Minocycline 100 mg bd versus placebo

1.1 Inflamed lesion count - percentage change from baseline

Study or Subgroup	Minocycline Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.1.1 Week 12 - per-protocol - inflamed lesions							
Leyden 2004	49.2	41.2	34	26.8	36	37	22.40 [4.34, 40.46]

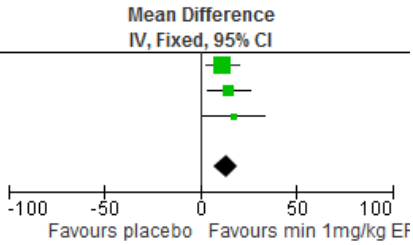


2 - Minocycline ER versus placebo

2.1 Percentage change in inflamed lesion counts

Study or Subgroup	Minocycline 1 mg/kg ER Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fleisch 2006a (MP010404)	43.1	44.16	300	31.7	44.16	151	53.7%	11.40 [2.76, 20.04]
Fleisch 2006b (MP010405)	45.8	59.49	315	30.8	59.49	158	31.0%	15.00 [3.63, 26.37]
Stewart 2006 (MP010401)	56.8	44.05	59	39.4	44.05	55	15.3%	17.40 [1.22, 33.58]
Total (95% CI)			**674**			**364**	**100.0%**	**13.43 [7.10, 19.76]**

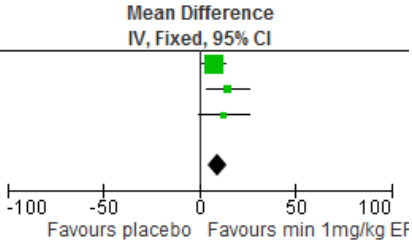
Heterogeneity: Chi² = 0.52, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 4.16 (P < 0.0001)



2.2 Percentage change in total lesion counts

Study or Subgroup	Minocycline 1 mg/kg ER Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fleisch 2006a (MP010404)	31.8	31.6	300	24.1	31.6	151	65.5%	7.70 [1.52, 13.88]
Fleisch 2006b (MP010405)	32.1	57.91	315	17.5	57.91	158	20.4%	14.60 [3.54, 25.66]
Stewart 2006 (MP010401)	43	36.22	59	30.1	36.22	55	14.1%	12.90 [-0.41, 26.21]
Total (95% CI)			**674**			**364**	**100.0%**	**9.84 [4.84, 14.84]**

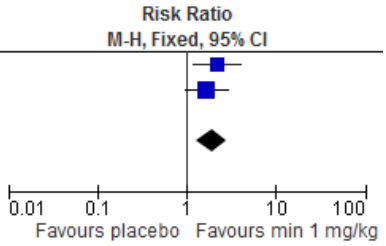
Heterogeneity: Chi² = 1.37, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.86 (P = 0.0001)



2.3 Investigator global severity - successful treatment

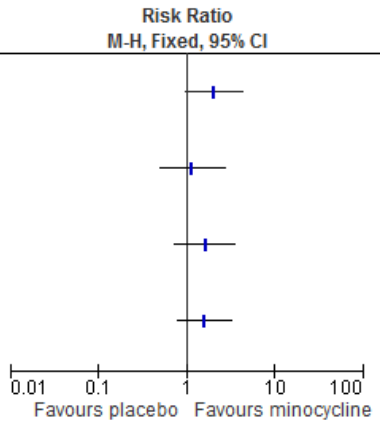
Study or Subgroup	Minocycline 1 mg/kg ER Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fleisch 2006a (MP010404)	52	300	12	151	44.4%	2.18 [1.20, 3.96]
Fleisch 2006b (MP010405)	50	315	15	158	55.6%	1.67 [0.97, 2.88]
Total (95% CI)		**615**		**309**	**100.0%**	**1.90 [1.27, 2.84]**
Total events	102		27			

Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.13 (P = 0.002)



2.4 Clear or almost clear 12 weeks

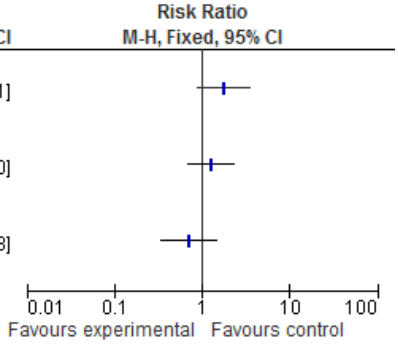
Study or Subgroup	Minocycline Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
2.4.1 3 mg versus placebo					
Stewart 2006 (MP010401)	18	60	8	55	2.06 [0.98, 4.36]
2.4.2 2 mg versus placebo					
Stewart 2006 (MP010401)	10	59	8	55	1.17 [0.50, 2.74]
2.4.3 1 mg versus placebo					
Stewart 2006 (MP010401)	14	59	8	55	1.63 [0.74, 3.58]
2.4.4 Pooled					
Stewart 2006 (MP010401)	42	178	8	55	1.62 [0.81, 3.24]



3 - Minocycline ER dose response

3.1 Clear or almost clear 12 weeks

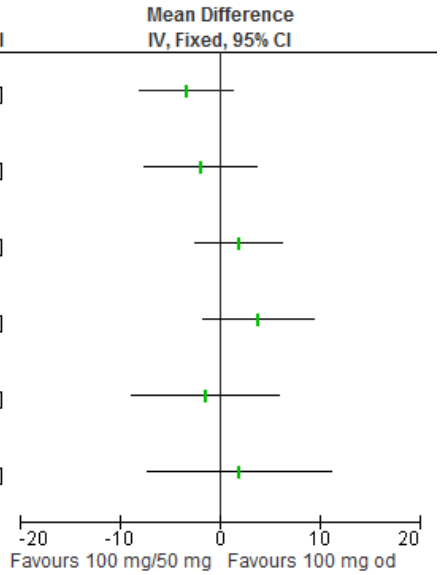
Study or Subgroup	Experimental Events	Total	Control Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.1.1 3 mg/kg versus 2 mg					
Stewart 2006 (MP010401)	18	60	10	59	1.77 [0.89, 3.51]
3.1.2 3 mg versus 1 mg					
Stewart 2006 (MP010401)	18	60	14	59	1.26 [0.69, 2.30]
3.1.3 2 mg versus 1 mg					
Stewart 2006 (MP010401)	10	59	14	59	0.71 [0.35, 1.48]



4 - Minocycline 100 mg od versus 100 mg/50 mg od

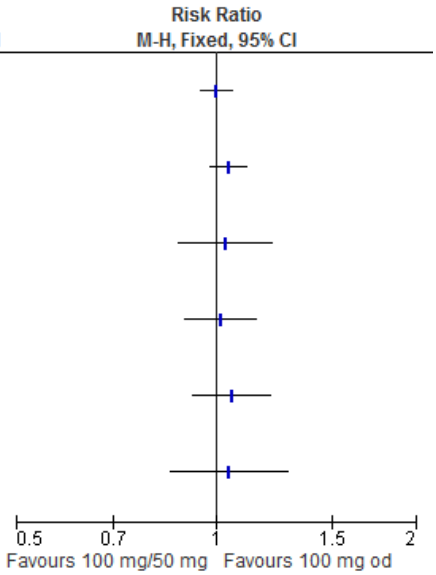
4.1 Lesion counts - reduction from baseline after 60 days therapy

Study or Subgroup	100 mg od Mean	SD	Total	100 mg/50 mg od Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.1.1 Non-inflamed: intention-to-treat analysis							
Dreno 1998 [pers comm]	11.44	17.05	160	14.77	23.8	147	-3.33 [-8.00, 1.34]
4.1.2 Non-inflamed lesions: per-protocol analysis							
Dreno 1998 [pers comm]	12.45	17.23	110	14.39	23.92	104	-1.94 [-7.55, 3.67]
4.1.3 Inflamed lesions: intention-to-treat analysis							
Dreno 1998 [pers comm]	25.54	18.75	160	23.63	20.28	147	1.91 [-2.47, 6.29]
4.1.4 Inflamed lesions: per-protocol analysis							
Dreno 1998 [pers comm]	28.31	20.19	110	24.4	21.07	104	3.91 [-1.62, 9.44]
4.1.5 Total lesions: intention-to-treat analysis							
Dreno 1998 [pers comm]	36.99	28.89	160	38.39	36.54	147	-1.40 [-8.81, 6.01]
4.1.6 Total lesions: per-protocol analysis							
Dreno 1998 [pers comm]	40.76	30.43	110	38.8	37.63	104	1.96 [-7.24, 11.16]



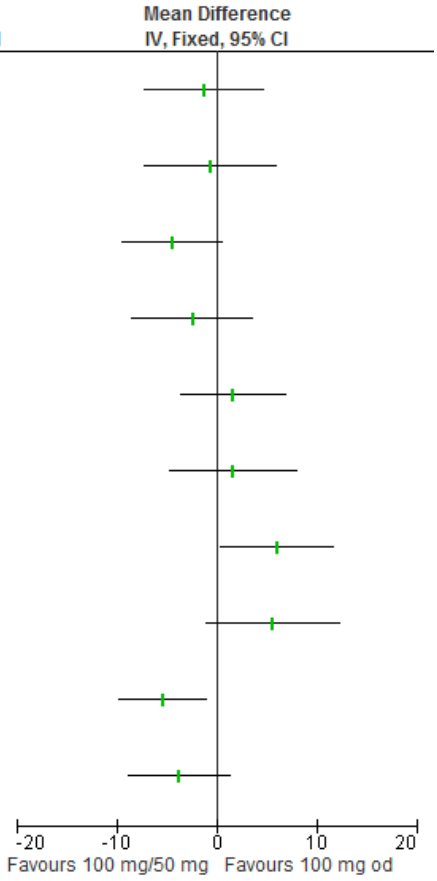
4.2 Overall clinical improvement - dr-assessed

Study or Subgroup	100 mg od Events	Total	100 mg/50 mg od Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Any improvement: intention-to-treat analysis					
Dreno 1998 [pers comm]	147	155	125	132	1.00 [0.95, 1.06]
4.2.2 Any improvement: per-protocol analysis					
Dreno 1998 [pers comm]	107	110	95	102	1.04 [0.98, 1.11]
4.2.3 Any improvement: worse-case analysis					
Dreno 1998 [pers comm]	107	160	95	147	1.03 [0.88, 1.22]
4.2.4 Moderate or excellent improvement: intention-to-treat analysis					
Dreno 1998 [pers comm]	122	155	102	132	1.02 [0.90, 1.15]
4.2.5 Moderate or excellent improvement: per-protocol analysis					
Dreno 1998 [pers comm]	90	110	79	102	1.06 [0.92, 1.21]
4.2.6 Moderate or excellent improvement: worse-case analysis					
Dreno 1998 [pers comm]	90	160	79	147	1.05 [0.85, 1.28]



4.3 Participant evaluations - 10 cm visual analogue scales

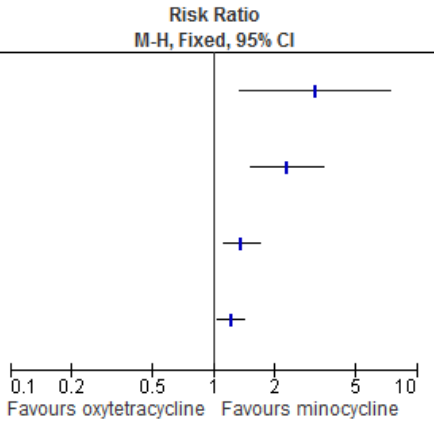
Study or Subgroup	Favours 100 mg/50 mg Mean	SD	Total	100 mg/50 mg od Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.3.1 Overall efficacy: intention-to-treat analysis							
Dreno 1998 [pers comm]	63.2	26.39	147	64.45	24.29	130	-1.25 [-7.22, 4.72]
4.3.2 Overall efficacy: per-protocol analysis							
Dreno 1998 [pers comm]	64.66	24.66	106	65.3	23.34	100	-0.64 [-7.19, 5.91]
4.3.3 Importance of acne - change from baseline: intention-to-treat analysis							
Dreno 1998 [pers comm]	26.85	23.61	158	31.26	20.72	147	-4.41 [-9.39, 0.57]
4.3.4 Importance of acne - change from baseline: per-protocol analysis							
Dreno 1998 [pers comm]	27.67	23.34	109	30.08	21.76	104	-2.41 [-8.47, 3.65]
4.3.5 Impact on relationships - change from baseline: intention-to-treat analysis							
Dreno 1998 [pers comm]	18.08	23.57	158	16.38	23.42	147	1.70 [-3.58, 6.98]
4.3.6 Impact on relationships - change from baseline: per-protocol analysis							
Dreno 1998 [pers comm]	16.02	23.07	109	14.32	24.1	104	1.70 [-4.64, 8.04]
4.3.7 Impact on sexual relationships - change from baseline: intention-to-treat analysis							
Dreno 1998 [pers comm]	18.6	25.96	158	12.6	24.04	147	6.00 [0.39, 11.61]
4.3.8 Impact on sexual relationships - change from baseline: per-protocol analysis							
Dreno 1998 [pers comm]	18.31	25.17	109	12.68	24.3	104	5.63 [-1.01, 12.27]
4.3.9 Impact on physical appearance - change from baseline: intention-to-treat analysis							
Dreno 1998 [pers comm]	10.69	20.57	158	16.1	18.54	147	-5.41 [-9.80, -1.02]
4.3.10 Impact on physical appearance - change from baseline: per-protocol analysis							
Dreno 1998 [pers comm]	11.89	19.84	109	15.61	17.54	104	-3.72 [-8.74, 1.30]



5 - Minocycline 50 mg bd/100 mg od versus (oxy)tetracycline 250 mg qd/bd

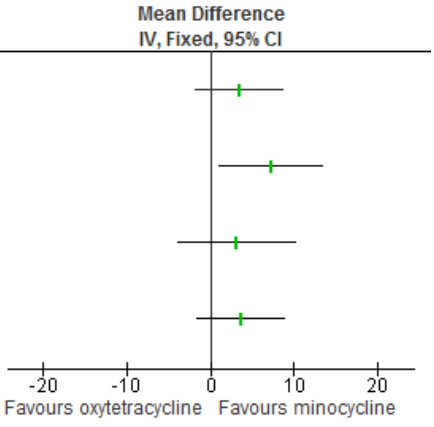
5.1 Cook grading scale - number of participants improved by at least two grades

Study or Subgroup	Minocycline Events	Total	Oxytetracycline Events	Total	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Week 2					
Blecschmidt 1987	22	104	6	90	3.17 [1.35, 7.48]
5.1.2 Week 4					
Blecschmidt 1987	56	104	21	90	2.31 [1.52, 3.49]
5.1.3 Week 8					
Blecschmidt 1987	81	104	51	90	1.37 [1.12, 1.69]
5.1.4 Week 12					
Blecschmidt 1987	90	104	64	90	1.22 [1.05, 1.42]



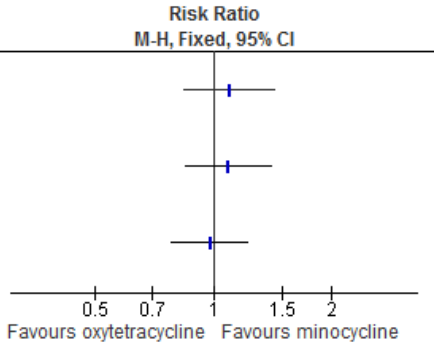
5.2 Decrease in inflamed lesion count from baseline

Study or Subgroup	Minocycline Mean	SD	Total	Oxytetracycline Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.2.1 Week 6							
Ozolins 2005	18.6	21	130	15.1	22	131	3.50 [-1.72, 8.72]
5.2.2 Week 12							
Ozolins 2005	23.3	26.2	130	16	24.7	131	7.30 [1.12, 13.48]
5.2.3 Week 18							
Ozolins 2005	22.3	29.9	130	19.2	27.8	131	3.10 [-3.91, 10.11]
5.2.4 Week 18: least squares mean adjusted							
Ozolins 2005	22	21.2	130	18.4	21.3	131	3.60 [-1.56, 8.76]



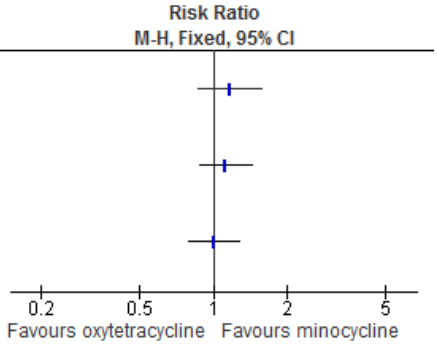
5.3 At least moderate improvement according to participant

Study or Subgroup	Minocycline Events	Total	Oxytetracycline Events	Total	Risk Ratio M-H, Fixed, 95% CI
5.3.1 6 weeks					
Ozolins 2005	62	130	57	131	1.10 [0.84, 1.43]
5.3.2 12 weeks					
Ozolins 2005	66	130	61	131	1.09 [0.85, 1.40]
5.3.3 18 weeks					
Ozolins 2005	70	130	72	131	0.98 [0.78, 1.22]



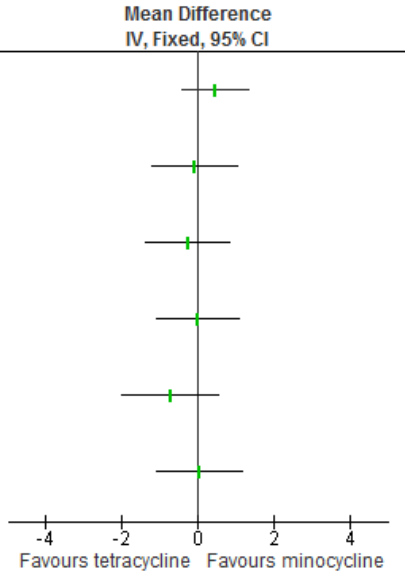
5.4 At least moderate improvement according to assessor

Study or Subgroup	Minocycline Events	Total	Oxytetracycline Events	Total	Risk Ratio M-H, Fixed, 95% CI
5.4.1 6 weeks					
Ozolins 2005	58	130	50	131	1.17 [0.87, 1.56]
5.4.2 12 weeks					
Ozolins 2005	69	130	62	131	1.12 [0.88, 1.43]
5.4.3 18 weeks					
Ozolins 2005	66	130	66	131	1.01 [0.79, 1.28]



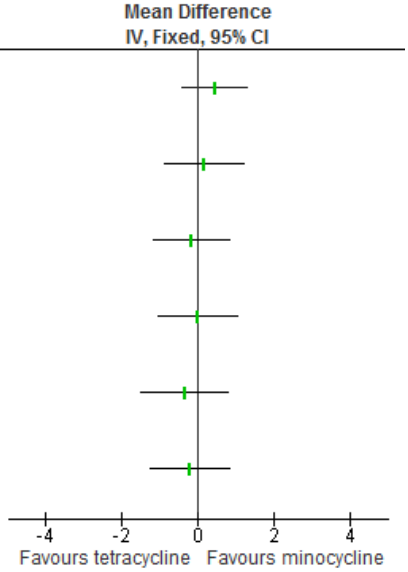
5.5 Samuelson lesion grade as assessed by physician

Study or Subgroup	Minocycline Mean	SD	Total	Tetracycline Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.5.1 Baseline							
Samuelson 1985	5.5	1.85	28	5.04	1.45	27	0.46 [-0.42, 1.34]
5.5.2 Week 2							
Samuelson 1985	4.65	2.25	23	4.74	1.71	27	-0.09 [-1.21, 1.03]
5.5.3 Week 4							
Samuelson 1985	3.74	2.13	27	4	1.95	25	-0.26 [-1.37, 0.85]
5.5.4 Week 6							
Samuelson 1985	3.96	2.35	26	3.96	1.66	27	0.00 [-1.10, 1.10]
5.5.5 Week 8							
Samuelson 1985	3	2.25	25	3.73	2.35	26	-0.73 [-1.99, 0.53]
5.5.6 Week 12							
Samuelson 1985	2.88	1.99	26	2.85	2.23	27	0.03 [-1.11, 1.17]



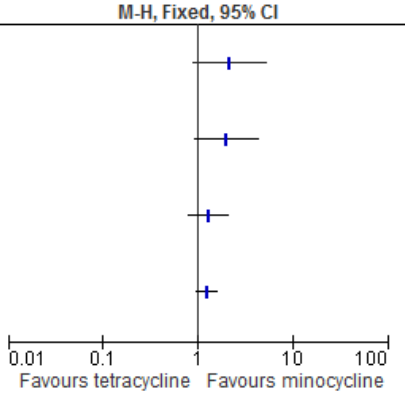
5.6 Samuelson lesion grade as assessed by participant

Study or Subgroup	Minocycline Mean	SD	Total	Tetracycline Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.6.1 Baseline							
Samuelson 1985	5.32	1.85	28	4.89	1.4	27	0.43 [-0.44, 1.30]
5.6.2 Week 2							
Samuelson 1985	4.83	2.01	23	4.67	1.66	27	0.16 [-0.87, 1.19]
5.6.3 Week 4							
Samuelson 1985	4.07	1.97	27	4.24	1.75	25	-0.17 [-1.18, 0.84]
5.6.4 Week 6							
Samuelson 1985	3.92	2.24	26	3.93	1.56	27	-0.01 [-1.05, 1.03]
5.6.5 Week 8							
Samuelson 1985	3.68	2.25	25	4.04	1.89	26	-0.36 [-1.50, 0.78]
5.6.6 Week 12							
Samuelson 1985	3.27	1.94	26	3.48	1.97	27	-0.21 [-1.26, 0.84]



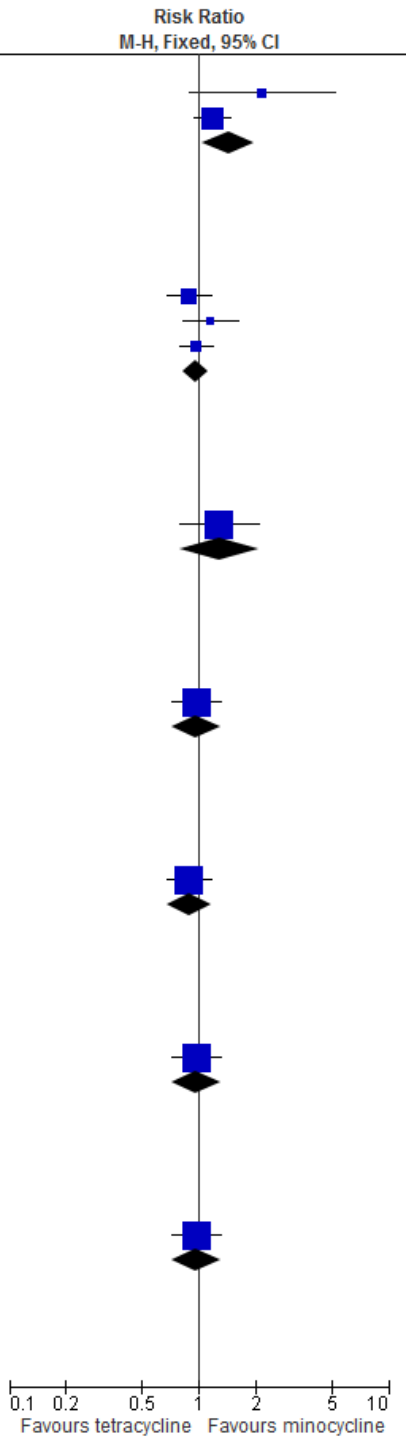
5.7 Number of participants converting to Pillsbury grade I

Study or Subgroup	Minocycline Events	Total	Tetracycline Events	Total	Risk Ratio M-H, Fixed, 95% CI
5.7.1 Week 6: intention-to-treat analysis					
Hubbell 1982	13	52	6	52	2.17 [0.89, 5.26]
5.7.2 Week 6: per-protocol analysis					
Hubbell 1982	13	25	6	23	1.99 [0.91, 4.37]
5.7.3 Week 24: intention-to-treat analysis					
Hubbell 1982	23	52	18	52	1.28 [0.79, 2.07]
5.7.4 Week 24: per-protocol analysis					
Hubbell 1982	23	25	18	24	1.23 [0.95, 1.59]



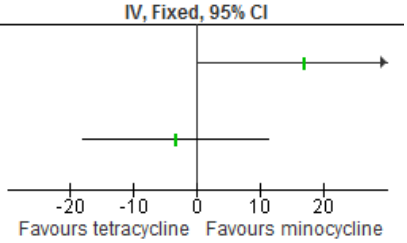
5.8 Overall improvement

Study or Subgroup	Minocycline Events	Minocycline Total	Tetracycline Events	Tetracycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.8.1 Week 6: investigator-assessed						
Hubbell 1982	13	52	6	52	25.2%	2.17 [0.89, 5.26]
Khanna 1993	22	23	17	21	74.8%	1.18 [0.94, 1.48]
Subtotal (95% CI)		**75**		**73**	**100.0%**	**1.43 [1.04, 1.96]**
Total events	35		23			
Heterogeneity: Chi² = 3.61, df = 1 (P = 0.06); I² = 72%						
Test for overall effect: Z = 2.22 (P = 0.03)						
5.8.2 Week 12: investigator-assessed						
Cullen 1976	32	50	36	50	47.3%	0.89 [0.68, 1.16]
Khanna 1993	19	23	15	21	20.6%	1.16 [0.83, 1.61]
Samuelson 1985	24	28	24	27	32.1%	0.96 [0.79, 1.18]
Subtotal (95% CI)		**101**		**98**	**100.0%**	**0.97 [0.83, 1.13]**
Total events	75		75			
Heterogeneity: Chi² = 1.51, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.40 (P = 0.69)						
5.8.3 Week 24: investigator-assessed						
Hubbell 1982	23	52	18	52	100.0%	1.28 [0.79, 2.07]
Subtotal (95% CI)		**52**		**52**	**100.0%**	**1.28 [0.79, 2.07]**
Total events	23		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
5.8.4 Week 12: participant-assessed						
Samuelson 1985	31	50	32	50	100.0%	0.97 [0.72, 1.31]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.97 [0.72, 1.31]**
Total events	31		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
5.8.5 Week 18: satisfactory overall clinical response: participant-assessed						
Cullen 1976	32	50	36	50	100.0%	0.89 [0.68, 1.16]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.89 [0.68, 1.16]**
Total events	32		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.39)						
5.8.6 Week 18: participant-assessed						
Cullen 1976	31	50	32	50	100.0%	0.97 [0.72, 1.31]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.97 [0.72, 1.31]**
Total events	31		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
5.8.7 Week 18: investigator-assessed						
Cullen 1976	31	50	32	50	100.0%	0.97 [0.72, 1.31]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.97 [0.72, 1.31]**
Total events	31		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						



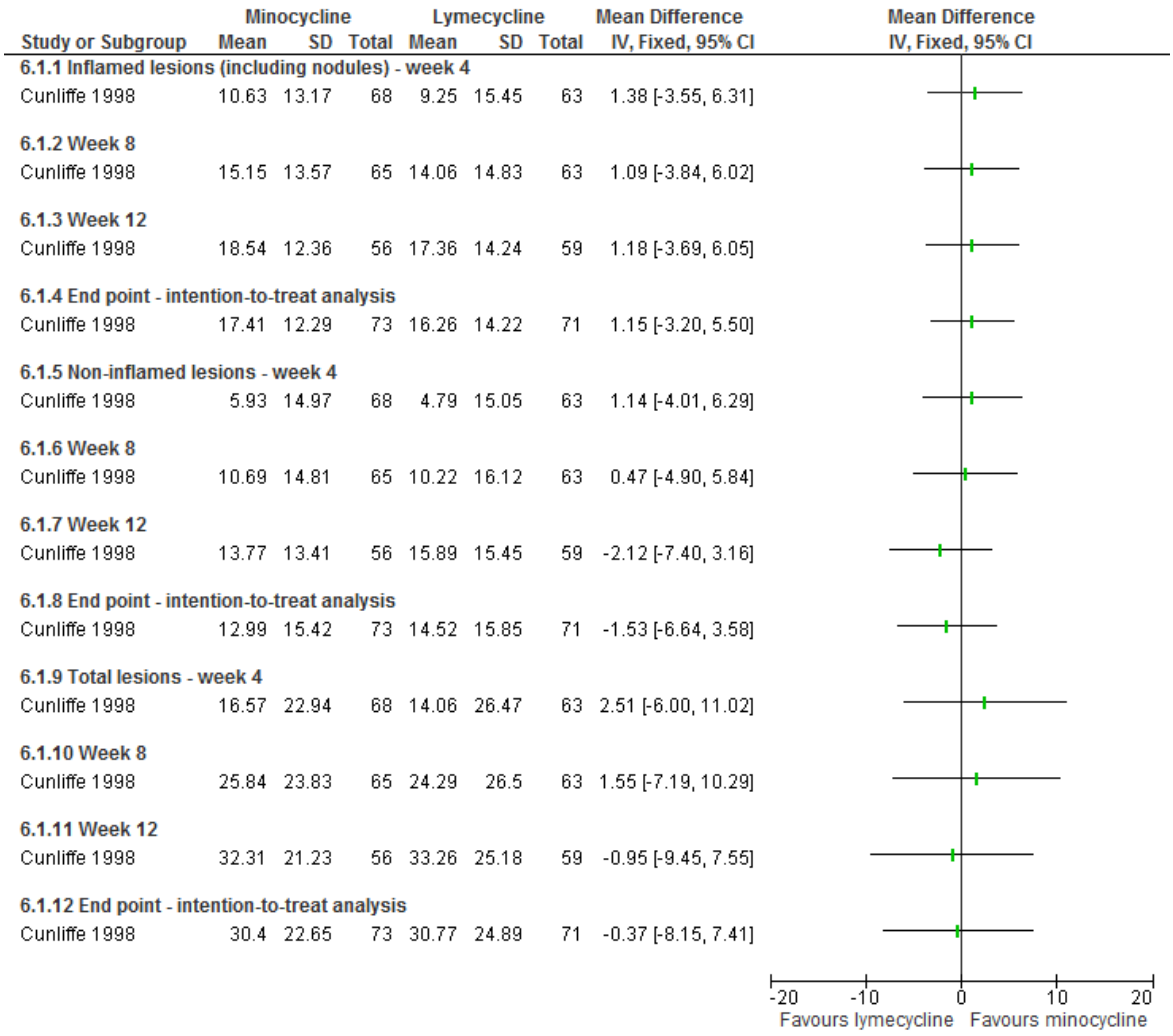
5.9 Khanna acne lesion score: absolute reduction from baseline

Study or Subgroup	Minocycline Mean	Minocycline SD	Minocycline Total	Tetracycline Mean	Tetracycline SD	Tetracycline Total	Mean Difference IV, Fixed, 95% CI
5.9.1 Week 6							
Khanna 1993	45.87	29.97	23	28.76	27.63	21	17.11 [0.09, 34.13]
5.9.2 Week 12							
Khanna 1993	63.1	23.21	19	66.43	20.42	15	-3.33 [-18.02, 11.36]

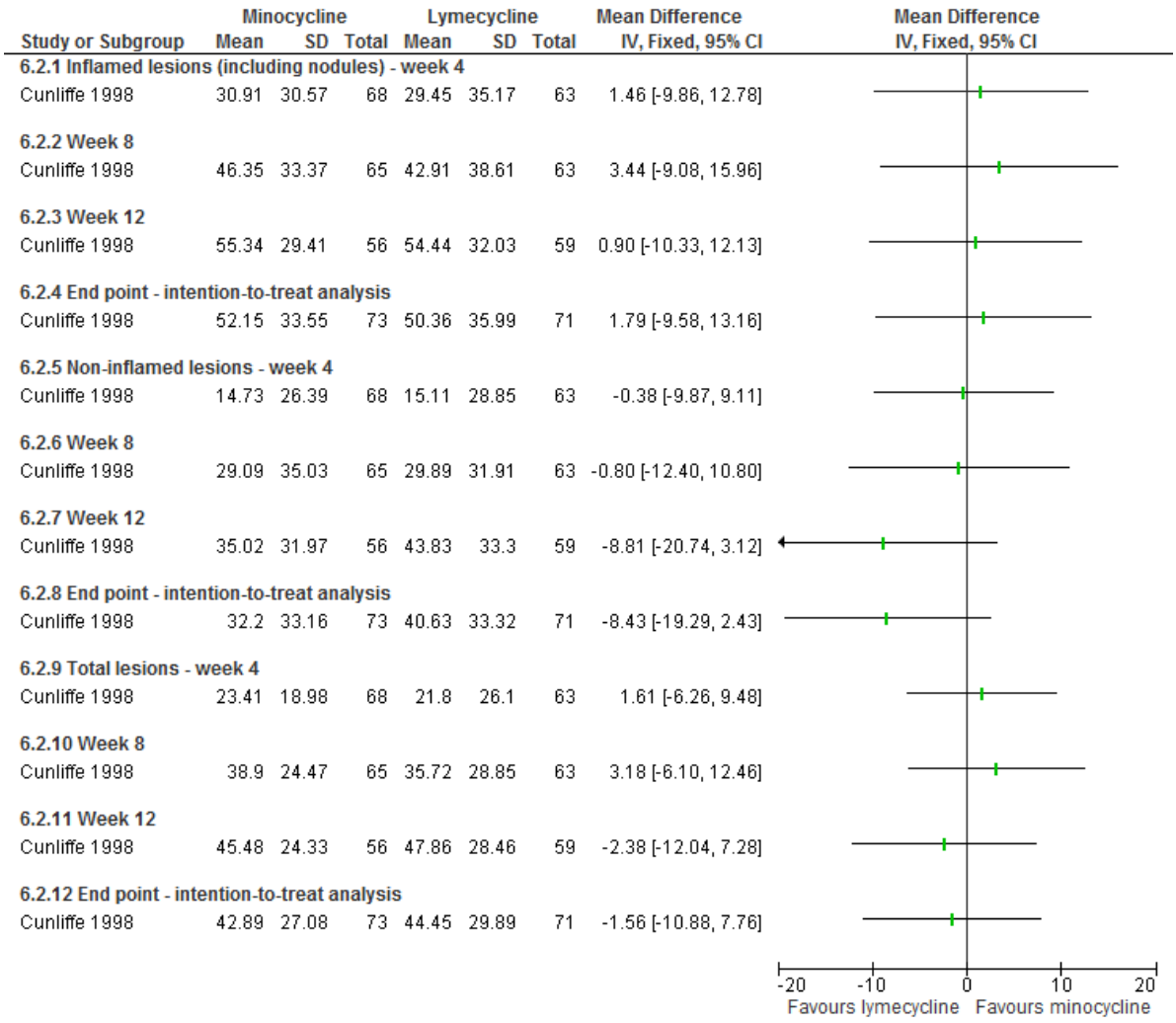


6 - Minocycline versus lymecycline

6.1 Lesion count - absolute change from baseline

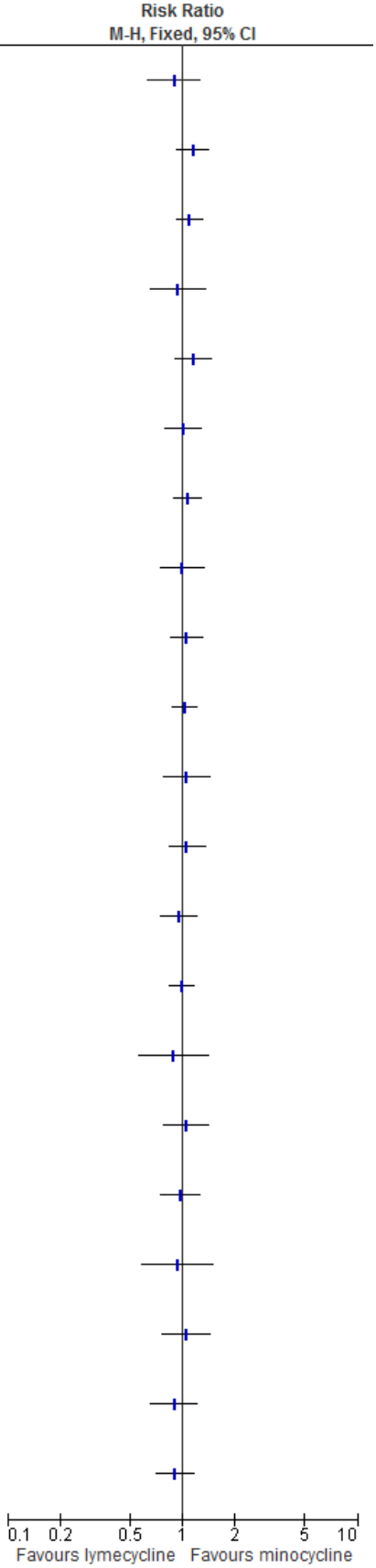


6.2 Lesion count - percentage change from baseline

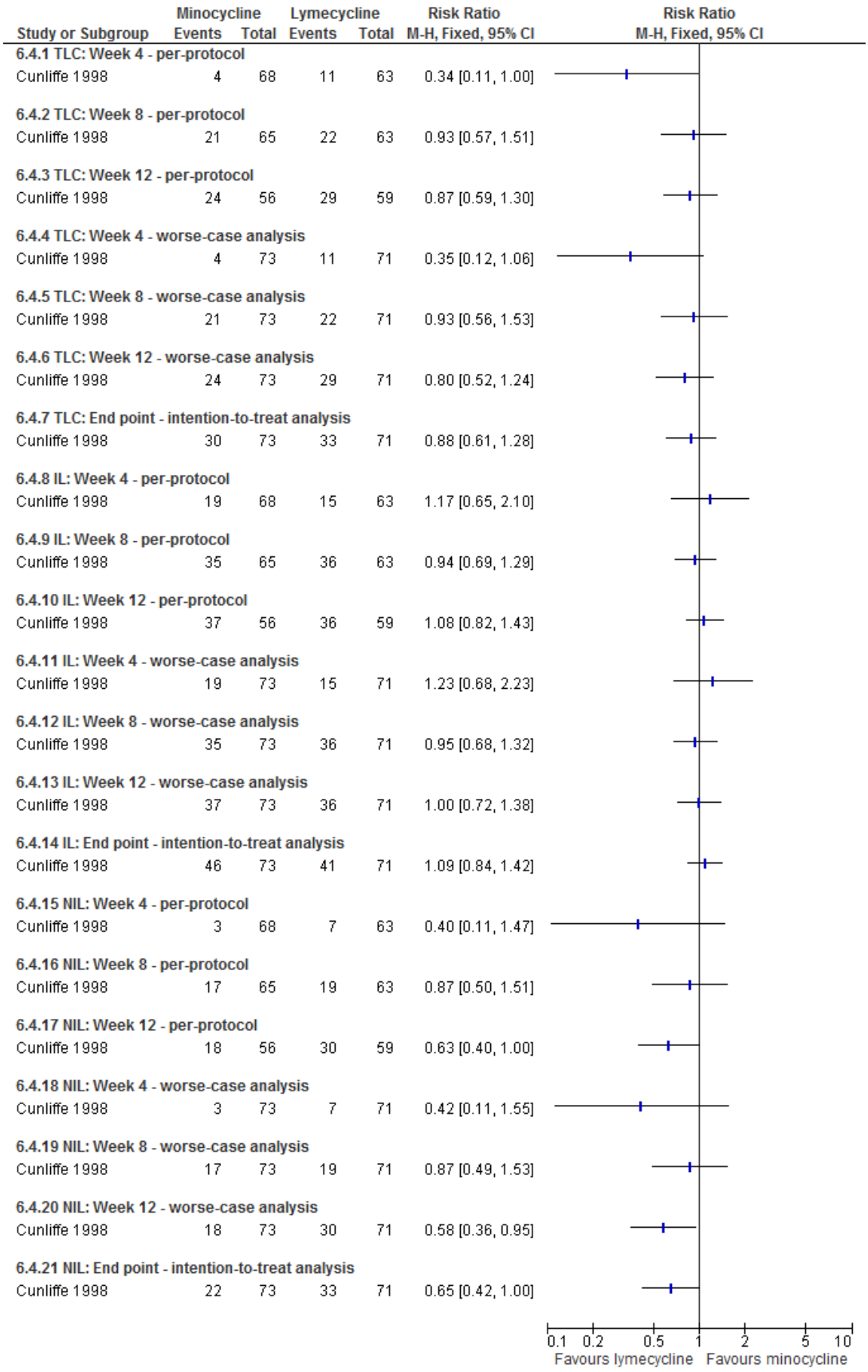


6.3 Lesion count - number of participants achieving > 25% reduction

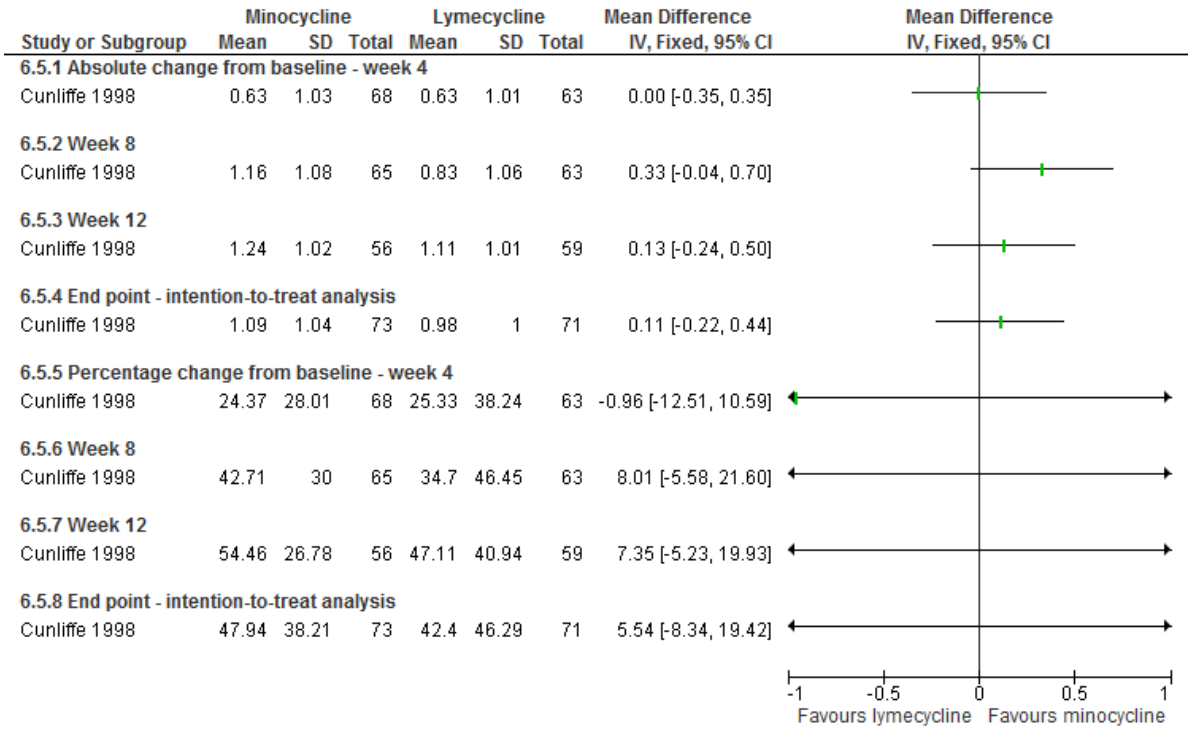
Study or Subgroup	Minocycline Events	Total	Lymecycline Events	Total	Risk Ratio M-H, Fixed, 95% CI
6.3.1 TLC: Week 4 - per-protocol					
Cunliffe 1998	32	68	33	63	0.90 [0.64, 1.27]
6.3.2 TLC: Week 8 - per-protocol					
Cunliffe 1998	51	65	43	63	1.15 [0.93, 1.42]
6.3.3 TLC: Week 12 - per-protocol					
Cunliffe 1998	48	56	46	59	1.10 [0.92, 1.31]
6.3.4 TLC: Week 4 - worse-case analysis					
Cunliffe 1998	32	73	33	71	0.94 [0.66, 1.35]
6.3.5 TLC: Week 8 - worse-case analysis					
Cunliffe 1998	51	73	43	71	1.15 [0.91, 1.47]
6.3.6 TLC: Week 12 - worse-case analysis					
Cunliffe 1998	48	73	46	71	1.01 [0.80, 1.29]
6.3.7 TLC: End point - intention-to-treat analysis					
Cunliffe 1998	58	73	53	71	1.06 [0.89, 1.27]
6.3.8 IL : Week 4 - per-protocol					
Cunliffe 1998	40	68	37	63	1.00 [0.75, 1.33]
6.3.9 IL: Week 8 - per-protocol					
Cunliffe 1998	49	65	45	63	1.06 [0.86, 1.30]
6.3.10 IL: Week 12 - per-protocol					
Cunliffe 1998	47	56	48	59	1.03 [0.87, 1.22]
6.3.11 IL: Week 4 - worse-case analysis					
Cunliffe 1998	40	73	37	71	1.05 [0.77, 1.43]
6.3.12 IL: Week 8 - worse-case analysis					
Cunliffe 1998	49	73	45	71	1.06 [0.83, 1.34]
6.3.13 IL: Week 12 - worse-case analysis					
Cunliffe 1998	47	73	48	71	0.95 [0.75, 1.20]
6.3.14 IL: End point - intention-to-treat analysis					
Cunliffe 1998	57	73	56	71	0.99 [0.83, 1.17]
6.3.15 NIL: Week 4 - per-protocol					
Cunliffe 1998	23	68	24	63	0.89 [0.56, 1.40]
6.3.16 NIL: Week 8 - per-protocol					
Cunliffe 1998	39	65	36	63	1.05 [0.78, 1.41]
6.3.17 NIL: Week 12 - per-protocol					
Cunliffe 1998	37	56	40	59	0.97 [0.75, 1.26]
6.3.18 NIL: Week 4 - worse-case analysis					
Cunliffe 1998	23	73	24	71	0.93 [0.58, 1.49]
6.3.19 NIL: Week 8 - worse-case analysis					
Cunliffe 1998	39	73	36	71	1.05 [0.77, 1.44]
6.3.20 NIL: Week 12 - worse-case analysis					
Cunliffe 1998	37	73	40	71	0.90 [0.66, 1.22]
6.3.21 NIL: End point - intention-to-treat analysis					
Cunliffe 1998	44	73	47	71	0.91 [0.71, 1.17]



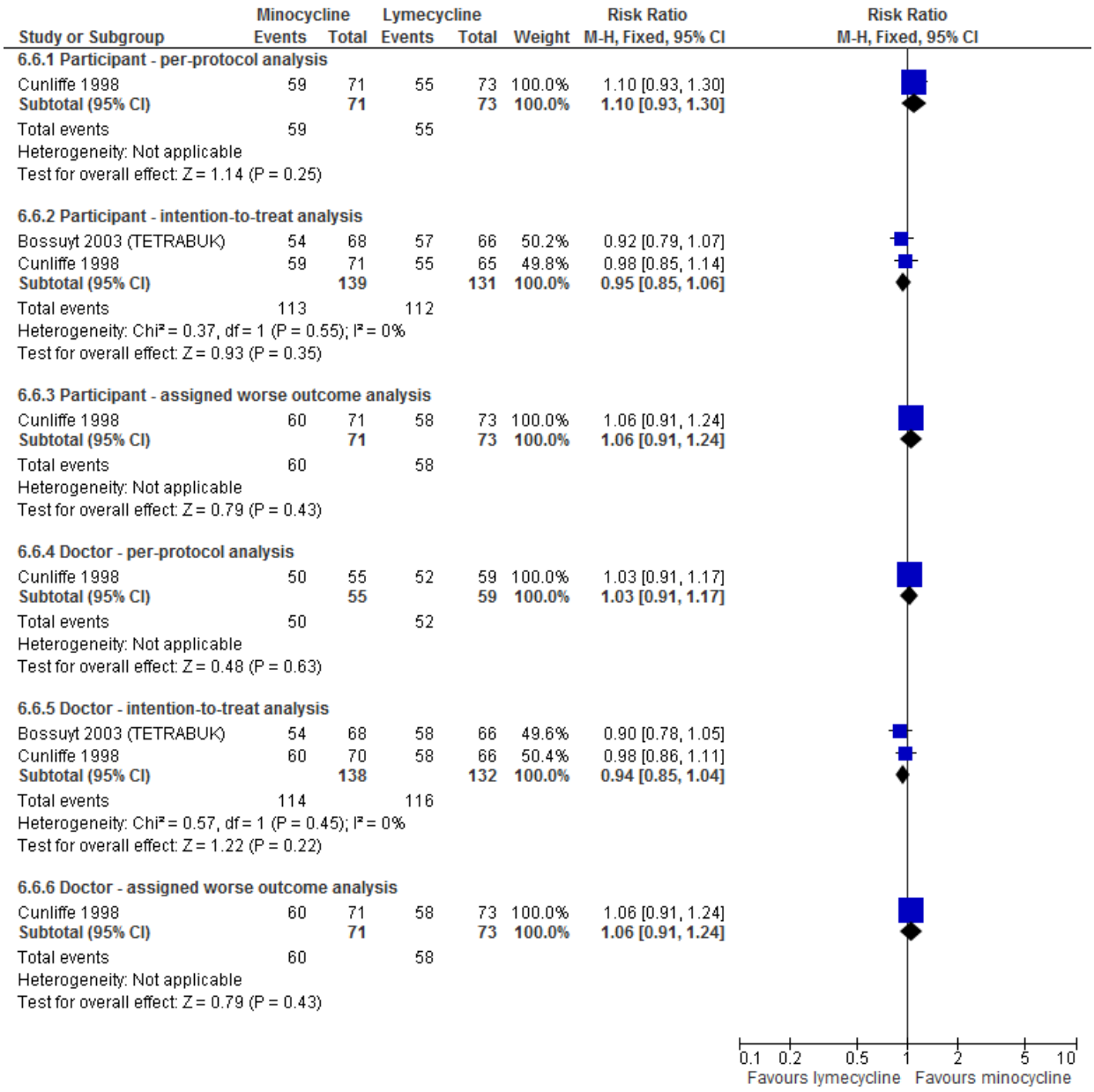
6.4 Lesion count - number of participants achieving > 50% reduction



6.5 Leeds grade

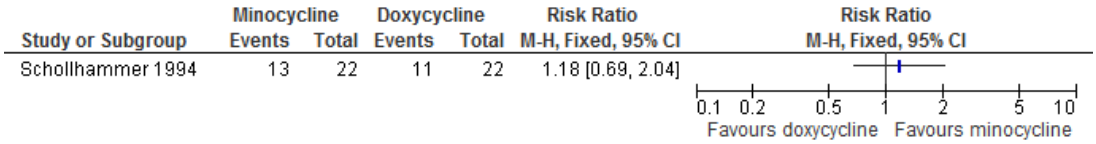


6.6 Global assessment - number of participants with overall improvement

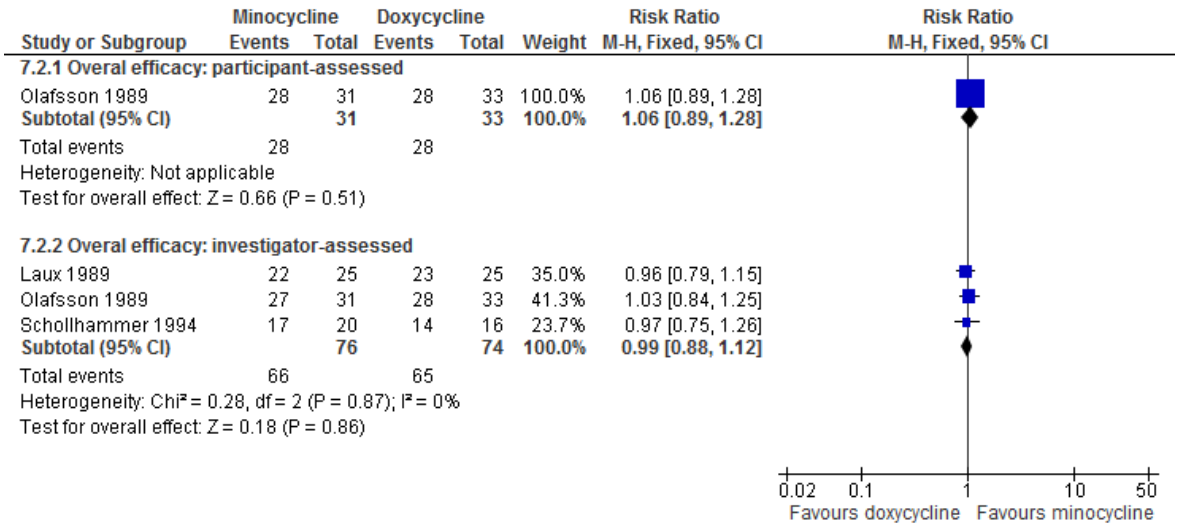


7 - Minocycline versus doxycycline

7.1 Number of participants with > 50% reduction in IL count



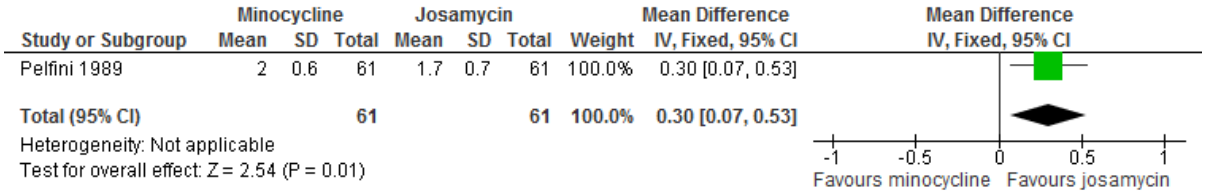
7.2 Global efficacy rating



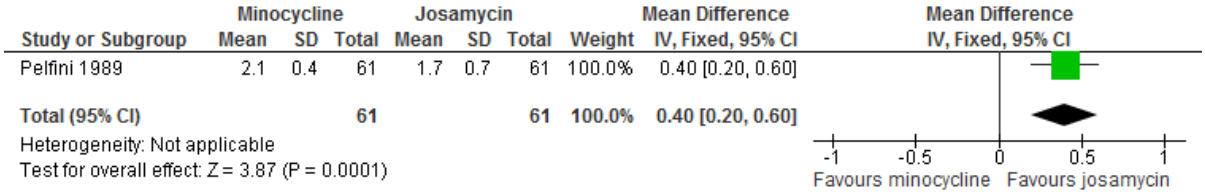
7.3 Cure

8 - Minocycline 100 mg/200 mg per day versus josamycin 500 mg/1000 mg

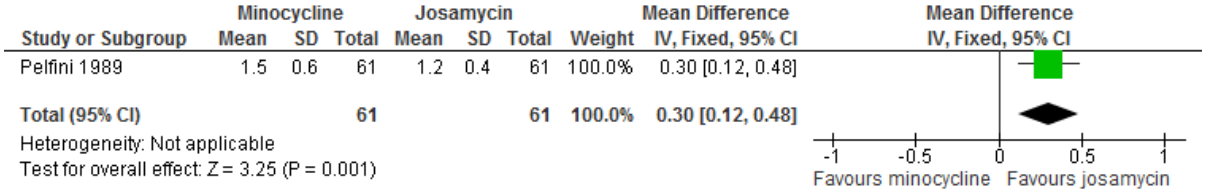
8.1 Pustules change in P&K severity grade 8 weeks



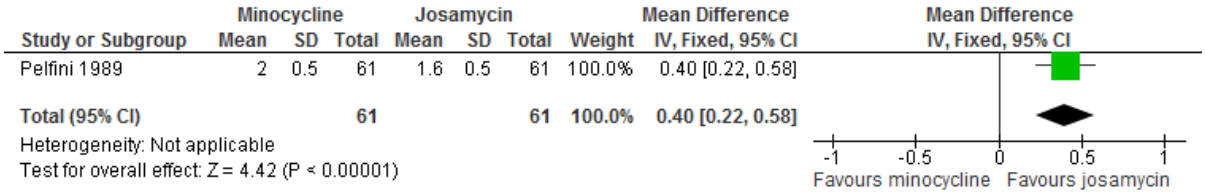
8.2 Nodulo-cysts change in P&K severity grade 8 weeks



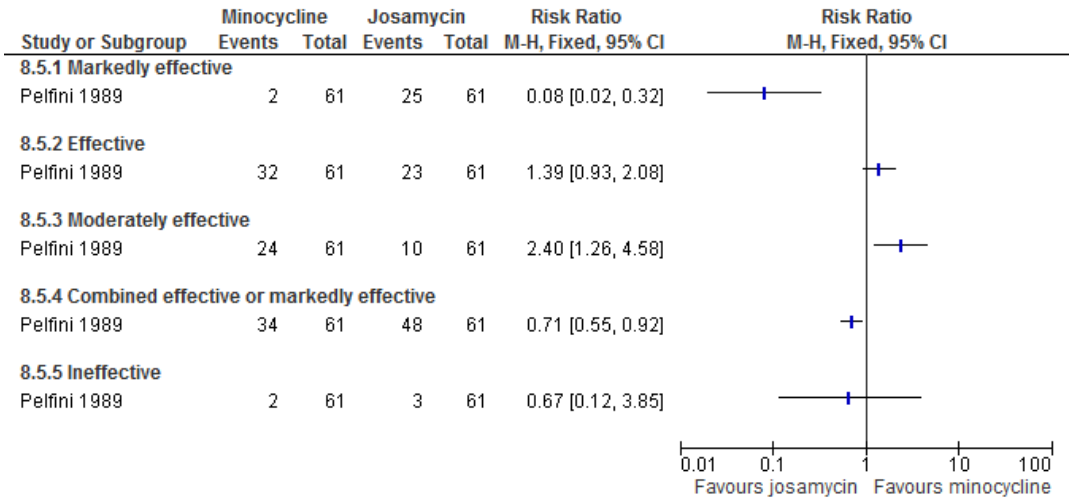
8.3 Erythema change in severity score 8 weeks



8.4 Seborrhea change in severity score 8 weeks

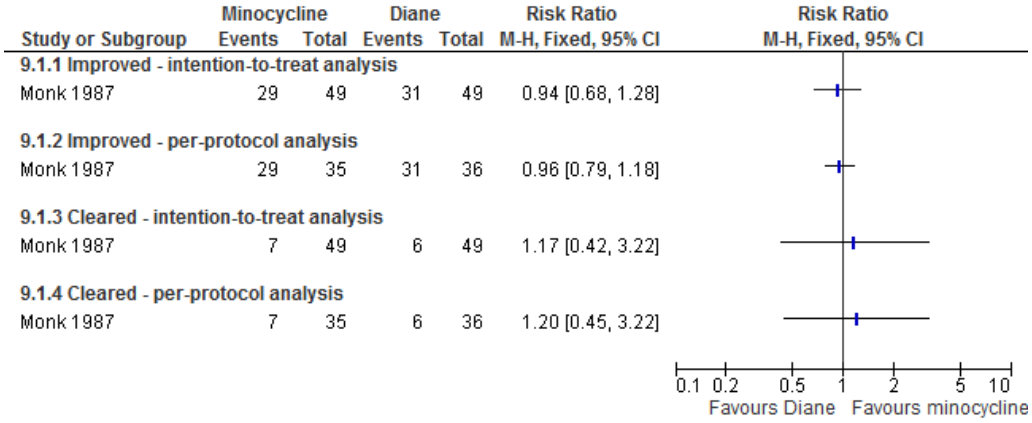


8.5 Evaluation of clinical efficacy 8 weeks



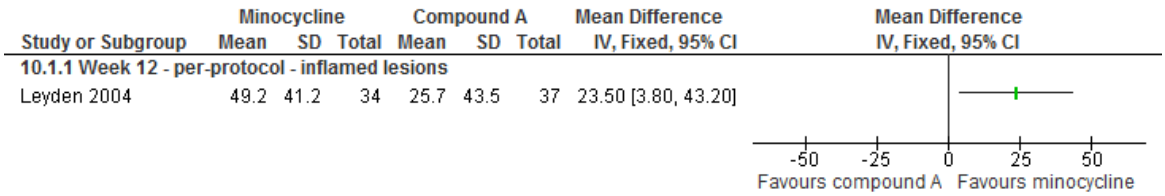
9 - Minocycline 50 mg bd versus Diane™ (cyproterone acetate 2 mg/ethinyloestradiol 50 mcg)

9.1 Participant-subjective evaluation



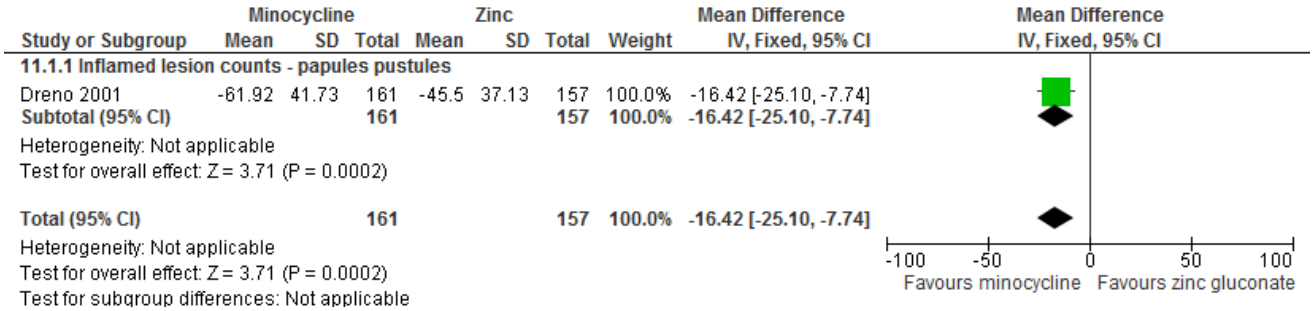
10 - Minocycline100 mg bd versus compound A

10.1 Inflamed lesion count - percentage change from baseline



11 - Minocycline 100 mg daily versus zinc gluconate 30 mg bd

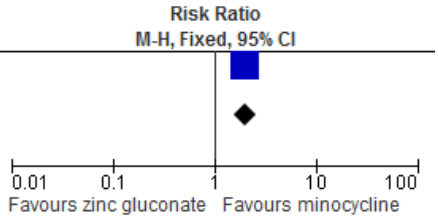
11.1 Lesion count - percentage change from baseline 90 days



11.2 Investigator global severity - successful treatment (2/3 reduction in IL)

Study or Subgroup	Minocycline Events	Total	Zinc Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dreno 2001	102	161	49	157	100.0%	2.03 [1.56, 2.63]
Total (95% CI)		**161**		**157**	**100.0%**	**2.03 [1.56, 2.63]**
Total events	102		49			

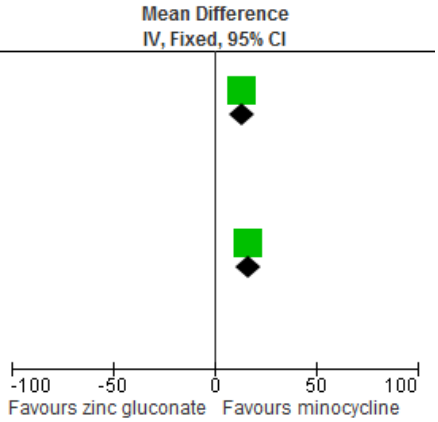
Heterogeneity: Not applicable
Test for overall effect: Z = 5.33 (P < 0.00001)



11.3 Overall opinion on efficacy (100 mm VAS)

Study or Subgroup	Minocycline Mean	SD	Total	Zinc Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
11.3.1 Clinician-assessed								
Dreno 2001	63.7	27	155	50	26.9	152	100.0%	13.70 [7.67, 19.73]
Subtotal (95% CI)			**155**			**152**	**100.0%**	**13.70 [7.67, 19.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.45 (P < 0.00001)								
11.3.2 Participant-assessed								
Dreno 2001	69.2	24.2	148	52.5	28.5	148	100.0%	16.70 [10.68, 22.72]
Subtotal (95% CI)			**148**			**148**	**100.0%**	**16.70 [10.68, 22.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.43 (P < 0.00001)								

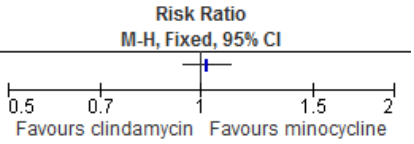
Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%



12 - Minocycline 50 mg bd versus clindamycin 1% lotion bd

12.1 Overall improvement - participant-assessed

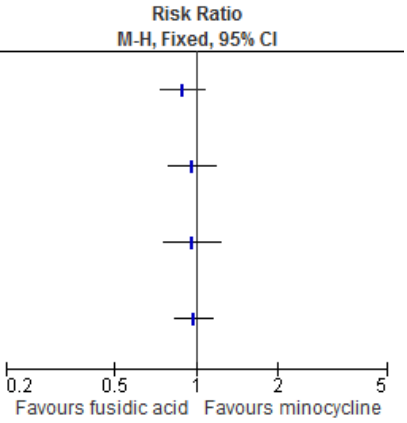
Study or Subgroup	Minocycline Events	Total	Clindamycin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Peacock 1990	37	38	40	42	1.02 [0.94, 1.11]



13 - Minocycline 50 mg bd versus fusidic acid 2% lotion bd

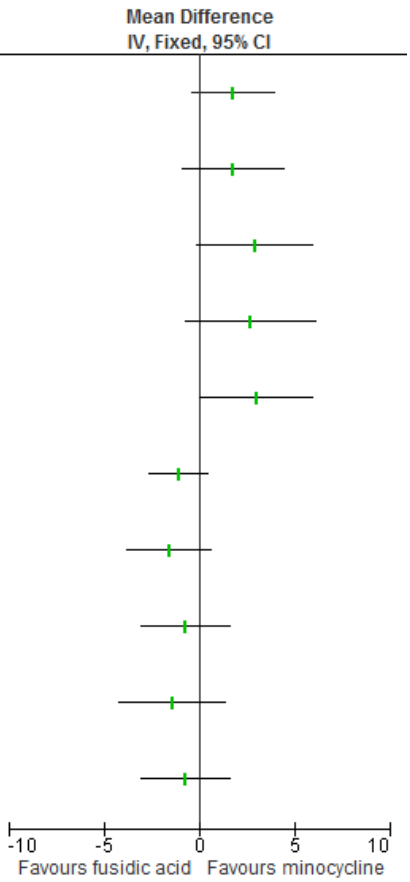
13.1 Participants achieving > 40% reduction in lesion counts

Study or Subgroup	Minocycline Events	Total	Fusidic acid Events	Total	Risk Ratio M-H, Fixed, 95% CI
13.1.1 Total lesion counts					
Darrah 1996	60	91	65	88	0.89 [0.74, 1.08]
13.1.2 Inflammatory lesions					
Darrah 1996	62	91	62	88	0.97 [0.80, 1.18]
13.1.3 Non-inflammatory lesions					
Darrah 1996	53	91	53	88	0.97 [0.76, 1.23]
13.1.4 Any lesion count					
Darrah 1996	69	91	68	88	0.98 [0.83, 1.15]



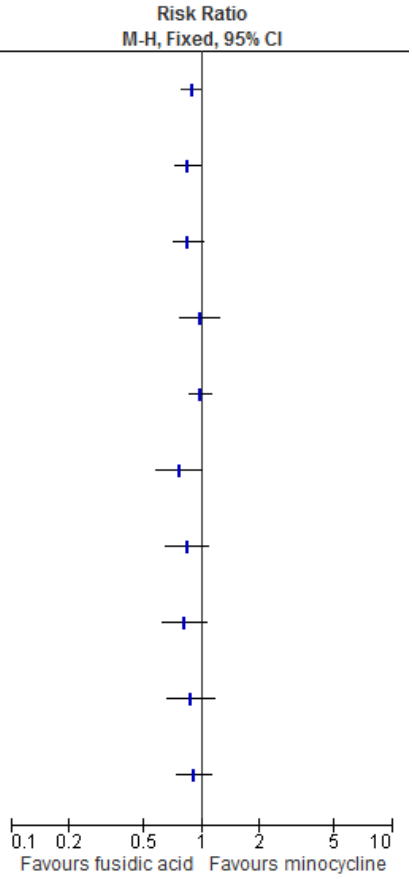
13.2 Lesion count changes from baseline

Study or Subgroup	Minocycline Mean	SD	Total	Fusidic acid Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
13.2.1 Inflamed lesions - week 2							
Darrah 1996	7.7	7.56	81	5.9	6.47	83	1.80 [-0.36, 3.96]
13.2.2 Week 4							
Darrah 1996	10.9	8.52	74	9.1	8.18	79	1.80 [-0.85, 4.45]
13.2.3 Week 6							
Darrah 1996	13	9.58	67	10.1	8.59	71	2.90 [-0.14, 5.94]
13.2.4 Week 8							
Darrah 1996	14.4	9.22	59	11.7	9.91	60	2.70 [-0.74, 6.14]
13.2.5 End of treatment							
Darrah 1996	13.5	9.69	82	10.5	9.57	83	3.00 [0.06, 5.94]
13.2.6 Non-inflamed lesions - week 2							
Darrah 1996	2.5	4.86	81	3.6	5.1	83	-1.10 [-2.62, 0.42]
13.2.7 Week 4							
Darrah 1996	3.6	7.48	74	5.2	6.31	79	-1.60 [-3.80, 0.60]
13.2.8 Week 6							
Darrah 1996	5.6	7.43	67	6.3	6.61	70	-0.70 [-3.06, 1.66]
13.2.9 Week 8							
Darrah 1996	5.2	7.83	59	6.6	7.67	60	-1.40 [-4.19, 1.39]
13.2.10 End of treatment							
Darrah 1996	5.5	7.88	82	6.2	7.47	83	-0.70 [-3.04, 1.64]



13.3 Overall clinical response

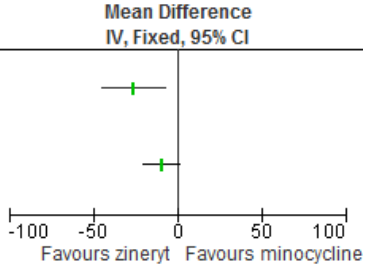
Study or Subgroup	Minocycline Events	Total	Fusidic acid Events	Total	Risk Ratio M-H, Fixed, 95% CI
13.3.1 Participants with average or greater response - week 2					
Darrah 1996	72	91	78	88	0.89 [0.78, 1.02]
13.3.2 Week 4					
Darrah 1996	65	91	74	88	0.85 [0.72, 1.00]
13.3.3 Week 6					
Darrah 1996	60	91	68	88	0.85 [0.71, 1.03]
13.3.4 Week 8					
Darrah 1996	55	91	54	88	0.98 [0.78, 1.25]
13.3.5 End of treatment					
Darrah 1996	76	91	74	88	0.99 [0.87, 1.13]
13.3.6 Participants with good or very good response - week 2					
Darrah 1996	42	91	53	88	0.77 [0.58, 1.01]
13.3.7 Week 4					
Darrah 1996	48	91	55	88	0.84 [0.66, 1.09]
13.3.8 Week 6					
Darrah 1996	45	91	53	88	0.82 [0.63, 1.07]
13.3.9 Week 8					
Darrah 1996	43	91	47	88	0.88 [0.66, 1.18]
13.3.10 End of treatment					
Darrah 1996	57	91	60	88	0.92 [0.74, 1.14]



14 - Minocycline 50 mg bd versus zineryt bd (erythromycin 4%/zinc 1.2% lotion)

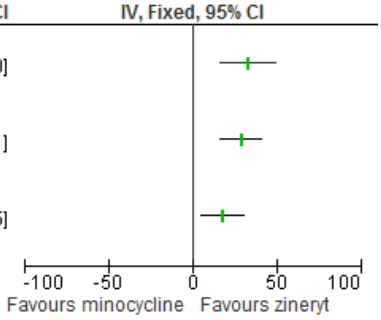
14.1 12-week lesion count - change from baseline

Study or Subgroup	Minocycline Mean	SD	Total	Zineryt Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
14.1.1 Non-inflamed week 12							
Stainforth 1993	20.1	48.46	51	46.3	49.8	54	-26.20 [-45.00, -7.40]
14.1.2 Inflamed lesions week 12							
Stainforth 1993	21.7	29.83	51	31.1	28.35	54	-9.40 [-20.54, 1.74]



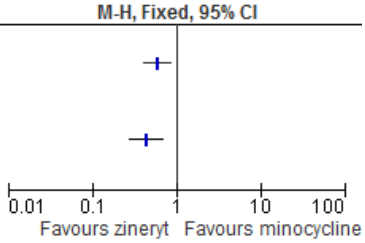
14.2 12-week percentage of baseline lesion counts

Study or Subgroup	Minocycline Mean	SD	Total	Zineryt Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
14.2.1 Non-inflamed lesions							
Stainforth 1993	77.4	45.3	51	44.5	40.6	51	32.90 [16.20, 49.60]
14.2.2 Superficial inflamed lesions							
Stainforth 1993	64.2	40.2	51	35.1	20.9	52	29.10 [16.69, 41.51]
14.2.3 Total inflamed lesions							
Stainforth 1993	64.7	36.3	51	46.8	32.2	54	17.90 [4.75, 31.05]



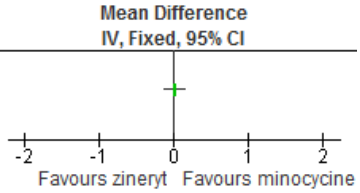
14.3 Number of participants attaining > 45% reduction in lesion counts from baseline

Study or Subgroup	Minocycline Events	Total	Zineryt Events	Total	Risk Ratio M-H, Fixed, 95% CI
14.3.1 Inflamed week 12					
Stainforth 1993	22	51	39	54	0.60 [0.42, 0.85]
14.3.2 Non-inflamed week 12					
Stainforth 1993	15	51	36	54	0.44 [0.28, 0.70]



14.4 Leeds grade - change from baseline

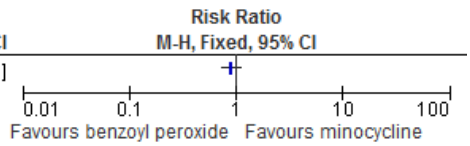
Study or Subgroup	Minocycline Mean	SD	Total	Zineryt Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
14.4.1 Week 12							
Stainforth 1993	0.58	0.44	54	0.57	0.29	55	0.01 [-0.13, 0.15]



15 - Minocycline 100 mg ER od versus benzoyl peroxide bd

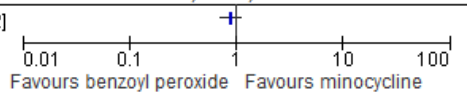
15.1 Overall improvement - participant assessed at least moderate improvement at 18 weeks

Study or Subgroup	Minocycline Events	Total	Benozyl peroxide Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ozolins 2005	70	130	78	130	0.90 [0.73, 1.11]

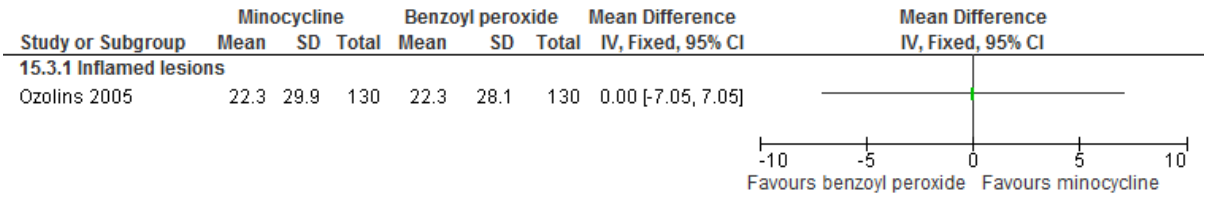


15.2 Overall improvement - assessor at least moderate improvement at 18 weeks

Study or Subgroup	Minocycline Events	Total	Benzoyl peroxide Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ozolins 2005	66	130	74	130	0.89 [0.71, 1.12]

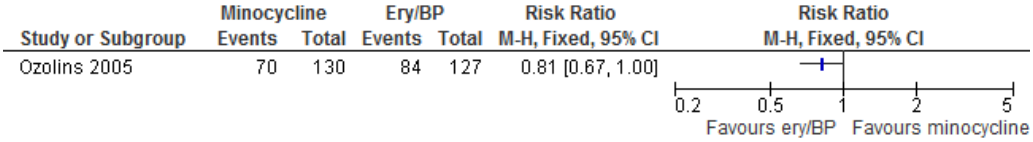


15.3 Lesion count - change from baseline

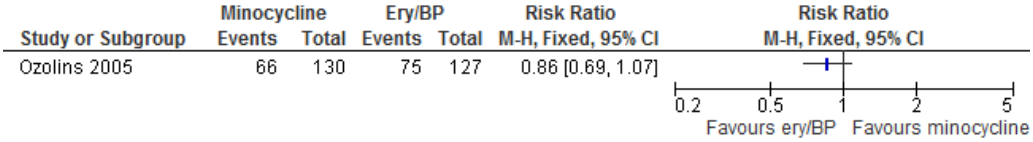


16 - Minocycline 100 mg ER od versus erythromycin/benzoyl peroxide (ery/BP) bd

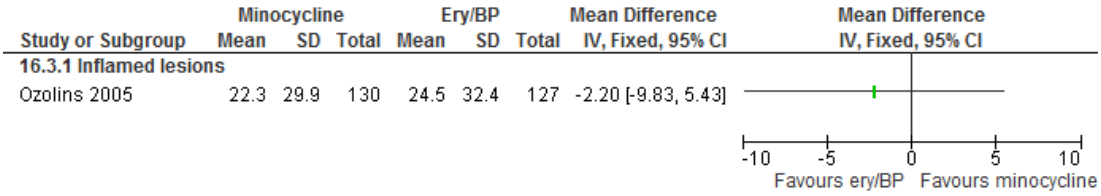
16.1 Overall improvement - participant assessed at least moderate improvement at 18 weeks



16.2 Overall improvement - assessor at least moderate improvement at 18 weeks

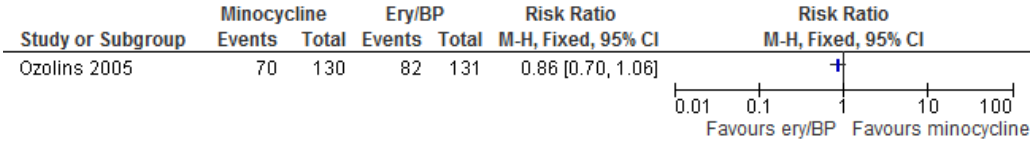


16.3 Lesion count - change from baseline

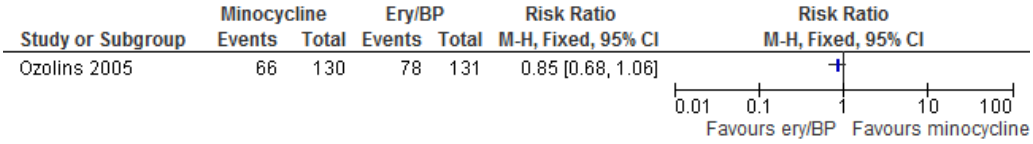


17 - Minocycline 100 mg ER od versus erythromycin od/benzoyl peroxide (ery/BP) od

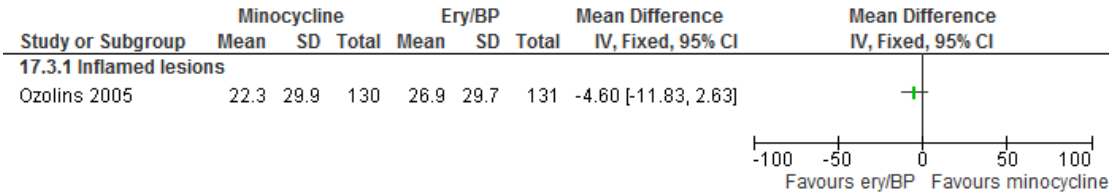
17.1 Overall improvement - participant assessed at least moderate improvement at 18 weeks



17.2 Overall improvement - assessor at least moderate improvement at 18 weeks



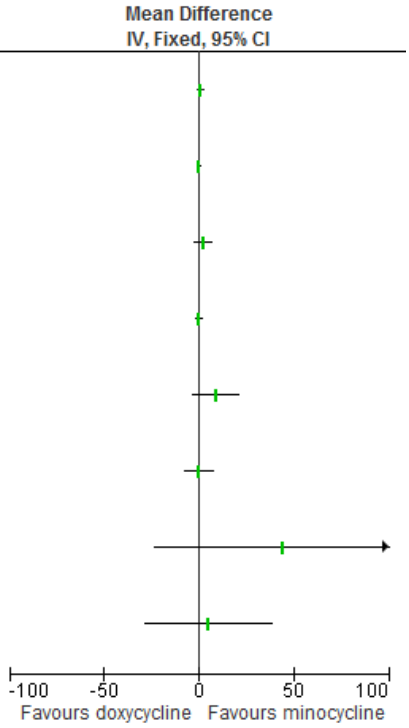
17.3 Lesion count - change from baseline



18 - Combination with 5% benzoyl peroxide/4% chlorhexidine

18.1 Lesion count

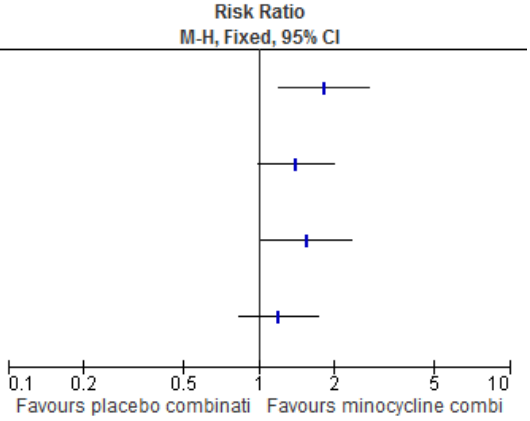
Study or Subgroup	Minocycline Mean	SD	Total	Doxycycline Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
18.1.1 Pustules (active) - actual values							
Harrison 1988	5	3.07	19	4.3	2.12	15	0.70 [-1.05, 2.45]
18.1.2 Pustules (active) - adjusted values							
Harrison 1988	4.7	0.87	19	4.8	1.16	15	-0.10 [-0.81, 0.61]
18.1.3 Papules (active) - actual values							
Harrison 1988	11	9.5	19	9	3.93	15	2.00 [-2.71, 6.71]
18.1.4 Papules (active) - adjusted values							
Harrison 1988	10	3.05	19	10	3.1	15	0.00 [-2.08, 2.08]
18.1.5 Total lesion count - actual values							
Harrison 1988	34	22.77	19	25	12.17	15	9.00 [-2.95, 20.95]
18.1.6 Total lesion count - adjusted values							
Harrison 1988	30	10.9	19	30	10.84	15	0.00 [-7.36, 7.36]
18.1.7 Lesion score - actual values							
Harrison 1988	206	128.41	19	162	68.52	15	44.00 [-23.35, 111.35]
18.1.8 Lesion score - adjusted values							
Harrison 1988	189	47.95	19	184	50.35	15	5.00 [-28.38, 38.38]



19 - Minocycline versus placebo plus combination erythromycin/tretinoin gel (strength unspecified)

19.1 Global grade - good/very good response

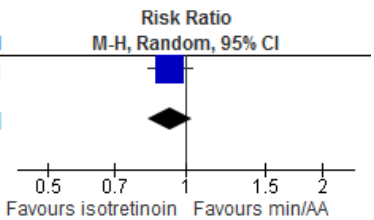
Study or Subgroup	Minocycline combination Events	Total	Placebo combination Events	Total	Risk Ratio M-H, Fixed, 95% CI
19.1.1 Dr-assessed: 'worse-case' analysis					
Revuz 1985	30	43	18	47	1.82 [1.21, 2.75]
19.1.2 Dr-assessed: per-protocol analysis					
Revuz 1985	30	39	18	33	1.41 [0.99, 2.01]
19.1.3 Participant-assessed: 'worse-case' analysis					
Revuz 1985	27	43	19	47	1.55 [1.02, 2.36]
19.1.4 Participant-assessed: per-protocol analysis					
Revuz 1985	27	39	19	33	1.20 [0.84, 1.72]



20 - Minocycline/azelaic acid (min/AA) versus isotretinoin

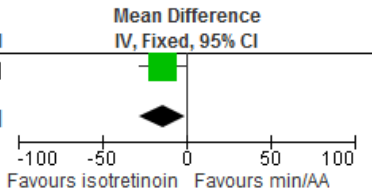
20.1 Number of participants with good or very good response after 6 months

Study or Subgroup	Minocycline/Azelaic acid Events	Total	Isotretinoin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gollnick 1997	45	50	34	35	100.0%	0.93 [0.83, 1.03]
Total (95% CI)		**50**		**35**	**100.0%**	**0.93 [0.83, 1.03]**
Total events	45		34			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						



20.2 Reduction in NIL: percentage change from baseline

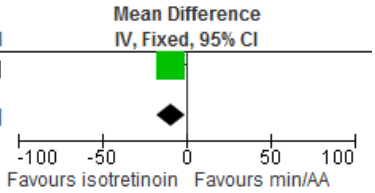
Study or Subgroup	Minocycline/Azelaic acid Mean	SD	Total	Isotretinoin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gollnick 1997	66	31.94	50	80	31.94	35	100.0%	-14.00 [-27.80, -0.20]
Total (95% CI)			**50**			**35**	**100.0%**	**-14.00 [-27.80, -0.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.99 (P = 0.05)								



20.3 Reduction in IL: percentage change from baseline

Study or Subgroup	Minocycline/Azelaic acid Mean	SD	Total	Isotretinoin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Gollnick 1997	88.2	20.3	50	97.1	20.3	35	100.0%	-8.90 [-17.67, -0.13]
Total (95% CI)			**50**			**35**	**100.0%**	**-8.90 [-17.67, -0.13]**

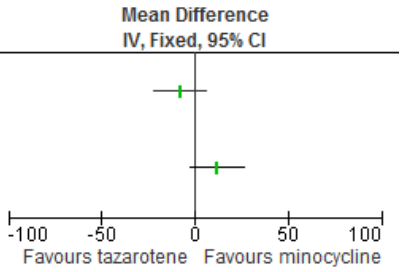
Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)



21 - Minocycline 100 mg od maintenance

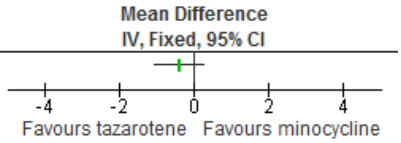
21.1 Lesion count - percentage change from baseline versus tazarotene

Study or Subgroup	Minocycline Mean	SD	Total	Tazorotene Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
21.1.1 NIL							
Leyden 2006 (Part 2)	52	30.4	31	60	22.9	26	-8.00 [-21.86, 5.86]
21.1.2 IL							
Leyden 2006 (Part 2)	66	29.4	31	54	25.1	26	12.00 [-2.15, 26.15]



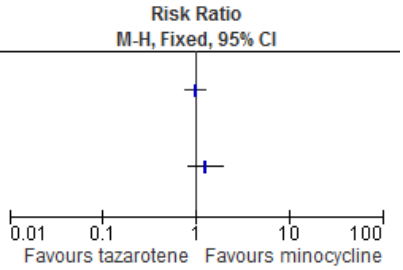
21.2 Overall disease severity score versus tazarotene

Study or Subgroup	Minocycline Mean	SD	Total	Tazorotene Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Leyden 2006 (Part 2)	2.3	1.32	31	2.7	1.22	26		-0.40 [-1.06, 0.26]



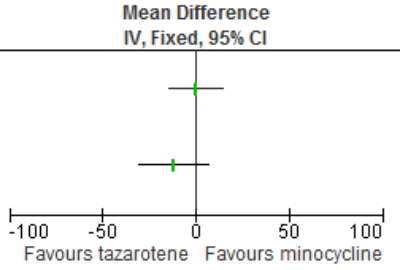
21.3 Overall clinical improvement - Dr-assessed versus tazarotene

Study or Subgroup	Minocycline Events	Total	Tazorotene Events	Total	Risk Ratio M-H, Fixed, 95% CI
21.3.1 < = 50%					
Leyden 2006 (Part 2)	25	31	21	26	1.00 [0.77, 1.29]
21.3.2 > = 75%					
Leyden 2006 (Part 2)	21	31	14	26	1.26 [0.82, 1.94]



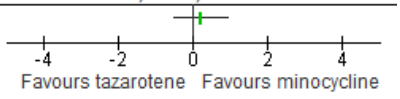
21.4 Lesion count - percentage change from baseline versus tazarotene/minocycline combination

Study or Subgroup	Minocycline Mean	SD	Total	Tazorotene/minocycline Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
21.4.1 IL							
Leyden 2006 (Part 2)	66	29.4	31	66	27.2	30	0.00 [-14.21, 14.21]
21.4.2 NIL							
Leyden 2006 (Part 2)	52	30.4	31	64	42.1	30	-12.00 [-30.48, 6.48]



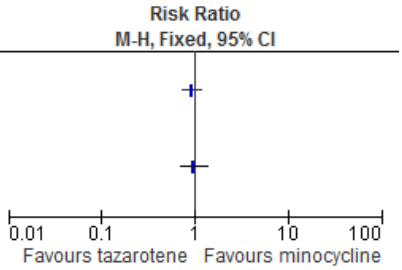
21.5 Overall disease severity score versus tazarotene/minocycline combination

Study or Subgroup	Minocycline Mean	SD	Total	Tazarotene min combin Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Leyden 2006 (Part 2)	2.3	1.32	31	2.1	1.52	30		0.20 [-0.52, 0.92]



21.6 Overall clinical improvement - Dr-assessed versus tazarotene/minocycline combination

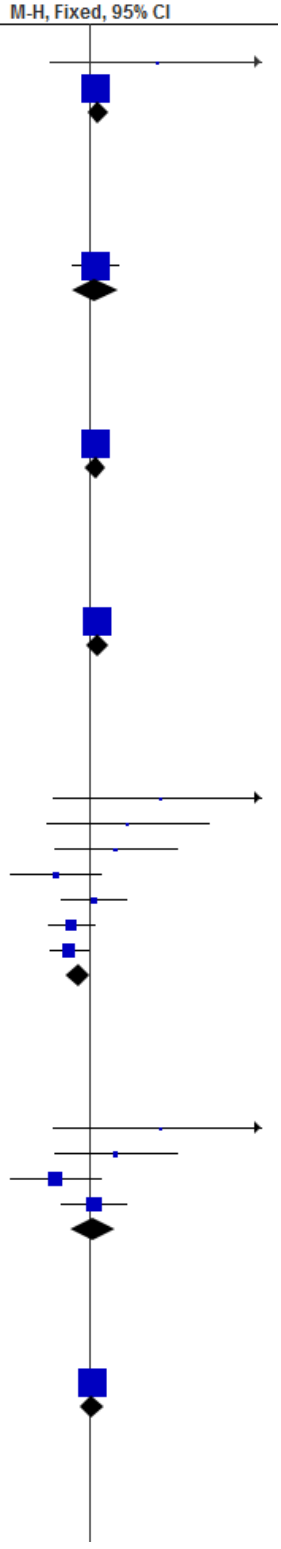
Study or Subgroup	Minocycline Events	Total	Tazarotene/minocycline Events	Total	Risk Ratio M-H, Fixed, 95% CI
21.6.1 < = 50%					
Leyden 2006 (Part 2)	25	31	26	30	0.93 [0.75, 1.16]
21.6.2 > = 75%					
Leyden 2006 (Part 2)	21	31	21	30	0.97 [0.69, 1.36]

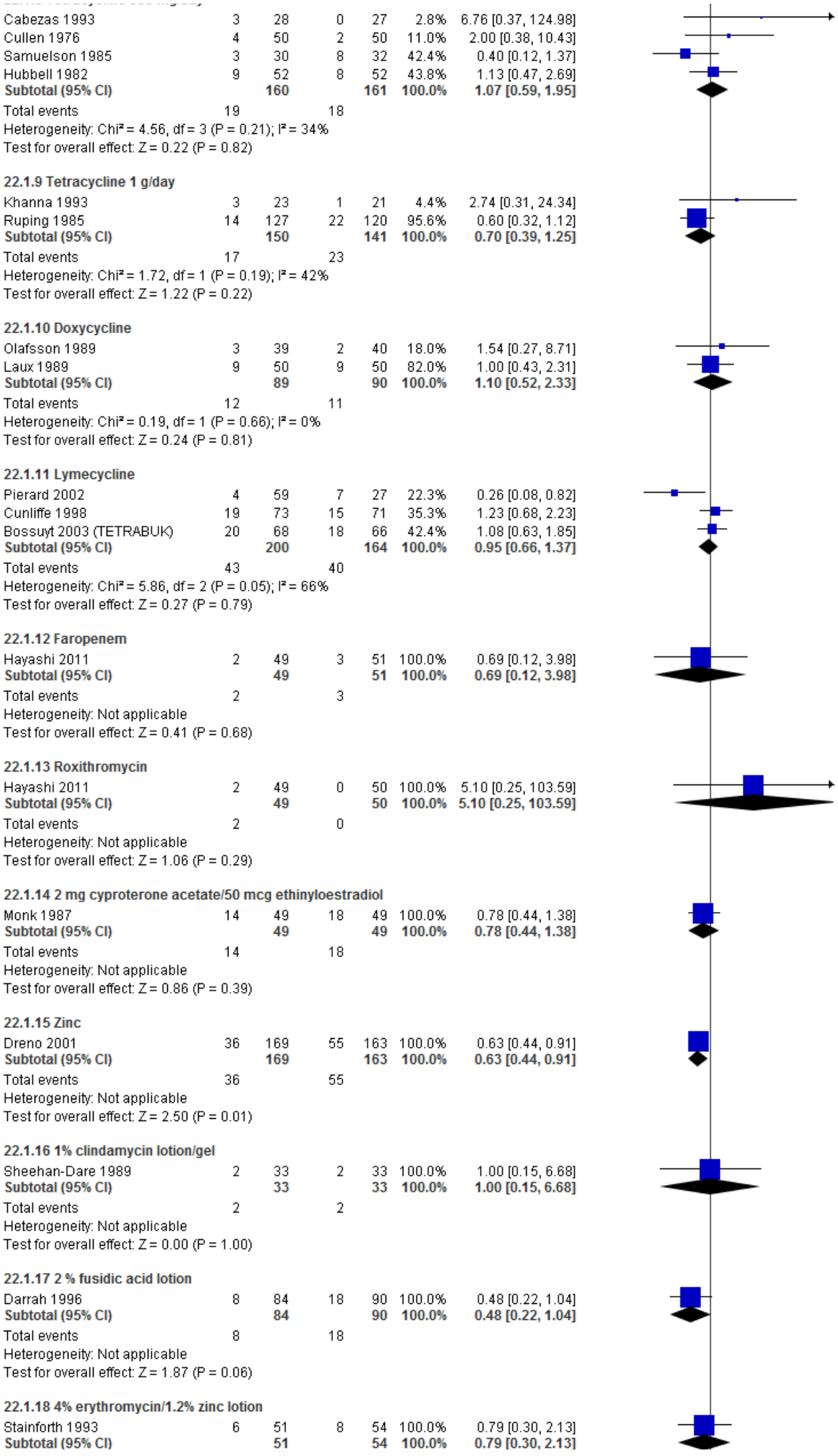


22 - Adverse drug reactions

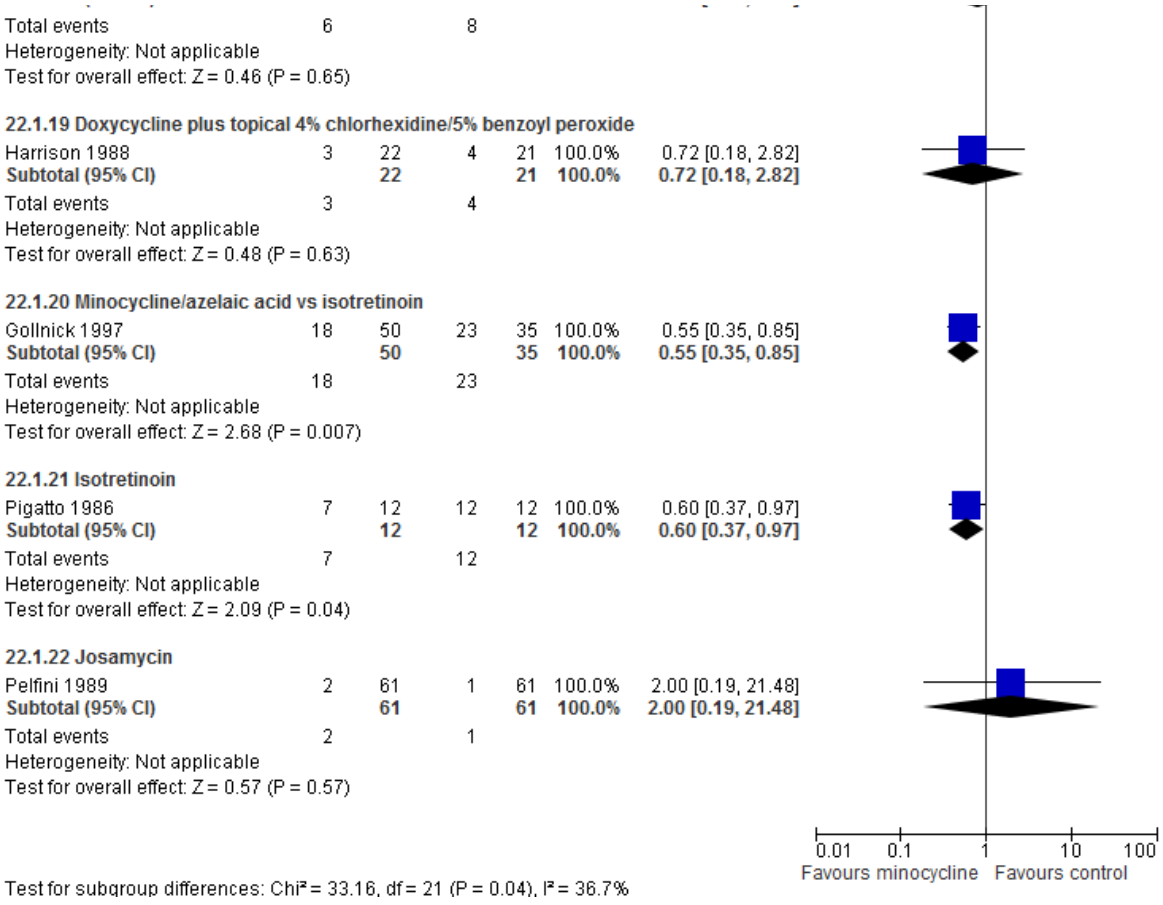
22.1 All reactions

Study or Subgroup	Minocycline Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
22.1.1 Placebo						
Cabezas 1993	3	28	0	25	1.2%	6.28 [0.34, 115.84]
Stewart 2006 (MP010401)	103	158	28	51	98.8%	1.19 [0.90, 1.56]
Subtotal (95% CI)		**186**		**76**	**100.0%**	**1.25 [0.95, 1.65]**
Total events	106		28			
Heterogeneity: Chi² = 1.31, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 1.59 (P = 0.11)						
22.1.2 100 mg od versus 100 mg/50 mg od						
Dreno 1998 [pers comm]	20	169	16	156	100.0%	1.15 [0.62, 2.15]
Subtotal (95% CI)		**169**		**156**	**100.0%**	**1.15 [0.62, 2.15]**
Total events	20		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
22.1.3 Dose response 3 mg/kg vs 2 mg/kg						
Stewart 2006 (MP010401)	39	60	33	59	100.0%	1.16 [0.87, 1.56]
Subtotal (95% CI)		**60**		**59**	**100.0%**	**1.16 [0.87, 1.56]**
Total events	39		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
22.1.4 Dose response 3 mg/kg vs 1 mg/kg						
Stewart 2006 (MP010401)	39	60	31	59	100.0%	1.24 [0.91, 1.68]
Subtotal (95% CI)		**60**		**59**	**100.0%**	**1.24 [0.91, 1.68]**
Total events	39		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
22.1.5 (Oxy)tetracycline						
Cabezas 1993	3	28	0	27	0.7%	6.76 [0.37, 124.98]
Khanna 1993	3	23	1	21	1.4%	2.74 [0.31, 24.34]
Cullen 1976	4	50	2	50	2.7%	2.00 [0.38, 10.43]
Samuelson 1985	3	30	8	32	10.6%	0.40 [0.12, 1.37]
Hubbell 1982	9	52	8	52	11.0%	1.13 [0.47, 2.69]
Ruping 1985	14	127	22	120	31.0%	0.60 [0.32, 1.12]
Blecschmidt 1987	19	104	29	90	42.6%	0.57 [0.34, 0.94]
Subtotal (95% CI)		**414**		**392**	**100.0%**	**0.73 [0.53, 1.01]**
Total events	55		70			
Heterogeneity: Chi² = 8.30, df = 6 (P = 0.22); I² = 28%						
Test for overall effect: Z = 1.89 (P = 0.06)						
22.1.6 (Oxy)tetracycline (Bleschmidt removed)						
Cabezas 1993	3	28	0	27	2.8%	6.76 [0.37, 124.98]
Cullen 1976	4	50	2	50	11.0%	2.00 [0.38, 10.43]
Samuelson 1985	3	30	8	32	42.4%	0.40 [0.12, 1.37]
Hubbell 1982	9	52	8	52	43.8%	1.13 [0.47, 2.69]
Subtotal (95% CI)		**160**		**161**	**100.0%**	**1.07 [0.59, 1.95]**
Total events	19		18			
Heterogeneity: Chi² = 4.56, df = 3 (P = 0.21); I² = 34%						
Test for overall effect: Z = 0.22 (P = 0.82)						
22.1.7 Dose response 2 mg/kg vs 1 mg/kg						
Stewart 2006 (MP010401)	33	59	31	59	100.0%	1.06 [0.76, 1.48]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**1.06 [0.76, 1.48]**
Total events	33		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
22.1.8 Tetracycline 500 mg/day						



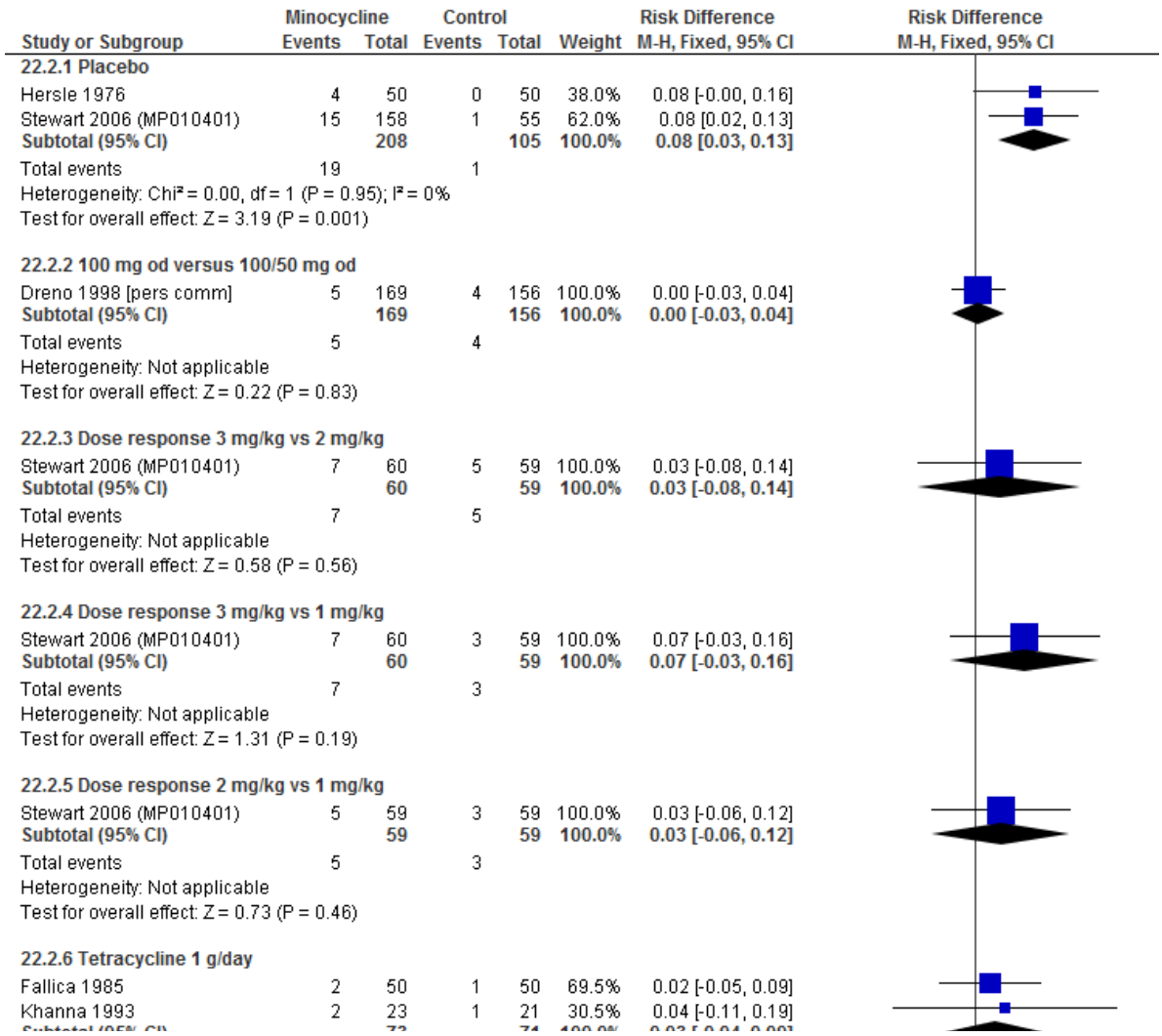


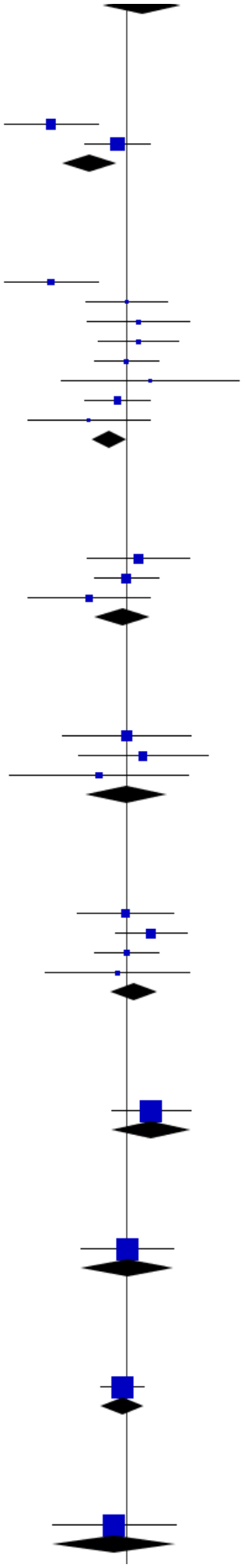
Cabezas 1993	3	28	0	27	2.8%	6.76 [0.37, 124.98]
Cullen 1976	4	50	2	50	11.0%	2.00 [0.38, 10.43]
Samuelson 1985	3	30	8	32	42.4%	0.40 [0.12, 1.37]
Hubbell 1982	9	52	8	52	43.8%	1.13 [0.47, 2.69]
Subtotal (95% CI)		**160**		**161**	**100.0%**	**1.07 [0.59, 1.95]**
Total events	19		18			
Heterogeneity: Chi² = 4.56, df = 3 (P = 0.21); I² = 34%						
Test for overall effect: Z = 0.22 (P = 0.82)						
22.1.9 Tetracycline 1 g/day						
Khanna 1993	3	23	1	21	4.4%	2.74 [0.31, 24.34]
Ruping 1985	14	127	22	120	95.6%	0.60 [0.32, 1.12]
Subtotal (95% CI)		**150**		**141**	**100.0%**	**0.70 [0.39, 1.25]**
Total events	17		23			
Heterogeneity: Chi² = 1.72, df = 1 (P = 0.19); I² = 42%						
Test for overall effect: Z = 1.22 (P = 0.22)						
22.1.10 Doxycycline						
Olafsson 1989	3	39	2	40	18.0%	1.54 [0.27, 8.71]
Laux 1989	9	50	9	50	82.0%	1.00 [0.43, 2.31]
Subtotal (95% CI)		**89**		**90**	**100.0%**	**1.10 [0.52, 2.33]**
Total events	12		11			
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
22.1.11 Lymecycline						
Pierard 2002	4	59	7	27	22.3%	0.26 [0.08, 0.82]
Cunliffe 1998	19	73	15	71	35.3%	1.23 [0.68, 2.23]
Bossuyt 2003 (TETRABUK)	20	68	18	66	42.4%	1.08 [0.63, 1.85]
Subtotal (95% CI)		**200**		**164**	**100.0%**	**0.95 [0.66, 1.37]**
Total events	43		40			
Heterogeneity: Chi² = 5.86, df = 2 (P = 0.05); I² = 66%						
Test for overall effect: Z = 0.27 (P = 0.79)						
22.1.12 Faropenem						
Hayashi 2011	2	49	3	51	100.0%	0.69 [0.12, 3.98]
Subtotal (95% CI)		**49**		**51**	**100.0%**	**0.69 [0.12, 3.98]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
22.1.13 Roxithromycin						
Hayashi 2011	2	49	0	50	100.0%	5.10 [0.25, 103.59]
Subtotal (95% CI)		**49**		**50**	**100.0%**	**5.10 [0.25, 103.59]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
22.1.14 2 mg cyproterone acetate/50 mcg ethinyloestradiol						
Monk 1987	14	49	18	49	100.0%	0.78 [0.44, 1.38]
Subtotal (95% CI)		**49**		**49**	**100.0%**	**0.78 [0.44, 1.38]**
Total events	14		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
22.1.15 Zinc						
Dreno 2001	36	169	55	163	100.0%	0.63 [0.44, 0.91]
Subtotal (95% CI)		**169**		**163**	**100.0%**	**0.63 [0.44, 0.91]**
Total events	36		55			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.50 (P = 0.01)						
22.1.16 1% clindamycin lotion/gel						
Sheehan-Dare 1989	2	33	2	33	100.0%	1.00 [0.15, 6.68]
Subtotal (95% CI)		**33**		**33**	**100.0%**	**1.00 [0.15, 6.68]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
22.1.17 2 % fusidic acid lotion						
Darrah 1996	8	84	18	90	100.0%	0.48 [0.22, 1.04]
Subtotal (95% CI)		**84**		**90**	**100.0%**	**0.48 [0.22, 1.04]**
Total events	8		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						
22.1.18 4% erythromycin/1.2% zinc lotion						
Stainforth 1993	6	51	8	54	100.0%	0.79 [0.30, 2.13]
Subtotal (95% CI)		**51**		**54**	**100.0%**	**0.79 [0.30, 2.13]**



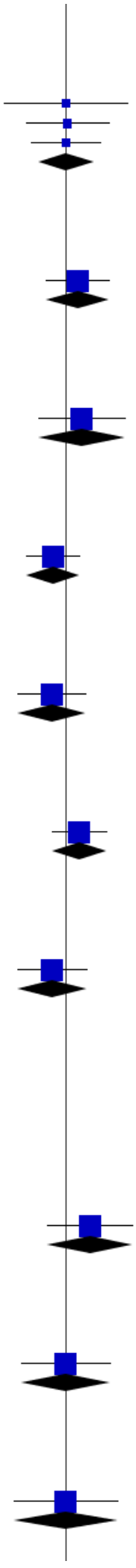
Test for subgroup differences: Chi² = 33.16, df = 21 (P = 0.04), I² = 36.7%

22.2 Requiring therapy cessation





Subtotal (95% CI)		**73**		**71**	**100.0%**	**0.03 [-0.04, 0.09]**
Total events	4		2			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
22.2.7 Oxytetracycline						
Blecschmidt 1987	2	104	13	90	42.5%	-0.13 [-0.20, -0.05]
Ozolins 2005	6	130	8	131	57.5%	-0.01 [-0.07, 0.04]
Subtotal (95% CI)		**234**		**221**	**100.0%**	**-0.06 [-0.11, -0.02]**
Total events	8		21			
Heterogeneity: Chi² = 5.42, df = 1 (P = 0.02); I² = 82%						
Test for overall effect: Z = 2.67 (P = 0.008)						
22.2.8 (Oxy)tetracycline						
Blecschmidt 1987	2	104	13	90	21.0%	-0.13 [-0.20, -0.05]
Cabezas 1993	0	28	0	27	6.0%	0.00 [-0.07, 0.07]
Cullen 1976	3	50	2	50	10.9%	0.02 [-0.07, 0.11]
Fallica 1985	2	50	1	50	10.9%	0.02 [-0.05, 0.09]
Hubbell 1982	1	52	1	52	11.3%	0.00 [-0.05, 0.05]
Khanna 1993	2	23	1	21	4.8%	0.04 [-0.11, 0.19]
Ozolins 2005	6	130	8	131	28.4%	-0.01 [-0.07, 0.04]
Samuelson 1985	0	30	2	32	6.7%	-0.06 [-0.16, 0.04]
Subtotal (95% CI)		**467**		**453**	**100.0%**	**-0.03 [-0.06, -0.00]**
Total events	16		28			
Heterogeneity: Chi² = 12.58, df = 7 (P = 0.08); I² = 44%						
Test for overall effect: Z = 1.98 (P = 0.05)						
22.2.9 Tetracycline 500 mg/day						
Cullen 1976	3	50	2	50	37.6%	0.02 [-0.07, 0.11]
Hubbell 1982	1	52	1	52	39.1%	0.00 [-0.05, 0.05]
Samuelson 1985	0	30	2	32	23.3%	-0.06 [-0.16, 0.04]
Subtotal (95% CI)		**132**		**134**	**100.0%**	**-0.01 [-0.05, 0.04]**
Total events	4		5			
Heterogeneity: Chi² = 1.62, df = 2 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
22.2.10 Doxycycline						
Laux 1989	4	50	4	50	44.8%	0.00 [-0.11, 0.11]
Olafsson 1989	3	39	2	40	35.4%	0.03 [-0.08, 0.13]
Schollhammer 1994	1	22	2	22	19.7%	-0.05 [-0.19, 0.10]
Subtotal (95% CI)		**111**		**112**	**100.0%**	**0.00 [-0.07, 0.07]**
Total events	8		8			
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.99)						
22.2.11 Lymecycline						
Bossuyt 2003 (TETRABUK)	4	68	4	66	33.1%	-0.00 [-0.08, 0.08]
Cunliffe 1998	4	73	1	71	35.6%	0.04 [-0.02, 0.10]
Pierard 2002	0	59	0	27	18.3%	0.00 [-0.05, 0.05]
Schollhammer 1994	1	22	2	33	13.0%	-0.02 [-0.13, 0.10]
Subtotal (95% CI)		**222**		**197**	**100.0%**	**0.01 [-0.03, 0.05]**
Total events	9		7			
Heterogeneity: Chi² = 1.41, df = 3 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
22.2.12 Roxithromycin						
Hayashi 2011	2	49	0	50	100.0%	0.04 [-0.03, 0.11]
Subtotal (95% CI)		**49**		**50**	**100.0%**	**0.04 [-0.03, 0.11]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
22.2.13 Faropenem						
Hayashi 2011	2	49	2	51	100.0%	0.00 [-0.08, 0.08]
Subtotal (95% CI)		**49**		**51**	**100.0%**	**0.00 [-0.08, 0.08]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
22.2.14 Zinc						
Dreno 2001	4	169	5	163	100.0%	-0.01 [-0.04, 0.03]
Subtotal (95% CI)		**169**		**163**	**100.0%**	**-0.01 [-0.04, 0.03]**
Total events	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.69)						
22.2.15 2 mg cyproterone acetate/50 mcg ethinyloestradiol						
Monk 1987	3	49	4	49	100.0%	-0.02 [-0.12, 0.08]
Subtotal (95% CI)		**49**		**49**	**100.0%**	**-0.02 [-0.12, 0.08]**



Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.69)						
22.2.16 1% clindamycin lotion/gel						
Drake 1990	2	37	2	37	33.7%	0.00 [-0.10, 0.10]
Peacock 1990	1	38	1	42	36.3%	0.00 [-0.07, 0.07]
Sheehan-Dare 1989	0	33	0	33	30.0%	0.00 [-0.06, 0.06]
Subtotal (95% CI)		**108**		**112**	**100.0%**	**0.00 [-0.05, 0.05]**
Total events	3		3			
Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
22.2.17 4% erythromycin/zinc 1.2% lotion						
Stainforth 1993	1	51	0	54	100.0%	0.02 [-0.03, 0.07]
Subtotal (95% CI)		**51**		**54**	**100.0%**	**0.02 [-0.03, 0.07]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
22.2.18 Tazarotene						
Leyden 2006 (Part 2)	1	37	0	36	100.0%	0.03 [-0.05, 0.10]
Subtotal (95% CI)		**37**		**36**	**100.0%**	**0.03 [-0.05, 0.10]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						
22.2.19 2% fusidic acid lotion						
Darrah 1996	1	84	3	90	100.0%	-0.02 [-0.07, 0.02]
Subtotal (95% CI)		**84**		**90**	**100.0%**	**-0.02 [-0.07, 0.02]**
Total events	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
22.2.20 Benzoyl peroxide 5% twice-daily						
Ozolins 2005	6	130	9	130	100.0%	-0.02 [-0.08, 0.03]
Subtotal (95% CI)		**130**		**130**	**100.0%**	**-0.02 [-0.08, 0.03]**
Total events	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
22.2.21 Benzoyl peroxide 5% plus 3% erythromycin twice-daily						
Ozolins 2005	6	130	3	127	100.0%	0.02 [-0.02, 0.07]
Subtotal (95% CI)		**130**		**127**	**100.0%**	**0.02 [-0.02, 0.07]**
Total events	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
22.2.22 Benzoyl peroxide 5% evening plus 2% erythromycin morning						
Ozolins 2005	6	130	9	131	100.0%	-0.02 [-0.08, 0.03]
Subtotal (95% CI)		**130**		**131**	**100.0%**	**-0.02 [-0.08, 0.03]**
Total events	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.43)						
22.2.23 Placebo plus topical erythromycin/tretinoin gel						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
22.2.24 Minocycline/azelaic acid versus isotretinoin						
Gollnick 1997	2	50	0	35	100.0%	0.04 [-0.03, 0.11]
Subtotal (95% CI)		**50**		**35**	**100.0%**	**0.04 [-0.03, 0.11]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
22.2.25 Tazorotene/minocycline combination						
Leyden 2006 (Part 2)	1	37	1	37	100.0%	0.00 [-0.07, 0.07]
Subtotal (95% CI)		**37**		**37**	**100.0%**	**0.00 [-0.07, 0.07]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
22.2.26 Doxycycline plus topical 4% chlorhexidine/5% benzoyl peroxide						
Harrison 1988	0	22	0	21	100.0%	0.00 [-0.09, 0.09]
Subtotal (95% CI)		**22**		**21**	**100.0%**	**0.00 [-0.09, 0.09]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

22.2.27 Isotretinoin

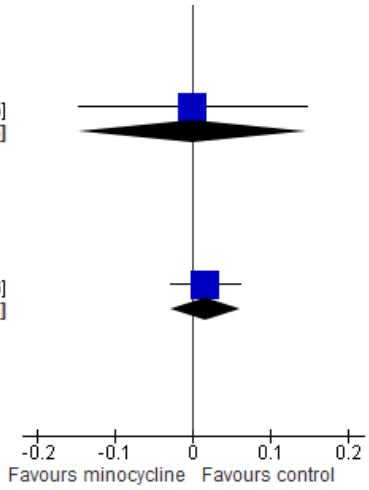
Pigatto 1986	0	12	0	12	100.0%	0.00 [-0.15, 0.15]
Subtotal (95% CI)		**12**		**12**	**100.0%**	**0.00 [-0.15, 0.15]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

22.2.28 Josamycin

Pelfini 1989	1	61	0	61	100.0%	0.02 [-0.03, 0.06]
Subtotal (95% CI)		**61**		**61**	**100.0%**	**0.02 [-0.03, 0.06]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)



22.3 Gastro-intestinal disturbances

Study or Subgroup	Minocycline Events	Total	Control Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
22.3.1 Placebo						
Cabezas 1993	1	28	0	25	25.5%	0.04 [-0.06, 0.13]
Stewart 2006 (MP010401)	43	158	18	51	74.5%	-0.08 [-0.23, 0.07]
Subtotal (95% CI)		**186**		**76**	**100.0%**	**-0.05 [-0.16, 0.06]**
Total events	44		18			

Heterogeneity: Chi² = 3.27, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 0.88 (P = 0.38)

22.3.2 100 mg od versus 100 mg/50 mg od

Dreno 1998 [pers comm]	8	169	7	156	100.0%	0.00 [-0.04, 0.05]
Subtotal (95% CI)		**169**		**156**	**100.0%**	**0.00 [-0.04, 0.05]**
Total events	8		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.92)

22.3.3 50 mg bd for 4 weeks then 50 mg od for 8 weeks versus 50 mg od for 8 weeks

Pierard 2002	0	31	1	28	100.0%	-0.04 [-0.13, 0.06]
Subtotal (95% CI)		**31**		**28**	**100.0%**	**-0.04 [-0.13, 0.06]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)

22.3.4 Dose response 3 mg/kg vs 2 mg/kg

Stewart 2006 (MP010401)	20	60	14	59	100.0%	0.10 [-0.07, 0.26]
Subtotal (95% CI)		**60**		**59**	**100.0%**	**0.10 [-0.07, 0.26]**
Total events	20		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.17 (P = 0.24)

22.3.5 Dose response 3 mg/kg vs 1 mg/kg

Stewart 2006 (MP010401)	20	60	9	59	100.0%	0.18 [0.03, 0.33]
Subtotal (95% CI)		**60**		**59**	**100.0%**	**0.18 [0.03, 0.33]**
Total events	20		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)

22.3.6 Dose response 2 mg/kg vs 1 mg/kg

Stewart 2006 (MP010401)	14	59	9	59	100.0%	0.08 [-0.06, 0.23]
Subtotal (95% CI)		**59**		**59**	**100.0%**	**0.08 [-0.06, 0.23]**
Total events	14		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.17 (P = 0.24)

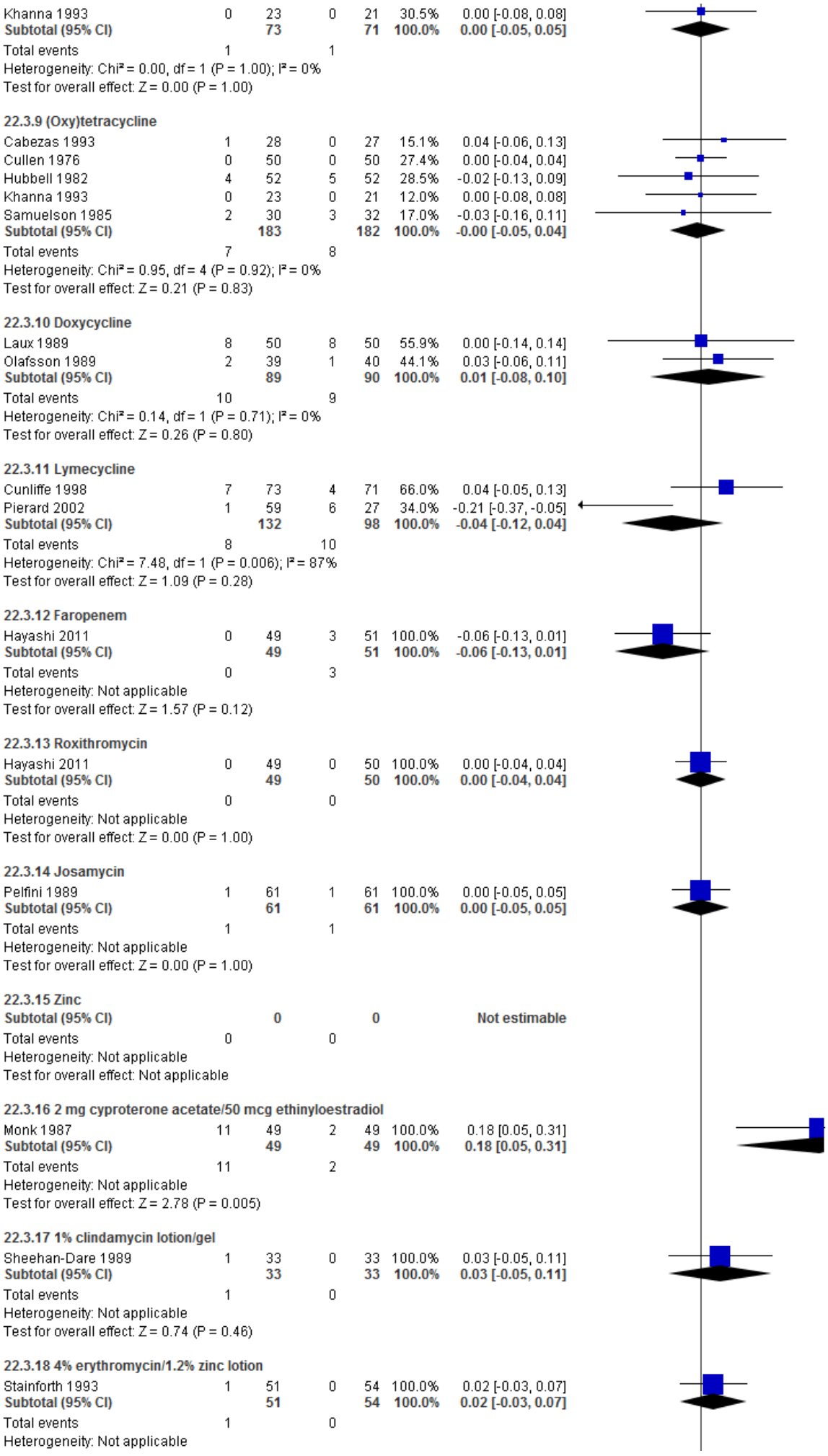
22.3.7 Tetracycline 500 mg/day

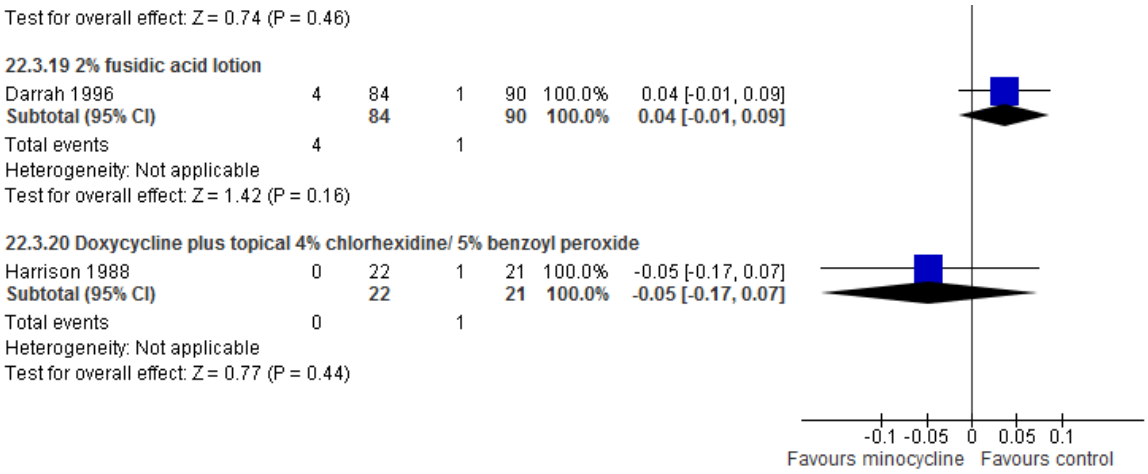
Cabezas 1993	1	28	0	25	16.6%	0.04 [-0.06, 0.13]
Cullen 1976	0	50	0	50	31.4%	0.00 [-0.04, 0.04]
Hubbell 1982	4	52	5	52	32.6%	-0.02 [-0.13, 0.09]
Samuelson 1985	2	30	3	32	19.4%	-0.03 [-0.16, 0.11]
Subtotal (95% CI)		**160**		**159**	**100.0%**	**-0.01 [-0.05, 0.04]**
Total events	7		8			

Heterogeneity: Chi² = 0.95, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

22.3.8 Tetracycline 1 g/day

Fallica 1985	1	50	1	50	69.5%	0.00 [-0.05, 0.05]


Khanna 1993 0 23 0 21 30.5% 0.00 [-0.08, 0.08]
Subtotal (95% CI) 73 71 100.0% 0.00 [-0.05, 0.05]
Total events 1 1
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
22.3.9 (Oxy)tetracycline
Cabezas 1993 1 28 0 27 15.1% 0.04 [-0.06, 0.13]
Cullen 1976 0 50 0 50 27.4% 0.00 [-0.04, 0.04]
Hubbell 1982 4 52 5 52 28.5% -0.02 [-0.13, 0.09]
Khanna 1993 0 23 0 21 12.0% 0.00 [-0.08, 0.08]
Samuelson 1985 2 30 3 32 17.0% -0.03 [-0.16, 0.11]
Subtotal (95% CI) 183 182 100.0% -0.00 [-0.05, 0.04]
Total events 7 8
Heterogeneity: Chi² = 0.95, df = 4 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)
22.3.10 Doxycycline
Laux 1989 8 50 8 50 55.9% 0.00 [-0.14, 0.14]
Olafsson 1989 2 39 1 40 44.1% 0.03 [-0.06, 0.11]
Subtotal (95% CI) 89 90 100.0% 0.01 [-0.08, 0.10]
Total events 10 9
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)
22.3.11 Lymecycline
Cunliffe 1998 7 73 4 71 66.0% 0.04 [-0.05, 0.13]
Pierard 2002 1 59 6 27 34.0% -0.21 [-0.37, -0.05]
Subtotal (95% CI) 132 98 100.0% -0.04 [-0.12, 0.04]
Total events 8 10
Heterogeneity: Chi² = 7.48, df = 1 (P = 0.006); I² = 87%
Test for overall effect: Z = 1.09 (P = 0.28)
22.3.12 Faropenem
Hayashi 2011 0 49 3 51 100.0% -0.06 [-0.13, 0.01]
Subtotal (95% CI) 49 51 100.0% -0.06 [-0.13, 0.01]
Total events 0 3
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)
22.3.13 Roxithromycin
Hayashi 2011 0 49 0 50 100.0% 0.00 [-0.04, 0.04]
Subtotal (95% CI) 49 50 100.0% 0.00 [-0.04, 0.04]
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
22.3.14 Josamycin
Pelfini 1989 1 61 1 61 100.0% 0.00 [-0.05, 0.05]
Subtotal (95% CI) 61 61 100.0% 0.00 [-0.05, 0.05]
Total events 1 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
22.3.15 Zinc
Subtotal (95% CI) 0 0 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
22.3.16 2 mg cyproterone acetate/50 mcg ethinyloestradiol
Monk 1987 11 49 2 49 100.0% 0.18 [0.05, 0.31]
Subtotal (95% CI) 49 49 100.0% 0.18 [0.05, 0.31]
Total events 11 2
Heterogeneity: Not applicable
Test for overall effect: Z = 2.78 (P = 0.005)
22.3.17 1% clindamycin lotion/gel
Sheehan-Dare 1989 1 33 0 33 100.0% 0.03 [-0.05, 0.11]
Subtotal (95% CI) 33 33 100.0% 0.03 [-0.05, 0.11]
Total events 1 0
Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)
22.3.18 4% erythromycin/1.2% zinc lotion
Stainforth 1993 1 51 0 54 100.0% 0.02 [-0.03, 0.07]
Subtotal (95% CI) 51 54 100.0% 0.02 [-0.03, 0.07]
Total events 1 0
Heterogeneity: Not applicable



22.4 Acute vestibular disturbances