Oral isotretinoin for acne (Review)

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TABLE OF CONTENTS

[Intervention Review]

Oral isotretinoin for acne

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A B S T R A C T

Background

Acne vulgaris, a chronic inflammatory disease of the pilosebaceous unit associated with socialisation and mental health problems, may affect more than 80% of teenagers. Isotretinoin is widely recognised as a very effective treatment for severe acne; however, it may cause adverse effects.

Objectives

To assess efficacy and safety of oral isotretinoin for acne vulgaris.

Search methods

We searched the following databases up to July 2017: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, PsycINFO and LILACS. We updated this search in March 2018, but these results have not yet been incorporated in the review. We also searched five trial registries, checked the reference lists of retrieved studies for further references to relevant trials, and handsearched dermatology conference proceedings. A separate search for adverse effects of oral isotretinoin was undertaken in MEDLINE and Embase up to September 2013.

Selection criteria

Randomised clinical trials (RCTs) of oral isotretinoin in participants with clinically diagnosed acne compared against placebo, any other systemic or topical active therapy, and itself in different formulation, doses, regimens, or course duration.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included 31 RCTs, involving 3836 participants (12 to 55 years) with mild to severe acne. There were twice as many male participants as females.

Most studies were undertaken in Asia, Europe, and North America. Outcomes were generally measured between eight to 32 weeks (mean 19.7) of therapy.

Assessed comparisons included oral isotretinoin versus placebo or other treatments such as antibiotics. In addition, different doses, regimens, or formulations of oral isotretinoin were assessed, as well as oral isotretinoin with the addition of topical agents.

Pharmaceutical companies funded 12 included trials. All, except three studies, had high risk of bias in at least one domain. Attrition bias was high in 20 trials, selective reporting bias was high in 12 trials, and performance bias was high in 11 trials.

Oral isotretinoin compared with oral antibiotics plus topical agents

These studies included participants with moderate or severe acne and assessed outcomes immediately after 20 to 24 weeks of treatment (short-term). Three studies (400 participants) showed no evidence that isotretinoin decreases trial investigator-assessed inflammatory lesion count more than antibiotics (RR 1.01 95% CI 0.96 to 1.06), with only one serious adverse effect found, which was Stevens-Johnson syndrome in the isotretinoin group (RR 3.00, 95% CI 0.12 to 72.98). However, we are uncertain about these results as they were based on very low-quality evidence.

Isotretinoin may slightly improve (by 15%) acne severity, assessed by physician's global evaluation (RR 1.15, 95% CI 1.00 to 1.32; 351 participants; 2 studies), but resulted in more less serious adverse effects (67% higher risk) (RR 1.67, 95% CI 1.42 to 1.98; 351 participants; 2 studies), such as dry lips/skin, cheilitis, vomiting, nausea (both outcomes, low-quality evidence).

Different doses/therapeutic regimens of oral isotretinoin

For our primary efficacy outcome, we found three RCTs, but heterogeneity precluded meta-analysis. One study (154 participants) reported 79%, 80% and 84% decrease in total inflammatory lesion count after 20 weeks of 0.05, 0.1, or 0.2 mg/kg/d of oral isotretinoin for severe acne (low-quality evidence). Another trial (150 participants, severe acne) compared 0.1, 0.5, and 1 mg/kg/d oral isotretinoin for 20 weeks and, respectively, 58%, 80% and 90% of participants achieved 95% decrease in total inflammatory lesion count. One 24-week RCT of participants with moderate acne compared isotretinoin at (a) continuous low dose (0.25 to 0.4 mg/kg/day), (b) continuous conventional dose (0.5 to 0.7 mg/kg/day), and (c) intermittent regimen (0.5 to 0.7 mg/kg/day, for one week in a month). Continuous low dose (MD 3.72 lesions; 95% CI 2.13 to 5.31; 40 participants; one study) and conventional dose (MD 3.87 lesions; 95% CI 2.31 to 5.43; 40 participants; one study) had a greater decrease in inflammatory lesion counts compared to intermittent treatment (all outcomes, low-quality evidence).

Fourteen RCTs (906 participants, severe and moderate acne) reported that no serious adverse events were observed when comparing different doses/therapeutic regimens of oral isotretinoin during treatment (from 12 to 32 weeks) or follow-up after end of treatment (up to 48 weeks). Thirteen RCTs (858 participants) analysed frequency of less serious adverse effects, which included skin dryness, hair loss, and itching, but heterogeneity regarding the assessment of the outcome precluded data pooling; hence, there is uncertainty about the results (low- to very low-quality evidence, where assessed).

Improvement in acne severity, assessed by physician's global evaluation, was not measured for this comparison.

None of the included RCTs reported birth defects, but oral isotretinoin is contraindicated during pregnancy due to known teratogenic effects.

Authors' conclusions

Evidence was low-quality for most assessed outcomes.

We did not find any clear evidence from RCTs that isotretinoin improves acne severity compared with standard oral antibiotic and topical treatment when assessed by a decrease in total inflammatory lesion count, but it may slightly improve physician-assessed acne severity. Only one serious adverse event was reported in the isotretinoin group, which means we are uncertain of the risk of serious adverse effects; however, isotretinoin may result in increased minor adverse effects.

Heterogeneity in the studies comparing different regimens, doses, or formulations of oral isotretinoin meant we were unable to undertake meta-analysis. Daily treatment may be more effective than treatment for one week each month. None of the randomised studies in this comparison reported serious adverse effects, or measured improvement in acne severity assessed by physician's global evaluation. We are uncertain if there is a difference in number of minor adverse effects, such as skin dryness, between doses/regimens.

Evidence quality was lessened due to imprecision and attrition bias. Further studies should ensure clearly reported long- and short-term standardised assessment of improvement in total inflammatory lesion counts, participant-reported outcomes, and safety. Oral isotretinoin is a well-established treatment for severe acne, and for acne that has not responded to oral antibiotics plus topical agents. The clinical trial evidence for oral isotretinoin conducted around 30 years ago was low quality. Further trials are needed to evaluate different dose/regimens of oral isotretinoin in acne of all severities.

PLAIN LANGUAGE SUMMARY

How effective and safe is a drug called 'isotretinoin', taken via tablet, for acne vulgaris?

Review question

How effective and safe is isotretinoin, taken in a tablet for people with acne? We reviewed the evidence about the effect of isotretinoin when compared either to itself at a different dose, to placebo (an identical but inactive treatment), or to other systemic (oral or injected medicines that work throughout the entire body) or topical (applied to the outside of the body) therapies. Eligible participants had to have been diagnosed with acne by a doctor.

Background

Acne is a persistent inflammatory disease that can affect more than 80% of teenagers. Acne (including blackheads, whiteheads, and pimples) mostly appears on the face, but can also appear on the back and chest. Mental health problems, depression, and suicidal thoughts have been associated with acne. Isotretinoin, a currently widely used therapy derived from vitamin A, transformed acne treatment. However, it may cause adverse effects and has been associated with still uncertain psychiatric events and inflammatory bowel disease.

Study characteristics

We searched the medical literature up to July 2017 and included 31 studies, involving 3836 dermatology outpatients worldwide. There were twice as many males than females; their ages ranged from 12 to 55 years old. Acne severity ranged from mild to severe, although most participants had severe acne.

The pharmaceutical industry funded 12 included studies.

We found studies that compared oral isotretinoin versus placebo or other treatments such as antibiotics. In addition, different doses, regimens (course of medical treatment), or formulations of oral isotretinoin were assessed, as well as oral isotretinoin with the addition of topical agents.

Key results

Three studies compared oral isotretinoin versus any oral antibiotic plus any topical agent given to participants with moderate or severe acne for between 20 to 24 weeks. Their outcomes were measured straight after treatment stopped.

There was no difference between therapies in decreasing the number of inflamed lesions (an area of an organ or tissue that has been damaged by disease or trauma). In one participant, isotretinoin led to the development of Stevens-Johnson syndrome (a serious disease where skin reacts severely, often in response to medication); there were no serious side effects in the other group. However, we are uncertain of these results because they were based on very low-quality evidence.

When assessed by a doctor, the severity of acne may be slightly improved by isotretinoin, but it may cause more side effects such as inflamed lips, dry skin, or nausea (low-quality evidence).

Fourteen studies compared different doses/courses of oral isotretinoin between 12 to 32 weeks. Participants had mainly severe or moderate acne.

Two studies, each comparing three different doses of isotretinoin at 20 weeks, found a greater improvement (measured by inflammatory lesion counts) with the higher dose (low-quality evidence). A third study showed that continuous (daily) low dose and continuous (daily) conventional dose may improve acne more than intermittent therapy, measured at 24 weeks (low-quality evidence). Conventional dose isotretinoin reduced inflammatory lesion counts more than low dose, but this was based on very low-quality evidence, indicating uncertainty.

During treatment (from 12 to 32 weeks) or follow-up after end of treatment (up to 48 weeks), no serious side effects occurred in 14 studies analysing different doses of isotretinoin (low-quality evidence). Doctor-measured severity of acne was not assessed in this comparison. Less serious side effects, including skin dryness, hair loss, and itching, were assessed in 13 studies, but we are uncertain if there were any differences between groups (low- to very low-quality evidence, where assessed).

No study reported birth defects.

Quality of the evidence

The overall quality of evidence for all of our key outcomes was low, due to serious limitations of study design and the limited amount of data. Thus, the identified clinical trials neither support nor challenge the established place of oral isotretinoin in acne treatment.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Oral isotretinoin compared with oral antibiotics plus topical agents for acne

Patient or population: participants with moderate and severe acne

Settings: outpatient

Intervention: oral isotretinoin

Comparison: oral antibiotics[a] plus topical agents[b]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral antibiotics plus topical agents	Oral isotretinoin				
Improvement in acne severity assessed by a decrease in total inflammatory lesion count, measured in participants who were treated for a minimum period of 16 weeks (Changes from baseline in total inflammatory lesion count and number of participants who cleared inflammatory lesion) 20 to 24 weeks	86 per 100	87 per 100 (83 to 91)	1.01 (0.96 to 1.06)	400 patients (3 RCTs)	⊕⊖⊖⊖ **very low**[c]	-
Frequency of serious adverse effects 20 to 24 weeks	0[d] See comment	0[d] See comment	RR 3.00 (0.12 to 72.98)	400 participants (3 RCTs)	⊕⊖⊖⊖ **very low**[e]	There was only one serious adverse effect in the intervention group (Stevens-Johnson syndrome). There were no serious adverse effects in the control group

Improvement in acne severity assessed by physician's global evaluation 20 to 24 weeks	78 per 100	90 per 100 (78 to 103)	1.15 (1.00 to 1.32)	351 participants (2 RCTs)	⊕⊕⊖⊖ **low**[f]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[a]Oral antibiotics were tetracycline hydrochloride, minocycline and doxycycline (one RCT for each one)

[b]Topical agents were adapalene (associated with oral tetracycline), azelaic acid (associated with minocycline) and adapalene/benzoyl peroxide gel (associated with doxycycline)

[c]Quality of the evidence was downgraded by three levels due to:

- very serious limitations of design - two levels (high risk of reporting bias in one study, Gollnick 2001, and high risk of performance and attrition bias in all three studies, Gollnick 2001; Oprica 2007; Tan 2014)
- serious indirectness - one level (two studies (Gollnick 2001; Tan 2014) measured our primary efficacy outcome by assessing a decrease in nodules and cysts or only in nodules, not in all inflammatory types of acne lesions (papules plus pustules, nodules and cysts))

[d]The low frequency of events did not allow estimating assumed and correspondent risks.

[e]Quality of the evidence was downgraded by three levels, from high to very low, due to:

- very serious limitations of design - lack of blinding of participants and personnel and high risk of attrition bias in all three analysed studies (Gollnick 2001; Oprica 2007; Tan 2014) and selective reporting of events in one study (Gollnick 2001)
- serious imprecision (the wide confidence interval of the effect included both beneficial and harmful clinically important differences of 25% between interventions)

[f]Quality of evidence was downgraded by two levels, from high to low, due to:

- very serious limitations of design - lack of blinding of participants and personnel and high risk of attrition bias in both analysed studies (Gollnick 2001; Tan 2014) and selective reporting of events in one study (Gollnick 2001)

BACKGROUND

Please see our glossary in Table 1 for an explanation of medical terms used throughout the text.

Description of the condition

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, which consists of a hair shaft, hair follicle, erector pili muscle, and sebaceous gland (Rocha 2014). Acne lesions predominantly affect the face and, to a lesser extent, the back and chest (Thiboutot 2009). The cause of this disease is attributed to four major factors that interact in complex ways to result in the appearance of acne lesions:

1. increased excretion of sebum by sebaceous glands inside the hair follicle (seborrhoea);
2. follicular hyperkeratinisation, which results in the formation of a plug of sebum and keratin called a microcomedone;
3. bacterial hypercolonisation within the pilosebaceous unit (mainly by the micro-organism *Propionibacterium acnes*); and
4. consequent innate and acquired immune reactions triggering inflammation in affected follicles (Gollnick 2003; Kim 2005; Kurokawa 2009).

Although it is well-established that microcomedones precede all acne lesions and the general causal mechanisms have been identified, the initial trigger for acne is not fully understood (Gollnick 2003). It is only known that inflammatory events precede hyperkeratinisation (Thiboutot 2009).

The diagnosis is clinical. Acne lesions are polymorphic and characterised by open comedones (blackheads), closed comedones (whiteheads), and inflammatory lesions (Zeichner 2016). Inflammatory lesions are more severe lesions and may take the form of papules (pinheads), pustules (pimples), or nodulocystic lesions (large nodules) (Katsambas 2014). The latter lesion type develops deeper within the dermis than the first two (Plewig 2000). Inflammatory lesions occur in acne when, due to extensive and continuous sebum production and inflammation, the follicular sac of the microcomedone ruptures into adjacent tissue (Kurokawa 2009). The surrounding dermis is affected by inflammation and becomes damaged (Gollnick 2003). Hyperpigmentation and scarring usually follows more severe acne lesions, but this may happen even after superficial lesions in those with scar-prone skin (Holland 2004). Grading is useful in the clinical assessment of acne, and there are many grading scales, though none are universally accepted. Lesion counts are usually essential for clinical trials, but not for daily clinical practice (Layton 2010).

According to epidemiological surveys around the globe, acne is the most common reason for visiting a dermatologist (SBD 2006; Stern 2004). The global burden of disease study from 2013 found that, among skin diseases, acne was the second leading cause of disability, second only to dermatitis (Karimkhani 2017). A peak in prevalence of acne appears between 16 and 20 years (Augustin 2011; Shen 2012). In population-based epidemiological studies which focus on adolescents, acne may affect more than 80% of the evaluated teenagers (Amado 2006; Ghodsi 2009; Tan 2007). The detrimental effects on quality of life in those with acne are now well recognised, and they are comparable to those caused by other chronic diseases, such as diabetes, asthma, and arthritis (Mallon 1999). Mental health problems, social impairment,

depressive symptoms, and even suicidal thoughts have been described in association with acne, mainly in older adolescents with severe forms of the disease (Halvorsen 2011; Yazici 2004). In the teenage years, acne is more prevalent in young men; boys are also more prone to severe acne (Ghodsi 2009; Uslu 2008). However, acne prevalence is higher in girls if the analysis covers only the first years of adolescence (Aksu 2012; Kilkenny 1998). Prevalence studies from the last 15 years emphasise that acne vulgaris should no longer be considered a disease restricted to teenagers (Goulden 1999). Currently, there is good evidence that acne can be a problem beyond the teenage years in as many as 50% of individuals (Thiboutot 2009), and women are more affected than men 20 years or older (Collier 2008). Heredity not only influences susceptibility to acne, but it is also a prognostic factor (Ghodsi 2009). Family history of acne is associated with earlier occurrence, increased number of retention lesions (comedones), and treatment difficulties (Ballanger 2006). Ethnicity plays a role in the frequency and severity of acne; in studies involving ethnic groups, adolescent Caucasians have higher prevalence of acne than those of African or Asian descent (Cheng 2010).

Description of the intervention

The drug isotretinoin (13-cis-retinoic acid) is derived from vitamin A (Layton 2009). It is available for topical and oral administration. Oral isotretinoin was approved by the US Food and Drug Administration for nodulocystic acne in 1982 and introduced into the United Kingdom in 1983 (Leyden 2014). Since then, it has revolutionised the treatment of acne and, three decades later, remains the most clinically effective anti-acne therapy according to physician opinion (Layton 2010). When isotretinoin was first introduced, it was almost exclusively used in those with severe nodular acne (Jones 1983). Nowadays, with the experience acquired in clinical management of oral isotretinoin, use of the drug has been widened to include those with a tendency to scarring and those who show no improvement with appropriate topical antimicrobial or retinoid-like therapies and long-term oral antibiotics (Cunliffe 1997; Layton 2010). Most physicians prescribe a daily dose of oral isotretinoin that varies from 0.5 to 1.0 mg/kg body weight (Del Rosso 2012); this dose results in approximately 85% of people who receive it becoming clear of acne within 16 weeks (Nast 2010). The remainder of people who receive it need about five or six months to achieve a complete response at this dose (Lehucher-Ceyrac 1999), and fewer than 1% of them may require up to 12 months of continuous treatment to be clear of their acne (Zouboulis 2003). Treatment regimens usually begin at 0.5 mg/kg/day and may be increased to 1.0 mg/kg/day, but some centres start treatment at the higher dose, which provides optimal benefit (Layton 2010). Because pharmacokinetic evaluations showed that the absorption rate can be doubled with the concomitant presence of fat in the intestine, the advice is to take the capsules together with the main meal of the day (Colburn 1983; Webster 2013). Whether starting on a higher or lower dose, physicians usually adjust the dose over the course of the treatment, considering the response and the presence of side effects (Rademaker 2013a). The treatment duration varies from 16 to 30 weeks, with a mean of between 16 and 20 weeks (Leyden 2014). There is no cumulative dose effect, but there is a definite effect of both dose and therapy duration: post-therapy relapse is minimised by doses that reach a total of at least 120 mg/kg (Rademaker 2013a). There is no added benefit of exceeding 150 mg/kg (Layton 2009). The duration of therapy is adjusted to produce a 90% clearance of acne lesions, which is followed by four weeks of

maintenance, with the aim of consolidating the treatment before withdrawing the drug (Harms 1986).

How the intervention might work

Isotretinoin is the only therapy that targets all the primary causal factors involved in acne (Leyden 2014). Oral isotretinoin, unlike antibiotics, does not act directly on microbial cells (Layton 2009). It markedly reduces the sebum excretion rate and the sebaceous gland size (Nast 2010). By reducing sebum secretion, the drug consequently decreases the follicular hyperkeratinisation and alters the microenvironment within the duct, providing greater *Propionibacterium acnes* (*P. acnes)* suppression than that seen with topical or oral antibiotics (King 1982). The drastic reduction in the *P. acnes* population contributes to the reduction in acne inflammation (Coates 1997). Oral isotretinoin also modifies inflammatory activity at the cellular level (Falcon 1986) and normalises exaggerated toll-like receptor-mediated innate immune responses in acne (Dispenza 2012). Today, it is already known that, during a course of oral isotretinoin, the effects of the drug on acne pathogenesis correlate with the pattern of skin gene regulation (Rademaker 2013a). Just after the commencement of treatment, oral isotretinoin activates tumour suppressor genes in skin; there is induction of apoptosis and cell cycle arrest within sebaceous glands (Nelson 2009a). Within about eight weeks of treatment, there is also a downregulation of genes related to lipidic metabolism and an upregulation of genes that encode proteins from the extracellular matrix, such as collagens and fibronectin (Nelson 2009b).

Why it is important to do this review

Oral isotretinoin has many side effects. Soon after its launch on the market, the use of isotretinoin was associated with a number of psychiatric side effects: mood changes, depression, suicidal thoughts, and psychoses (Hazen 1983). Although some studies have attempted to explain these adverse effects, they remain controversial and unclear. Psychiatric events associated with isotretinoin are considered by other authors to be rare and no greater than the background incidence (Ferahbas 2004). The occurrence of idiosyncratic reactions however persists as a possibility (Magin 2005).

Mucocutaneous and cutaneous changes are the most frequent clinical adverse effects during isotretinoin therapy. They are expected, dose-dependent, and seldom interfere with the physician's management of the condition (Rademaker 2013a). Cheilitis, xeroderma, facial dermatitis, discoid dermatitis, and blepharoconjunctivitis can usually be minimised by regular use of lip balms, eye lubricants, and moisturisers (Layton 2010). Flaring of acne lesions may occur in up to 6% of people early in the course of treatment with isotretinoin, with clinical importance in half of these (Clark 1995). Mild elevation of liver enzymes in liver function tests and fasting plasma lipids, uncommonly above the normal range, are seen in almost all those treated with isotretinoin. The discontinuation of the drug promotes a rapid return to pretreatment levels (Jones 1983;).

More uncommon side effects are headache (which may uncommonly be an early symptom of idiopathic intracranial hypertension), as well as muscle and joint pain (Hull 2000). Recently, the association of oral isotretinoin with the development of inflammatory bowel disease has been raised. Case-control studies, however, could not consistently confirm this association

(Bernstein 2009; Crockett 2010; Etminan 2013). Among its many other side effects, isotretinoin is teratogenic, which means that exposure to it during pregnancy can induce abnormalities of physiological development (Zomerdijk 2014). Approximately 20% of foetal exposures to isotretinoin may result in spontaneous abortion (Dai 1992; Lammer 1985). The risk of mental and physical birth defects associated with oral isotretinoin is 18% to 28% (Dai 1992; Lammer 1985). Any level of exposure seems to be a potential cause of malformation since there is no safe level of exposure (Sladden 2007). The most common deformities are craniofacial and cardiac (Bérard 2007; Schaefer 2010).

Due to the issue of isotretinoin teratogenicity, a Cochane review on the efficacy and safety of minocycline in acne (Garner 2012), which analysed an open randomised controlled trial comparing oral isotretinoin with a combined oral minocycline and topical azelaic acid regimen, has suggested that the minocycline and azelaic acid regimen is a safer option for women with nodular acne. In the reviewed trial, there were fewer adverse effects with the combination minocycline plus azelaic acid, and satisfactory percentage reductions in lesion counting occurred in both intervention groups during the therapy phase. Also, the onset of improvement was similar for both therapies.

Although isotretinoin is currently widely used in the treatment of acne, its efficacy and safety have not yet been assessed in a Cochrane systematic review.

The plans for this review were published as a protocol 'Oral isotretinoin for acne' (Costa 2011).

O B J E C T I V E S

To assess the efficacy and safety of oral isotretinoin for acne vulgaris.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We evaluated all randomised controlled trials (RCTs) examining either the efficacy or safety, or both, of oral isotretinoin in people with acne vulgaris.

We did not include cluster-randomised trials in our analysis, as we intended to analyse effects of oral isotretinoin on an individual basis. Also, we did not consider cross-over randomised trials: oral isotretinoin produces a long-term remission which hinders the definition of an adequate wash-out period between interventions.

Types of participants

Our review included all those with acne vulgaris who had been clinically diagnosed by a physician.

Types of interventions

We considered oral isotretinoin at any dose, course duration, or follow-up time, compared either to itself at a different dose, to placebo, or to other systemic or topical active therapies. We have also analysed oral isotretinoin versus oral isotretinoin plus systemic or topical active therapies.

Types of outcome measures

Primary outcomes

1. Improvement in acne severity assessed by a decrease in total inflammatory lesion count, measured in participants who were treated for a minimum period of 16 weeks.
2. Frequency of serious adverse effects.

Secondary outcomes

1. Improvement in acne severity assessed by the following tools:
   a. Participant's self-assessment of acne severity; and
   b. Physician's global evaluation of acne severity.
2. Changes in quality of life (QoL) assessed using a validated instrument.
3. Frequency of less serious adverse effects.
4. Dropout rates.

We classified an adverse effect as serious if it was: fatal, life threatening, permanently disabling, or required hospitalisation.

The following cut-off time points were defined for outcomes, where data were available:

- short-term follow-up: data measured within 48 weeks after randomisation;
- long-term follow-up: data measured 48 weeks after randomisation.

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

The Cochrane Skin Information Specialist searched the following databases up to 11 July 2017 using strategies based on the draft strategy for MEDLINE in our published protocol (Costa 2011). This review fully incorporated these search results.

- the Cochrane Skin Group Specialised Register, using the search strategy in Appendix 1;
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2017, Issue 6, in the Cochrane Library, using the strategy in Appendix 2;
- MEDLINE via Ovid (from 1946), using the strategy in Appendix 3;
- Embase via Ovid (from 1974), using the strategy in Appendix 4;
- PsycINFO via Ovid (from 1806), using the strategy in Appendix 5; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982), using the strategy in Appendix 6.

A further three reports of trials were identified by a search update conducted up to 14 March 2018. One was a secondary reference to a previously included study (Shetti 2013), one study was added to Studies awaiting classification and one was added to Ongoing studies. If appropriate, these latter two studies will be incorporated into the review at the next update.

Trials registries

We (CSC, RR and EB) searched the following trials registries up to 3 July 2018 using the terms 'acne' and 'isotretinoin':

- the ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch); and
- the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Adverse effects

We examined our included and excluded studies for common adverse effects of oral isotretinoin. In addition, we searched the following databases up to 17 September 2013 for nonrandomised studies (case-control and cohort) on adverse effects of isotretinoin, using an amended version of the Cochrane Skin standard adverse effects search strategy and our intervention terms:

- MEDLINE via Ovid (from 1946), using the strategy in Appendix 7; and
- Embase via Ovid (from 1974), using the strategy in Appendix 8.

Searching other resources

We searched reference lists from retrieved studies for further references to relevant trials.

We handsearched issues of the Journal of Investigative Dermatology, Archives of Dermatology (JAMA Dermatology after January 2013), and the British Journal of Dermatology which contained conference proceedings from 1975 up to 3 July 2018.

We contacted pharmaceutical companies and experts in the field for information on relevant ongoing or unpublished studies.

Data collection and analysis

We extracted data and recorded it using data extraction forms, which were developed and piloted by two authors (CSC and EB).

We entered the data into the Cochrane RevMan 5 software and performed forest plots when available data permitted (Review Manager 2014).

Selection of studies

Two of three authors (CSC, EB, and RR) independently assessed the titles and abstracts of studies retrieved in the search in order to ascertain whether or not they represented potentially relevant trials. Based on this first assessment, we obtained the full text of all potentially relevant articles. Any disagreements were resolved by a third author.

Data extraction and management

Two of us (CSC and EB) independently extracted data using data extraction forms, with any disagreements being resolved by a third author (RR). Where it was not available, we emailed authors of studies to request data of interest. We compiled the following information from the included studies:

- publication details (e.g. year, country, authors);
- study design;
- setting, inclusion/exclusion criteria, randomisation method, allocation concealment, blinding, and other issues relating to bias;
- population data (e.g. age, severity of the acne);
- interventions (details of dose, therapeutic regimen, and duration);
- outcome measures (scale and time points of measurement)
- dropouts;
- duration of follow-up; and
- types of data analysis (e.g. imputation, modified intention-to-treat, intention-to-treat).

We then populated Characteristics of included studies tables for each included study with the extracted information.

Assessment of risk of bias in included studies

Two authors (CSC and RR) independently assessed the methodological quality of included studies using Cochrane's 'Risk of bias' tool (Higgins 2011). A third author (RR) resolved any disagreements. For each 'Risk of bias' domain and specific question detailed below, we assigned a 'low', 'high', or an 'unclear' risk of bias. We reported on the following:

(a) random sequence generation;
(b) adequate concealment of allocation;
(c) blinding of participants and personnel;
(d) blinding of outcome assessment;
(e) incomplete outcome data;
(f) selective outcome reporting; and
(g) other potential threats to validity.

We considered each study as having: 1. low risk of bias, when we detected a low risk of bias for all key domains - listed from (a) to (f) above; 2. an unclear risk of bias, if one or more key domains had an unclear risk of bias; and 3. high risk of bias, where we verified the presence of high risk of bias for one or more key domains within the study.

Measures of treatment effect

We summarised estimates of treatment effect with 95% confidence intervals (CI) for each comparison. We reported dichotomous outcomes as risk ratios (RRs). We reported continuous outcomes as the mean difference (MD).

Unit of analysis issues

Our unit of analysis was the individual participant. We did not include cluster-randomised trials in our analysis. Also, we did not consider cross-over trials; oral isotretinoin produces a long-term remission which hinders definition of an adequate wash-out period between interventions. We evaluated included studies with more than two groups of intervention with the following approach: we outlined multiple pairwise comparisons of the groups of the study and analysed the pairs of comparisons which were relevant to our review (Higgins 2011).

Dealing with missing data

We asked for additional information from authors when we detected missing or unavailable data. If missing data did not allow the study to be statistically analysed, we only presented and discussed the available results within the main text of the review.

Assessment of heterogeneity

We treated clinical and methodological between-study variance as potential causes of the heterogeneity among the studies. In the presence of substantial heterogeneity, we analysed studies separately and presented them using a narrative approach.

We analysed statistical diversity by checking the estimates of treatment effect. We used the forest plots produced by Review Manager, version 5.3.5 (Review Manager 2014), and the I^2 statistic to identify the percentage of total variation across studies due to heterogeneity (Higgins 2003), rather than due to chance. We considered an I^2 statistic value higher than 50% as substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

We contacted study authors regarding reasons for the non-reporting of data outcomes and also sought unpublished data from our included studies. We performed searches for protocols and other versions of our included trials and sought to identify duplicate publication.

Data synthesis

We used Review Manager 5 software (RevMan 2013) to summarise data. We pooled data with a random-effects model when studies were considered to be methodologically and clinically similar. We assessed methodological or clinical heterogeneity among studies using the I^2 value, where greater than 50% meant significant heterogeneity (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

If possible, we intended to perform subgroup analysis to consider the following:

- severity of acne;
- treatment duration;
- different doses and regimens;
- degree of improvement in acne severity assessed by a percentage reduction in total inflammatory lesion count;
- age of the participants (preadolescents vs adolescents vs adults); and
- gender.

Sensitivity analysis

Due to the low number of trials in the meta-analyses, we could not carry out a sensitivity analysis by excluding trials of low and moderate risk of bias, as intended.

'Summary of findings' table

We created a 'Summary of findings' table for the most relevant comparison of clinical practice (oral isotretinoin versus oral antibiotics plus topical agent). The two primary outcomes ('Improvement in acne severity assessed by a decrease in total inflammatory lesion count' and 'Frequency of serious adverse effects') and one key secondary outcome ('Improvement in acne severity assessed by physician's global evaluation') were considered. For our predetermined primary and key secondary

outcomes, we then used the five GRADE parameters (inconsistency, risk of bias, imprecision, indirectness, and publication bias) to assess the quality of the evidence (Guyatt 2011). We applied the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* by entering the data into GRADEpro software (GRADEpro). We described the rationale for all decisions regarding the upgrade or the downgrade of the quality of the studies in the footnotes, where we also wrote comments to assist readers' understanding of the results and assessments of our review (Higgins 2011).

R E S U L T S

Description of studies

We systematically described the details of the included, excluded, awaiting classification, and ongoing studies in the following tables: Characteristics of included studies, Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies.

Results of the search

RCTs (efficacy and safety analysis)

The electronic searches for randomised controlled trials (RCTs) returned 449 records. We added to these references another five records from handsearching and 31 records from trials registers. After removing duplicates, we evaluated titles and abstracts (if available) of 464 records. We excluded 404 references based on titles and abstracts. We obtained the full text of the remaining 60 records. We excluded a further 10 full-text records (reporting nine studies). We identified two ongoing trials. We added one study to the awaiting classification section, as results from this trial, when identified at a late stage at the last search update, would not impact the conclusions of our review. Finally, we included 47 records reporting 31 studies in the qualitative synthesis. We entered data from seven RCTs in our quantitative synthesis (meta-analysis). For a further description of our screening process, see the study flow diagram (Figure 1).

Figure 1. Study flow diagram.

449 records found after searching the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, PsycINFO, LILACS, and deduplicating the results

36 additional records identified through other sources:

- 5 records from handsearching the Journal of Investigative Dermatology, Archives of Dermatology, and British Journal of Dermatology which contained conference proceedings from 1975 up to the October 2015;

- 31 references from trial registers: ISRCTN (1), ClinicalTrials.gov (18), ANZCTR (5), Clinicaltrials.eu (3), ICTRP-WHO (4)

464 records after duplicates removed

464 records screened

404 records excluded based on titles and abstracts

10 records (reporting 9 studies) were excluded with reasons:

- ineligible population (n = 1);

- inappropriate comparator intervention (n = 4);

- other interventions (n = 4)

Figure 1.   (Continued)

Nonrandomised studies (safety analysis)

The additional search for nonrandomised studies (case-control and cohort) reporting serious adverse effects of oral isotretinoin for acne returned 349 records. After removing one duplicate, we analysed 348 references on the basis of titles and abstracts. Of these, 318 were eliminated and 30 were evaluated in full text. From the 30, eight nonrandomised studies were considered for the safety analysis (Figure 2); these nonRCTs are included under Additional references. The characteristics of these included nonrandomised studies are detailed in Table 2, and the safety data from these nonRCTs are presented in the Discussion (Summary of main results).

Figure 2.   Study (nonRCT, cohort and case-control) flow diagram.
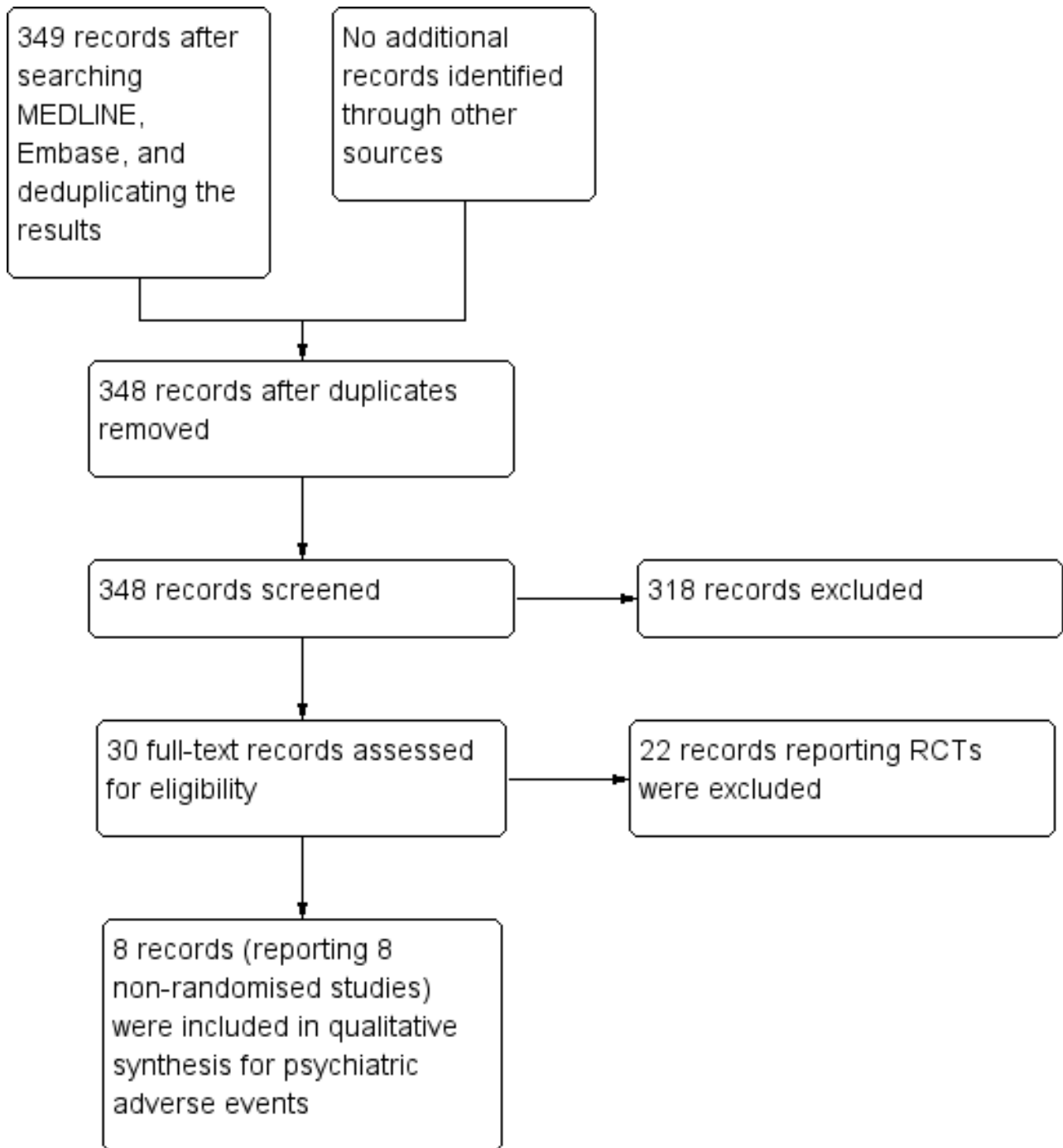
Included studies

We included 31 RCTs with a parallel design, involving a total of 3836 participants. We sent emails to authors from 23 included RCTs for additional data. Despite all efforts, we could not find recent email addresses for authors of eight studies (De 2011; Leheta 2011; King 1982; Jones 1983a; Jones 1983b; Lester 1985; Peck 1982; Shetti 2013).

Design

All 31 included studies were RCTs with a parallel design. Only four included RCTs (Dhir 2008; Faghihi 2014; Wahab 2008; Webster 2014) reported clearly the entire duration of the study, and the mean duration was 23 months (ranging from 17 to 40 months).

All but two (Cumurcu 2009; Leheta 2011) of the 31 trials stated the duration of treatment phase. The time point when outcomes were measured ranged from eight to 32 weeks (mean 19.7 weeks) of therapy.

The follow-up period after the treatment phase was clearly stated in all but 11 of the 31 included studies (Ahmad 2015; Corlin 1984; De 2011; Gollnick 2001; Kapadia 2005; King 1982; Leheta 2011; Pigatto 1986; Strauss 2001; Tan 2014; Webster 2014). Mean follow-up after therapy ended was 26.5 weeks (ranging from four to 152 weeks).

Participants

Where reported, there were 2229 men and 1081 women across the included studies.

Most of the studies provided age data for all participants as a range, and the age of participants ranged from 12 to 55 years (Agarwal 2011; Ahmad 2015; Corlin 1984; Dhaked 2016; Faghihi 2014; Farrell 1980; Goldstein 1982; Gollnick 2001; Lee 2011; Lester 1985; Oprica 2007; Pigatto 1986; Prendiville 1988; Rademaker 2013b; Strauss 2001; Van der Meeren 1983; Tan 2014; Wahab 2008; Webster 2014). Four included RCTs had reported age data only as a mean and by group without respective ranges. These mean values ranged from 19.9 to 28.5 years (Akman 2007; Cumurcu 2009; Jones 1983a; Strauss 1984). One included RCT provided age data for all participants only as mean, and the value was 25 years (standard deviation not provided) (King 1982). Another included study only reported the percentage of participants in each age range, with 81.5% of them being between 16 to 25 years (Dhir 2008). In Shetti 2013, authors only cited that participants were of either gender and more than 18 years. There was no information regarding age and gender of participants in five studies (De 2011; Jones 1983b; Kapadia 2005; Leheta 2011; Peck 1982). Six included studies did not report demographic data for all initially randomised participants. These studies described age and gender data only for participants who did not have missing data (Agarwal 2011; Akman 2007; Oprica 2007; Rademaker 2013b; Strauss 1984; Strauss 2001).

Only nine included trials reported mean duration of disease (Faghihi 2014; Goldstein 1982; Gollnick 2001; Lee 2011; Lester 1985; Oprica 2007; Strauss 1984; Van der Meeren 1983; Wahab 2008), and the mean duration of acne reported by these studies ranged from three to 12.9 years.

Fifteen trials exclusively involved participants with severe acne (Corlin 1984; De 2011; Dhir 2008; Farrell 1980; Goldstein 1982; Gollnick 2001; Lester 1985; Peck 1982; Pigatto 1986; Prendiville 1988; Strauss 2001; Strauss 1984; Tan 2014; Van der Meeren 1983; Webster 2014), and two of them (Strauss 2001; Webster 2014) included only participants with recalcitrant severe nodular acne (a total of 1527 participants). Nine studies enrolled participants with both moderate and severe acne (Akman 2007; Dhaked 2016; Faghihi 2014; Jones 1983a; Jones 1983b; Kapadia 2005; Oprica 2007; Shetti 2013; Wahab 2008). Leheta 2011 included participants with mild to moderate acne. Two trials recruited participants with all grades of acne severity: mild, moderate, and severe (Agarwal 2011; Ahmad 2015), and another enrolled only participants with moderate acne (Lee 2011). Cumurcu 2009 and King 1982 did not mention any data about acne severity. Rademaker 2013b studied low dose oral isotretinoin for participants who had persistent mild grade acne.

Sample sizes

Sample sizes of included studies varied from 16 to 925 participants.

Settings

Twelve studies were from the 1980s and 16 were from 2001 to 2017. The 31 included trials involved dermatologic outpatients from Africa (Leheta 2011), Asia (Agarwal 2011; Ahmad 2015; De 2011; Dhaked 2016; Dhir 2008; Faghihi 2014; Kapadia 2005; Lee 2011; Shetti 2013; Wahab 2008), Europe (Akman 2007; Corlin 1984; Cumurcu 2009; Gollnick 2001; Jones 1983a; Jones 1983b; King 1982; Oprica 2007; Pigatto 1986; Prendiville 1988; Van der Meeren 1983), North America (Farrell 1980; Goldstein 1982; Lester 1985; Peck 1982; Strauss 1984; Strauss 2001; Tan 2014; Webster 2014) and Oceania (Rademaker 2013b).

Ten studies were multicentric and involved more than two centres in the same country (Akman 2007; Corlin 1984; Goldstein 1982; Kapadia 2005; Leheta 2011; Strauss 1984; Strauss 2001; Tan 2014; Van der Meeren 1983; Wahab 2008) and two studies enrolled participants from multiple centres, with locations in different countries (Gollnick 2001; Webster 2014). Fifteen trials took place in a single centre (Agarwal 2011; Ahmad 2015; Cumurcu 2009; De 2011; Dhaked 2016; Dhir 2008; Faghihi 2014; Farrell 1980; Jones 1983b; Lee 2011; Oprica 2007; Peck 1982; Pigatto 1986; Rademaker 2013b; Shetti 2013), and four studies involved two centres in the same country (Jones 1983a; King 1982; Lester 1985; Prendiville 1988).

Only one of the included RCTs was not published in English: Corlin 1984 had two reports, both in German.

Interventions

RCTs tested oral isotretinoin for acne vulgaris through the following comparisons:

1. Oral isotretinoin versus oral antibiotics plus topical agents: oral isotretinoin versus azelaic acid cream plus minocycline (Gollnick 2001), oral isotretinoin versus tetracycline plus topical adapalene gel (Oprica 2007), and oral isotretinoin versus adapalene/benzoyl peroxide gel plus doxycycline (Tan 2014);
2. Oral isotretinoin versus oral isotretinoin plus topical agents: clindamycin 1% daytime plus adapalene 0.1% at bedtime (Dhir 2008), and 5% dapsone gel (Faghihi 2014);
3. Oral isotretinoin versus 0,1% tretinoin cream plus 5% benzoyl peroxide gel (Leheta 2011);
4. Oral isotretinoin versus chemical peeling with trichloroacetic acid (TCA) 25% (Leheta 2011);
5. Oral isotretinoin versus oral isotretinoin plus oral antibiotic: azithromycin pulse (De 2011), and erythromycin (Jones 1983b);
6. Oral isotretinoin versus azithromycin (Wahab 2008);
7. Oral isotretinoin versus erythromycin (Jones 1983b);
8. Oral isotretinoin versus minocycline (Pigatto 1986);
9. Oral isotretinoin versus tetracycline (Lester 1985);
10. Oral isotretinoin versus dapsone (Prendiville 1988);
11. Oral isotretinoin versus etretinate (Goldstein 1982);
12. Different doses or therapeutic regimens of oral isotretinoin (Agarwal 2011; Ahmad 2015; Akman 2007; Corlin 1984; Cumurcu 2009; Dhaked 2016; Farrell 1980; Jones 1983a; Kapadia 2005; King 1982; Lee 2011; Shetti 2013; Strauss 1984; Van der Meeren 1983);
13. Standard oral isotretinoin versus other formulations of oral isotretinoin: standard isotretinoin versus micronised

isotretinoin (Strauss 2001), and standard isotretinoin versus isotretinoin-Lidose (Webster 2014);

14. Oral isotretinoin versus placebo (Peck 1982; Rademaker 2013b).

Outcomes

Ten included RCTs addressed the primary outcome, improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks), in a way which matched with that prespecified in our protocol, and we incorporated their results in this review. Five of these studies reported only continuous data for our primary efficacy outcome, such as mean change from baseline in total inflammatory lesion count for each intervention group and comparisons of mean total inflammatory lesion counts between intervention groups at different time points of assessment (Corlin 1984; Lee 2011; Lester 1985; Prendiville 1988; Strauss 2001). One study presented only dichotomous data for the outcome and provided number of participants in each intervention group who achieved a specific percentage decrease in total inflammatory lesion count (Oprica 2007). The remaining four studies reported both continuous and dichotomous data related to our primary efficacy outcome (Gollnick 2001; Strauss 1984; Tan 2014; Webster 2014). Five studies assessed the primary outcome of this review indirectly, they did not consider the sum of all inflammatory acne lesions (papules, pustules, nodules and cysts) (Gollnick 2001; Lester 1985; Prendiville 1988; Tan 2014; Webster 2014). The other five included RCTs assessed our primary outcome directly, by performing counts of all types of inflammatory acne lesions (Van der Meeren 1983), or indirectly, by taking into account only one or two types of inflammatory lesions (Farrell 1980; Goldstein 1982; Peck 1982; Pigatto 1986). However, in all these five studies, participants received acne therapies for less than 16 weeks.

All 31 included RCTs had assessed the frequency of serious (our primary safety outcome) or less serious (our secondary safety outcome) adverse effects, with the exception of King 1982 and Leheta 2011. King 1982 was the only included RCT which did not address any of the prespecified outcomes from this review. Leheta 2011 only analysed efficacy outcomes. Regarding the tools for assessing the occurrence of adverse effects: in 17 RCTs, there was no clear description of how clinical side effects were monitored and detected (Ahmad 2015; Akman 2007; Corlin 1984; De 2011; Dhaked 2016; Dhir 2008; Jones 1983a; Jones 1983b; Kapadia 2005; Lee 2011; Lester 1985; Peck 1982; Pigatto 1986; Prendiville 1988; Shetti 2013; Van der Meeren 1983; Wahab 2008); in three RCTs, the safety outcomes were assessed by subjective report of participants and physician clinical assessment (Cumurcu 2009; Goldstein 1982; Gollnick 2001); two RCTs evaluated the occurrence of adverse effects only by the physician clinical assessments (Agarwal 2011; Faghihi 2014); two RCTs reported that they questioned participants generally about adverse effects (Oprica 2007) or employed a prespecified questionnaire (Farrell 1980); one RCT applied a checklist to participants with the most known clinical side effects of the drug (Strauss 1984); three RCTs conducted physician clinical assessments, applied specific questionnaires and also used the subjective report of participants (Strauss 2001; Tan 2014; Webster 2014); Rademaker 2013b analysed adverse effects via a daily diary reported by participants. All 31 included RCTs, again with the exception of King 1982 and Leheta 2011, reported they had performed laboratory assessments to monitor adverse effects related to therapy with isotretinoin. Only 12 included RCTs had available data on global frequency of less serious adverse effects

(Ahmad 2015; Faghihi 2014; Goldstein 1982; Gollnick 2001; Lee 2011; Lester 1985; Pigatto 1986; Rademaker 2013b; Strauss 2001; Tan 2014; Van der Meeren 1983; Webster 2014). The remaining 17 studies only provided data related to the frequencies of each detected less serious adverse event (Agarwal 2011; Akman 2007; Corlin 1984; Cumurcu 2009; Dhaked 2016; Jones 1983a; Kapadia 2005; Strauss 1984), or did not report detailed numerical data for less serious adverse effects by intervention group (De 2011; Dhir 2008; Farrell 1980; Jones 1983b; Oprica 2007; Peck 1982; Prendiville 1988; Shetti 2013; Wahab 2008).

Fifteen included trials measured the secondary efficacy outcome of this review, improvement in acne severity evaluated by physician's global evaluation of acne severity (Ahmad 2015; Akman 2007; Dhaked 2016; Dhir 2008; Faghihi 2014; Gollnick 2001; Jones 1983b; Kapadia 2005; Lee 2011 Leheta 2011; Shetti 2013; Strauss 2001; Tan 2014; Wahab 2008; Webster 2014). In seven of them (Dhaked 2016; Dhir 2008; Gollnick 2001; Kapadia 2005; Strauss 2001; Wahab 2008; Webster 2014), authors performed a subjective global evaluation of the improvement in acne and reported the number of participants from each intervention group who achieved a satisfactory result (complete, excellent or good clearing of acne lesions). Tan 2014 provided the number of participants in each group who had an improvement of at least 2 grades from baseline in the IGA (Investigator Global Assessment), a six-point scale from 0 (clear) to 5 (very severe acne). Ahmad 2015 used the Global Acne Scoring (GAS) system, in which there was the following grading of acne severity: mild (scores 1 to 18), moderate (scores 19 to 30), severe (scores 31 to 38), and very severe (scores > 39). Ahmad 2015 provided data for this secondary outcome as the mean decrease in GAS scores with each intervention. Lee 2011 measured the outcome, physician's global evaluation of acne severity, using the Global Acne Grading System (GAGS) score (Doshi 1997). In Akman 2007, investigators assessed the outcome as the mean decrease in FDA Global Grade as described in Cunliffe 2003. Jones 1983b cited the assessment of acne grade but did not provide any other detail. Leheta 2011 and Shetti 2013 also only reported the measurement of acne severity score and Global Acne Grading System (GAGS), respectively, without further specifications.

The secondary efficacy outcome, improvement in acne severity evaluated by participant's self-assessment, was an assessed outcome in only four included RCTs (De 2011; Prendiville 1988; Strauss 2001; Rademaker 2013b). De 2011 evaluated acne severity by participant's assessments using a 10-point visual analogue scale (VAS), for which the authors did not provide details in the report. Prendiville 1988 cited in the methods section of the report that the authors addressed the subjective improvement in acne assessed by each participant by a visual analogue scale (VAS), ranging from −5 to +5. However, there was no report of data related to this outcome among the results section of the study. In Strauss 2001, an efficacy outcome was the participant's subjective global assessment of the improvement in acne. The study reported the number of participants from each intervention group who achieved a satisfactory result (complete, excellent, or good clearing of acne lesions) according to their self-evaluations. In Rademaker 2013b, participants assessed the severity of their own condition by using a linear visual 10 cm scale graded from 0 to 10, with 0 being 'none' and 10 being 'very bad acne'.

Only two included RCTs (Oprica 2007; Rademaker 2013b) assessed changes in quality of life using a validated instrument. Both studies

had provided to participants the Dermatology Life Quality Index (DLQI), a self-administered questionnaire designed to quantify the impact of skin diseases on participants' quality of life (Finlay 1994). Maximum score for the DLQI questionnaire is 30, and the higher value coincides with more impairment in quality of life.

All 31 included RCTs, with exception of King 1982, Leheta 2011, and Shetti 2013 addressed dropout rates. Ten from these 28 RCTs also analysed reasons for dropouts (Corlin 1984; Cumurcu 2009; Gollnick 2001; Lee 2011; Lester 1985; Oprica 2007; Prendiville 1988; Rademaker 2013b; Tan 2014; Van der Meeren 1983).

Excluded studies

From the search for RCTs, we excluded 10 records (reporting nine studies), and the reasons for exclusion are presented in Characteristics of excluded studies tables.

Studies awaiting classification

One study is awaiting classification (Faghihi 2017). This study was screened after the final update search and will be included in any further updates of this review, as we realised it would not impact the conclusions at this late stage.

Ongoing studies

After searching for ongoing trials, we found two records from two trials (IRCT201104094310N6; IRCT2013110315246N1). We described these studies in a 'Characteristics of ongoing studies' table.

Risk of bias in included studies

Please see Figure 3, Figure 4 and Characteristics of included studies.

Figure 3.   Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. (Continued)

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
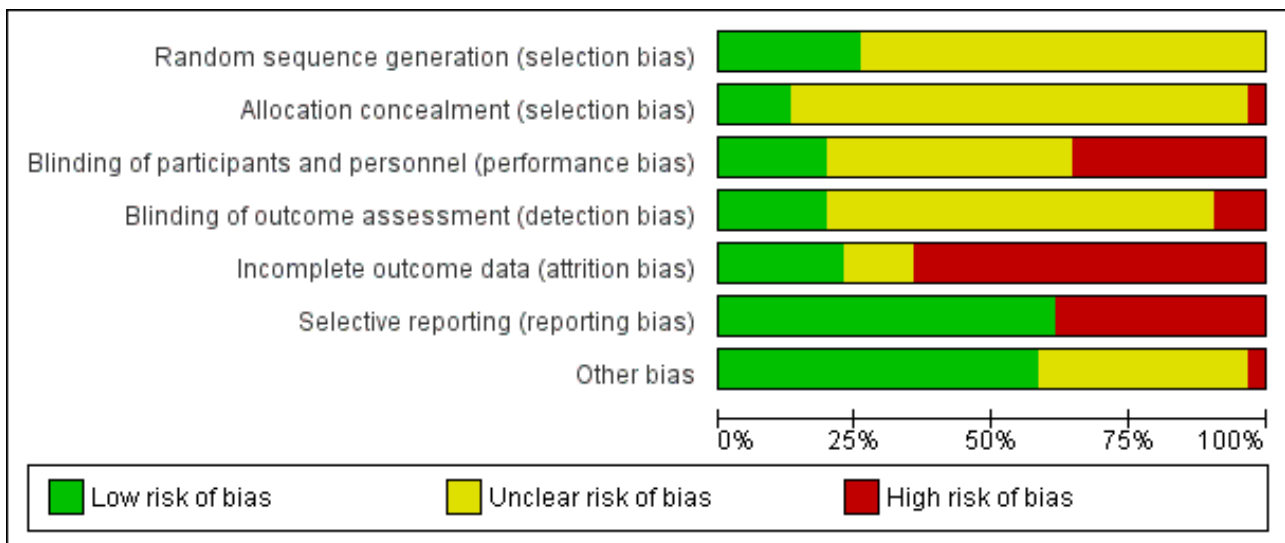
Allocation

Random sequence generation

All 31 included trials reported being randomised; however, only eight studies described an adequate method to generate the random sequence: Agarwal 2011 adopted shuffled cards; Farrell 1980, Oprica 2007, Peck 1982; Strauss 1984 and Tan 2014 used a computer-generated randomised code; Wahab 2008 declared by personal communication to us that they used drawing of lots; and Lee 2011 reported a restricted randomisation in a 1:1:1 ratio, also using a computer-generated schedule. We judged these eight trials to be at low risk of bias for this domain. We considered

the remaining 23 studies as presenting an unclear risk of bias for random sequence generation. From these 23 trials, two studies failed to report the method adopted to generate the random sequence (Strauss 2001; Webster 2014), despite claiming to have used methods to randomise with constraints, such as stratification and blocking. The other 21 studies did not provide any information about random sequence generation (Ahmad 2015; Akman 2007; Corlin 1984; Cumurcu 2009; De 2011; Dhaked 2016; Dhir 2008; Faghihi 2014; Goldstein 1982; Gollnick 2001; Jones 1983a; Jones 1983b; Kapadia 2005; King 1982; Lester 1985; Lester 1985; Pigatto 1986; Prendiville 1988; Rademaker 2013b; Shetti 2013; Van der

Meeren 1983). No trials were considered as at high risk of selection bias from random sequence generation.

Allocation sequence concealment

From 31 included trials, we judged 26 studies as at unclear risk of bias for the domain, since there was no statement regarding allocation concealment within their reports (Ahmad 2015; Akman 2007; Corlin 1984; Cumurcu 2009; De 2011; Dhaked 2016; Dhir 2008; Faghihi 2014; Farrell 1980; Goldstein 1982; Gollnick 2001; Jones 1983a; Jones 1983b; Kapadia 2005; King 1982; Lee 2011; Leheta 2011; Lester 1985; Peck 1982; Pigatto 1986; Prendiville 1988; Rademaker 2013b; Shetti 2013; Strauss 1984; Strauss 2001; Van der Meeren 1983). Authors from Wahab 2008 declared, after contact by email, that they did not use any concealment method while allocating interventions, and we considered this study at high risk of bias for allocation concealment. We assessed only four trials as being at low risk of allocation sequence concealment (Agarwal 2011; Oprica 2007; Tan 2014; Webster 2014). These studies reported a 'third-party' assignment.

Blinding

Participants and personnel (performance bias)

Fourteen included trials did not provide adequate information to permit judgement and we considered them as being at unclear risk of this type of bias (Akman 2007; Cumurcu 2009; De 2011; Dhaked 2016; Jones 1983a; Kapadia 2005; King 1982; Leheta 2011; Lester 1985; Peck 1982; Pigatto 1986; Strauss 1984; Strauss 2001; Van der Meeren 1983). From these studies, six declared a 'double-blind' design, but did not specify who exactly was blinded among participants and personnel during the trial (King 1982; Jones 1983a; Lester 1985; Peck 1982; Strauss 1984; Strauss 2001).

Nine trials reported an open design (Agarwal 2011; Corlin 1984; Dhir 2008; Gollnick 2001; Lee 2011; Oprica 2007; Prendiville 1988; Shetti 2013; Wahab 2008), one trial (Tan 2014) declared that the study was investigator-blinded only, and one trial compared single versus divided daily dose of isotretinoin without using a dummy capsule to ensure the blinding (Ahmad 2015). We considered these eleven studies as being at high risk of performance bias.

Only six trials had a low risk of performance bias. These trials cited the 'double-blind' design and described accurately who was blinded among participants and personnel (Faghihi 2014; Farrell 1980; Goldstein 1982; Rademaker 2013b; Webster 2014) or described an appropriate effort to ensure blinding (Jones 1983b). None of the 31 included RCTs reported having performed any assessment of the success of blinding of participants and personnel.

Outcome assessor (detection bias)

Six of the 31 included trials described blinding of outcome assessment in an adequate way (Faghihi 2014; Lee 2011; Rademaker 2013b; Tan 2014; Webster 2014), or described an appropriate effort to ensure blinding (Jones 1983b): we considered them as at low risk of detection bias, despite the fact they had not declared any assessment of the success of blinding. We classified three trials as having high risk of bias: two trials which described clearly an open design with no blinding of the outcome assessor (Agarwal 2011; Wahab 2008), and one study which compared single versus divided daily dose of isotretinoin without the use of a placebo (Ahmad 2015). From the remaining 22 studies, five trials

cited an open design and did not provide any information related to outcome assessments (Corlin 1984; Dhir 2008; Gollnick 2001; Shetti 2013; Oprica 2007), and 17 studies did not report in a precise way either who did the outcome assessments or if the people responsible for measurement or collection of all outcome data were blinded (Akman 2007; Cumurcu 2009; De 2011; Dhaked 2016; Farrell 1980; Goldstein 1982; Jones 1983a; Kapadia 2005; King 1982; Leheta 2011; Lester 1985; Peck 1982; Pigatto 1986; Prendiville 1988; Strauss 1984; Strauss 2001; Van der Meeren 1983). We judged all these 22 clinical trials as presenting an unclear risk of bias.

Incomplete outcome data

Four included studies presented an unclear risk of attrition bias: Goldstein 1982 and Jones 1983b did not report detailed numbers and reasons for missing data in each intervention group; Leheta 2011 and Shetti 2013 did not provide any information regarding loss to follow-up to permit judgement.

We judged seven studies as being free of attrition bias: in Ahmad 2015, Faghihi 2014, and Kapadia 2005 there were no losses; King 1982, Peck 1982, Pigatto 1986, and Wahab 2008 made no mention of missing data of interest to our analysis within their reports (from Peck 1982, we considered in our review only the first phase of the study).

All of the remaining 20 included trials had a high risk of bias due to incomplete outcome data in our assessment. From these studies, seven trials performed a 'per protocol' analysis for at least the main efficacy outcome (Agarwal 2011; Akman 2007; Corlin 1984; Dhaked 2016; Dhir 2008; Farrell 1980; Oprica 2007; Strauss 2001) and performed an analysis restricted to participants who complied adequately with the protocol. Seven trials did analyses including missing data and reported reasons for attrition, and there was imbalance in numbers of dropouts and reasons for them across intervention groups (Gollnick 2001; Lee 2011; Lester 1985; Prendiville 1988; Tan 2014; Van der Meeren 1983; Webster 2014). Cumurcu 2009 reported a low and equal number of participants with missing data in both interventions groups, but there was an imbalance in reasons for it across groups. As a result, we decided to consider this trial as having a high risk of bias for attrition. Four studies reported a high loss to follow-up, which could lead to considerable attrition bias (De 2011; Jones 1983a; Rademaker 2013b; Strauss 1984). Three of these studies had not clearly described the number of participants with missing data in each group (Jones 1983a; Rademaker 2013b; Strauss 1984).

Selective reporting

Four of the 31 included trials had an available written or published protocol (Faghihi 2014; Rademaker 2013b; Tan 2014; Webster 2014). We judged 19 trials as presenting a low of risk bias, as they presented an adequate report of results related to each one of all outcomes listed in the methods sections of published final texts or protocols (Agarwal 2011; Ahmad 2015; Akman 2007; Corlin 1984; De 2011; Dhaked 2016; Faghihi 2014; Farrell 1980; Goldstein 1982; Jones 1983a; King 1982; Lee 2011; Lester 1985; Oprica 2007; Rademaker 2013b; Tan 2014; Van der Meeren 1983; Wahab 2008; Webster 2014).

Twelve included studies had high risk of selective reporting:

- There were outcomes reported with inadequate detail in six studies (Cumurcu 2009; Jones 1983b; Leheta 2011; Kapadia 2005; Prendiville 1988; Shetti 2013).
- Selective choice of data for an outcome might have occurred in four trials, (Dhir 2008; Pigatto 1986; Strauss 1984; Strauss 2001), and selective reporting of subsets of the data in another one (Peck 1982).
- One study might have selectively omitted one of the outcomes listed in its methods section from the report (Gollnick 2001).

Other potential sources of bias

Eighteen studies appeared to be free from other potential source of bias (Ahmad 2015; Akman 2007; Cumurcu 2009; De 2011; Dhaked 2016; Dhir 2008; Faghihi 2014; Goldstein 1982; Gollnick 2001; Jones 1983b; Kapadia 2005; Lee 2011; Leheta 2011; Pigatto 1986; Shetti 2013; Strauss 1984; Van der Meeren 1983; Wahab 2008). In one study (Agarwal 2011), there was an inappropriate administration of two other co-interventions (pulsed oral azithromycin plus topical 1% clindamycin phosphate cream twice daily) in a similar way for all groups. We considered this as a potential risk of bias as the association with other active anti-acne drugs could overestimate the actual effect of oral isotretinoin in intervention groups using lower doses. In 12 studies, the funding body was a pharmaceutical industry; in nine of them, the company that has first developed and marketed oral isotretinoin provided funding. Due to the possibility of inappropriate influence of funding bodies, we considered all these 12 trials as being at unclear risk of bias for the domain (Corlin

1984; Farrell 1980; Jones 1983a; King 1982; Lester 1985; Oprica 2007; Peck 1982; Prendiville 1988; Rademaker 2013b; Strauss 2001; Tan 2014; Webster 2014).

Effects of interventions

See: **Summary of findings for the main comparison**

1. Oral isotretinoin versus oral antibiotics plus topical agents

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

Three RCTs assessed this outcome (Gollnick 2001; Oprica 2007; Tan 2014). Overall, oral isotretinoin did not have a greater effect on improving acne severity than any combination of oral antibiotic plus topical agent after 20 to 24 weeks therapy (RR 1.01 95% CI 0.96 to 1.06; participants = 400; studies = 3; I² = 46%) (Analysis 1.1) (Figure 5). Participants in these three trials had moderate or severe acne. We decide to downgrade the quality of this body of evidence from high to very low due to very serious design limitations - selective reporting in one study (Gollnick 2001) and high risk of performance and attrition bias in all three studies - and serious indirectness, as two studies (Gollnick 2001; Tan 2014) measured our primary efficacy outcome by assessing a clearance of nodules and cysts or only of nodules, not of all inflammatory types of acne lesions (papules plus pustules, nodules and cysts). All these data are in Summary of findings for the main comparison.

Figure 5. Forest plot of comparison: 1 Oral isotretinoin versus any oral antibiotic plus any topical agent, outcome: 1.1 Improvement in acne severity assessed by a decrease in total inflammatory lesion count, measured in participants who were treated for a minimum period of 16 weeks.
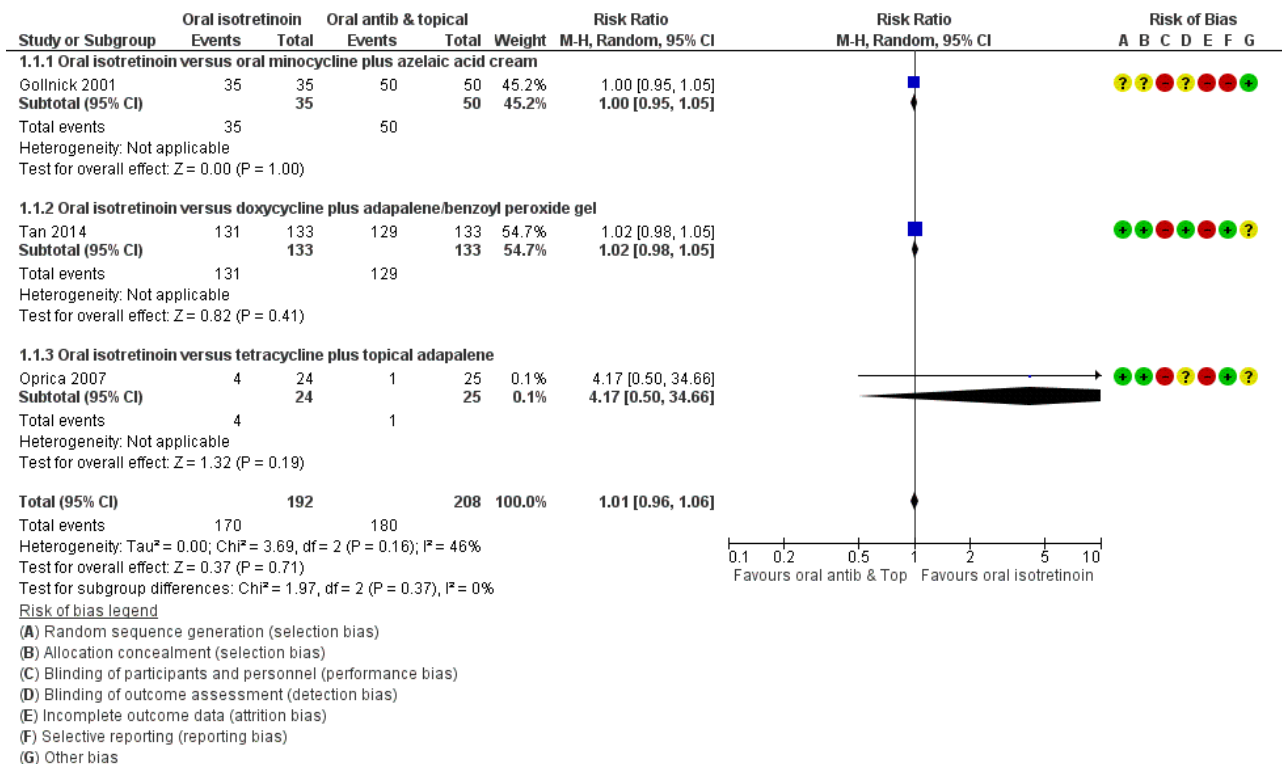
As there was statistical heterogeneity in pooling effects from these three studies (I^2 = 46%), that had analysed different combinations of oral antibiotics plus topical agents against oral isotretinoin during different periods of treatment, we also analysed the primary efficacy outcome of this review by study. The control intervention was equivalent to oral isotretinoin in one study (RR 1.00, 95% CI 0.95 to 1.05; participants = 85) (Analysis 1.1) (Gollnick 2001), which compared oral isotretinoin with azelaic acid cream plus minocycline (AA/mino) for severe acne during 24 weeks. The quality of the evidence was downgraded to low due to the very serious design limitations in Gollnick 2001 (high risk of selective reporting, performance and attrition bias). Oral isotretinoin produced only a 2% greater decrease in total inflammatory lesion count at the end of therapy phase (Tan 2014) where the control was doxycycline plus adapalene/benzoyl peroxide gel and participants with severe acne received treatment for 20 weeks (RR 1.02, 95% CI 0.98 to 1.05; participants = 266) (Analysis 1.1). The quality of this evidence was low due to the very serious limitations of design (high risk of performance and attrition bias) in the trial conducted by Tan 2014. In Oprica 2007, which evaluated oral isotretinoin versus tetracycline plus topical adapalene for moderate and severe acne during 24 weeks, the decrease in total inflammatory lesion count was more than four times higher with oral isotretinoin but the result had a very wide confidence interval including 1 showing uncertainty (RR 4.17, 95% CI 0.50 to 34.66; participants = 49) (Analysis 1.1). This study had the quality downgraded from high to very low due to the serious imprecision (the confidence interval of the effect was very wide) and the serious limitations of design in Oprica 2007 (high risk of performance and attrition bias).

Only Oprica 2007 provided data for the outcome at a two-month follow-up period after the end of therapy. Participants in the oral isotretinoin group were 11.4 times more likely to be clear of acne inflammatory lesions than those who received tetracycline plus adapalene; however, the confidence interval was very wide and included 1 showing uncertainty (RR 11.44, 95% CI 0.67 to 196.30; participants = 49; studies = 1). We downgraded the quality of this evidence from high to very low due to the very serious limitation

of design in the study (high risk of performance and attrition bias) and serious imprecision of the effect, which had a wide confidence interval. During the two-month follow-up period, participants from the tetracycline plus adapalene group applied adapalene once a day, while participants from the oral isotretinoin group did not use any maintenance therapy.

Gollnick 2001 and Tan 2014 also provided continuous data for our primary efficacy outcome. Gollnick 2001 reported a 97.1% reduction in the median number of facial papules and pustules for the oral isotretinoin group (n = 35) versus 88.2% for the azelaic acid cream plus minocycline group (n = 50) after six months of treatment (P < 0.05), which favoured the isotretinoin group. In Tan 2014, isotretinoin produced a higher decrease in nodule counts than doxycycline plus adapalene/benzoyl peroxide gel after 20 weeks of therapy (95.6 % versus 88.7 %, P < 0.01). In both studies, neither standard deviations, exact P value or a confidence interval were provided for these measurements.

Primary outcome: Frequency of serious adverse effects

Three RCTs assessed this outcome in participants with moderate or severe acne at 24 weeks follow-up and we pooled the results in meta-analysis (Gollnick 2001; Oprica 2007; Tan 2014). Only one serious adverse event was reported in the isotretinoin group (Stevens-Johnson syndrome just after the beginning of treatment, which required hospitalisation for 24 days). No adverse event was reported in the control group. The risk of serious adverse effects was three times higher with oral isotretinoin than with oral antibiotics plus topical agents but the confidence interval was very wide and included 1 (RR 3.00, 95% CI 0.12 to 72.98; participants = 400; studies = 3; I^2 = 0%) (Analysis 1.2) (Figure 6) (Summary of findings for the main comparison). We downgraded the quality of evidence from high to very low due to very serious limitations of design (lack of blinding of participants and personnel and high risk of attrition bias in all three analysed studies (Gollnick 2001; Oprica 2007; Tan 2014) and selective reporting of events in one study (Gollnick 2001)) and serious imprecision (the wide confidence interval of the effect, including 1).

Figure 6. Forest plot of comparison: 1 Oral isotretinoin versus any oral antibiotic plus any topical agent, outcome: 1.2 Frequency of serious adverse effects.

Study or Subgroup	Oral isotretinoin Events	Total	Oral antib & topical Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Oral isotretinoin versus oral minocycline plus azelaic acid cream						
Gollnick 2001	0	35	0	50		Not estimable
Subtotal (95% CI)		35		50		Not estimable
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.2 Oral isotretinoin versus tetracycline plus topical adapalene						
Oprica 2007	0	24	0	25		Not estimable
Subtotal (95% CI)		24		25		Not estimable
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.3 Oral isotretinoin versus doxycycline plus adapalene/benzoyl peroxide gel						
Tan 2014	1	133	0	133	100.0%	3.00 [0.12, 72.98]
Subtotal (95% CI)		133		133	100.0%	3.00 [0.12, 72.98]
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		192		208	100.0%	3.00 [0.12, 72.98]
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Not applicable						

Favours oral isotret   Favours oral antib & top

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

One RCT planned to assess this outcome, but did not report the respective result (Gollnick 2001).

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

Two RCTs (Gollnick 2001; Tan 2014) assessed the outcome in participants with severe acne and data from them had significant heterogeneity when pooled in meta-analysis (I^2 = 68%). These two studies used quite different criteria for judging acne severity improvement, with assessment of the physician's global evaluation by different scales, which may explain the heterogeneity.

Overall, when oral isotretinoin was compared with any combination of oral antibiotic plus topical agent, the meta-analysis showed a 15% higher improvement in acne severity with oral isotretinoin for this outcome (RR 1.15, 95% CI 1.00 to 1.32; participants = 351; studies = 2; I^2 = 68%) (Analysis 1.3; Summary of findings for the main comparison). The quality of the evidence was downgraded from high to very low due to very serious limitations of design (high risk of performance and attrition bias in both studies (Gollnick 2001; Tan 2014), besides selective reporting of events in Gollnick 2001) and serious imprecision related to the wide confidence interval of the effect. However, due to the significant clinical and statistical heterogeneity between these studies, we also analysed and presented the results for each one separately. In one study, oral isotretinoin had greater efficacy and produced an improvement in acne severity 22% higher than oral antibiotics plus topical agents. The quality of the evidence was low due to the very serious limitations of design cited above (RR 1.22, 95% CI 1.09 to 1.38; participants = 266) (Tan 2014). In the other study, both interventions had the same efficacy regarding this outcome (RR 1.08, 95% CI 0.97 to 1.20; participants = 85) (Gollnick 2001). The

quality of evidence was low due to the very serious limitations of design in Gollnick 2001.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

Only one study, Oprica 2007, assessed this outcome in participants with moderate and severe acne using the Dermatology Life Quality Index (DLQI) (Finlay 1994), a self-administered questionnaire designed to quantify the impact of skin diseases on participants' quality of life, where higher scores meant worse quality of life. Comparing final score values between groups, the mean final value of DLQI in participants on oral isotretinoin was 0.5 lower than of those in the control group but the confidence interval was wide and included zero (MD -0.50, 95% CI -3.58 to 2.58; participants = 49; studies = 1). The quality of evidence was considered very low according to GRADE due to very serious limitations of design in this study (high risk of attrition and performance bias) and serious imprecision of the effect (very wide confidence interval, which includes the clinically important difference in the effect size of 0.5 in either direction).

Secondary outcome: Frequency of less serious adverse effects

Two RCTs assessed the outcome in participants with severe acne, and we pooled data from them in a meta-analysis (Gollnick 2001; Tan 2014). The adverse effects considered included the following: local events (severe or persistent skin symptoms, or both, such as dry lips, dry skin, and cheilitis) and systemic events (vomiting and nausea). There was, respectively, a 90% and 66% higher frequency of less serious adverse effects in the isotretinoin group measured after four weeks (RR 1.90, 95% CI 1.03 to 3.51; participants = 85; studies = 1) (Analysis 1.4) (Gollnick 2001) and 20 weeks (RR 1.66, 95% CI 1.39 to 1.97); participants = 266 ; studies = 1) (Analysis 1.4) (Tan 2014). Oral isotretinoin therapy also had a 67% higher risk of less serious adverse effects in comparison to the use of

oral antibiotics plus topical agents in the meta-analysis of data from these studies (RR 1.67, 95% CI 1.42 to 1.98; participants = 351; studies = 2; I² = 0%) (Analysis 1.4). The quality of this body of evidence was downgraded from high to low due to very serious limitations of design in both studies (high risk of performance and attrition bias in both studies, besides high risk of reporting bias in Gollnick 2001). Additionally, we presented the data on each less serious adverse event reported among both RCTs in Table 3.

Secondary outcome: Dropout rates

Three RCTs assessed dropout rates in participants with moderate and severe acne. We pooled data from these three trials in a meta-analysis (Gollnick 2001; Oprica 2007; Tan 2014). Regarding dropout rates due to any reason, when oral isotretinoin was compared with any combination of oral antibiotic plus topical agent, the meta-analysis showed a 31% lower risk of dropout in the clinical trials among participants on isotretinoin but the confidence interval included 1 showing uncertainty (RR 0.69, 95% CI 0.44 to 1.09; participants = 403; studies = 3; I² = 0%) (Analysis 1.5). The quality of this body of evidence was downgraded from high to very low (three levels) after verifying the very serious limitations of design in all three studies (high risk of performance and attrition bias in the three studies, Gollnick 2001; Oprica 2007; Tan 2014, with also high risk of reporting bias in Gollnick 2001) and serious imprecision of the effect, which had a wide confidence interval. When compared to any oral antibiotics plus topical agents, oral isotretinoin was associated with a 27%, 70% and 10% reduction in risk of dropout, respectively, due to: adverse effects (RR 0.83, 95% CI 0.30 to 2.31; participants = 403; studies = 3; I² = 0%); no improvement or lack of efficacy (RR 0.30, 95% CI 0.03 to 2.64; participants = 137; studies = 2; I² = 0%); and loss to follow-up or no specified reason (RR 0.90, 95% CI 0.36 to 2.26; participants = 403; studies = 3; I² = 0%); however, the confidence intervals for these analyses were wide and included 1 showing uncertainty (Analysis 1.5). For all of these last three analyses, the quality of evidence was downgraded to very low due to very serious limitations of design (high risk of bias related to, at least, performance and attrition domains) in all three studies which had data on these outcomes (Gollnick 2001; Oprica 2007; Tan 2014) and serious imprecision (effects with wide confidence intervals, which included the clinically relevant difference of 25%). Additionally, we also presented the data concerning dropout rates from our 31 included RCTs in Table 4 and Table 5.

2. Oral isotretinoin versus oral isotretinoin plus topical agents

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

There were no available data for this outcome.

Primary outcome: Frequency of serious adverse effects

There were no serious adverse effects in either RCT which had addressed the comparison of oral isotretinoin versus oral isotretinoin plus topical agents (Dhir 2008 and Faghihi 2014) which involved 60 and 58 participants with moderate to severe acne, respectively. The quality of this evidence was low due to serious limitations of design in Faghihi 2014 (unclear risk of selection bias) and very serious limitations of design (high risk of performance, attrition and reporting bias) in the trial by Dhir 2008.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

Two RCTs assessed this outcome and assessed different comparisons at different time points (Dhir 2008; Faghihi 2014).

- Oral isotretinoin versus oral isotretinoin plus topical clindamycin 1% daytime plus adapalene 0.1% at bedtime (Dhir 2008): after 24 weeks, there was complete, excellent or good clearing of lesions in 100% (25/25) of the participants in the control group and 92% (23/25) of those participants on isotretinoin alone; hence, there was no clear difference between groups (RR 0.92, 95% CI 0.80 to 1.06; participants = 50; studies = 1). The definition used was as follows: 100% reduction in pretreatment score = complete clearing; from 75% to 99% = excellent; and from 50% to 74% = good. All participants had severe acne.

We downgraded the quality of evidence from this study from high to low (two levels) due to the very serious limitations of design (high risk of performance, attrition and reporting bias).

- Oral isotretinoin versus oral isotretinoin plus 5% dapsone gel (Faghihi 2014) for moderate to severe acne: the investigators assessed the mean score in Global Acne Assessment Scale (GAAS), a 5-point scale in which higher scores correlate with more severe acne, at baseline and at weeks 4, 8 and 12, and found the following results:
  * four weeks: participants in isotretinoin plus 5% dapsone gel group presented a 0.1 lower mean GAAS score but it was not statistically significant (MD 0.10, 95% CI -0.08 to 0.28; participants = 58; studies = 1);
  * eight weeks: participants on isotretinoin alone presented a 0.2 lower mean GAAS score, which means they achieved more clearance of acne lesions than participants in the isotretinoin plus 5% dapsone gel group (MD -0.20, 95% CI -0.35 to -0.05; participants = 58; studies = 1); and
  * 12 weeks: participants on isotretinoin plus 5% dapsone gel had a 0.2 lower mean GAAS score, (MD 0.20, 95% CI 0.07 to 0.33; participants = 58; studies = 1).

The quality of evidence from Faghihi 2014 was downgraded from high to moderate (one level), for the effects measured at 4, 8 and 12 weeks, due to serious limitations of design in the study, more specifically unclear risk of selection bias related to both domains, random sequence generation and allocation concealment.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

Two RCTs assessed this outcome (Dhir 2008; Faghihi 2014).

- Oral isotretinoin versus oral isotretinoin plus topical clindamycin 1% daytime plus adapalene 0.1% at bedtime for severe acne: Dhir 2008 reported the frequency of each less serious adverse event for all randomised participants,

without specifying the group. The exceptions were melasma-like pigmentation, with a risk 66% higher among participants on oral isotretinoin alone but the confidence interval was wide and included 1 showing uncertainty (RR 1.66, 95% CI 0.44 to 6.24; participants = 50; studies = 1); and flare-up during the first eight weeks of treatment, with an estimated risk 67% lower among participants in the oral isotretinoin alone group, though the confidence interval was also wide and included 1 (RR 0.33, 95% CI 0.10 to 1.09; participants =50; studies = 1). The quality of the evidence for 'melasma-like pigmentation' was downgraded by three levels due to very serious limitations of design in the study (high risk of bias in three domains: performance, attrition, and reporting) and serious imprecision of the effect, which had a wide confidence interval. For the other less serious adverse effects, flare-up at eight weeks of therapy, we downgraded the quality of evidence by two levels, from high- to low-quality, and the reason was the very serious limitations of design in Dhir 2008, which we already referred to above.

- Oral isotretinoin versus oral isotretinoin plus 5% dapsone gel for moderate to severe acne (Faghihi 2014): the frequency of less serious adverse effects was lower in the isotretinoin alone group (RR 0.17, 95% CI 0.06 to 0.51; participants = 58; studies = 1). We considered the quality of this evidence as moderate (a downgrade of one level) due to serious limitations of design in Faghihi 2014, more specifically unclear risk of selection bias related to both domains, random sequence generation and allocation concealment.

We also presented data of each less serious adverse event reported by all included RCTs in Table 3 and Table 6.

Secondary outcome: Dropout rates

Two RCTs assessed this outcome in participants with moderate and severe acne. We pooled data from these studies in meta-analysis for overall dropout rates (Dhir 2008; Faghihi 2014). There was no difference in effect between groups for this outcome (RR 1.00, 95% CI 0.32 to 3.10; participants = 118; studies = 2; I^2 = 0%) (Analysis 2.1). We downgraded the quality of evidence by three levels to very low due to very serious limitations of design in the involved studies (Dhir 2008 had high risk of performance, attrition and reporting bias; Faghihi 2014 presented unclear risk of selection bias) and serious imprecision related to the wide confidence interval of the effect.

Additionally, we presented the data concerning dropout rates reported for all included RCTs in Table 4 and Table 5.

3. Oral isotretinoin versus 0.1% tretinoin cream plus 5% benzoyl peroxide gel

We included one RCT on this comparison (Leheta 2011).

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

There were no available data for this outcome.

Primary outcome: Frequency of serious adverse effects

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

According to the report (conference abstract) of Leheta 2011, oral isotretinoin (0.5 mg/kg/day for 2 weeks, followed by 1 mg/kg/day until the end of therapy) was equivalent to 0.1% tretinoin cream each evening plus 5% benzoyl peroxide gel each morning to the face as regards improving acne severity score at the end of therapy in participants with mild to moderate acne. The authors presented a P value of 0.40, and no estimate of effect was reported in the text.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

There were no available data for this outcome.

Secondary outcome: Dropout rates

There were no available data for this outcome.

4. Oral isotretinoin versus chemical peeling with trichloroacetic acid (TCA) 25%

Leheta 2011 was the sole study which addressed this comparison.

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

There were no available data for this outcome.

Primary outcome: Frequency of serious adverse effects

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

In Leheta 2011, authors stated there was no difference between oral isotretinoin (0.5 mg/kg/day for 2 weeks, followed by 1 mg/kg/day until the end of therapy) versus chemical peeling with trichloroacetic acid (TCA) 25% (every two weeks for eight sessions; and monthly during follow-up) regarding acne severity score at the end of therapy in participants with mild to moderate acne. The report did not cite any figures for the estimate of effect or additional details except for a P value of 0.40.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

There were no available data for this outcome.

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Secondary outcome: Dropout rates

There were no available data for this outcome.

5. Oral isotretinoin versus oral isotretinoin plus oral antibiotic

We found two studies which analysed the comparison: De 2011 and Jones 1983b.

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

There were no available data for this outcome in De 2011. The trial by Jones 1983b assessed the outcome but did not provide any specific numerical data.

Primary outcome: Frequency of serious adverse effects

There were no serious adverse effects in De 2011 (n = 41) and Jones 1983b (n = 90). The quality of the evidence was low due to very serious limitations of design in both studies: unclear risk of selection, performance and detection bias and high risk of attrition bias in De 2011; unclear risk of selection bias and high risk of reporting bias in Jones 1983b.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

In the study by De 2011, which had focused on severe acne, participants in Group A (n = 21) received low dose isotretinoin (0.3 mg/kg/day) plus azithromycin pulse (500 mg daily on three consecutive days fortnightly) and had a 50% decrease in visual analogue scale (VAS) severity in a mean period of 3.37 months. Participants from Group B (n = 20) used standard-dose isotretinoin (0.5 mg/kg/day) in a total cumulative dose of 120 mg/kg and had a 50% decrease in VAS with a mean period of 3.82 months. No P value or standard deviations were provided. Participants in both groups received interventions over eight months.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

Only Jones 1983b assessed the outcome but did not provide any specific numerical data.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

Both studies for the comparison, De 2011 and Jones 1983b, did not provide adequate data related to frequency of less serious adverse effects, despite having measured this outcome.

Secondary outcome: Dropout rates

From both studies in the comparison, only Jones 1983b assessed the outcome but did not provide any specific numerical data. The study involved 90 participants with moderate and severe acne and compared isotretinoin 0.5 mg/kg/day for 16 weeks (Group A, n = not provided) with erythromycin 1 g/kg/day for 24 weeks (Group B, n = not provided) and isotretinoin 0.5 mg/kg/day for 16 weeks plus erythromycin 1 g/kg/day for 24 weeks (Group C, n = not provided).

6. Oral isotretinoin versus oral azithromycin

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

There were no available data for this outcome.

Primary outcome: Frequency of serious adverse effects

Wahab 2008 was the only included RCT in this comparison and no serious adverse effects were detected among 60 participants, who had moderate to severe acne. The quality of the evidence was low due to very serious limitations of design in the study, more specifically high risk of selection, performance, and detection bias.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

One trial assessed this outcome and compared oral isotretinoin 0.5 to 1.0 mg/kg/daily for five months versus azithromycin 500 mg 3 days a week during three months for moderate to severe acne (Wahab 2008). The proportion of participants who presented an excellent (complete clearance) or good (> 75% clearing) improvement of acne severity at the end of therapy was 93% higher in the isotretinoin group (RR 1.93, 95% CI 1.34 to 2.78; participants = 60; studies= 1). We considered the quality of evidence as being low due to the very serious limitations of design in the study (high risk of performance and detection bias, besides the absence of allocation concealment). The proportion of participants with moderate acne who presented an excellent (complete clearance) or good (> 75% clearing) response was again higher (75%) in the isotretinoin group (RR 1.75, 95% CI 1.24 to 2.48; participants = 60; studies= 1). The quality of the evidence was low due to very serious limitations of design in Wahab 2008. Among those participants with severe acne, oral isotretinoin was more than four times more effective than azithromycin in promoting an excellent or good clinical response but the confidence interval was wide and included 1 showing uncertainty (RR 4.50, 95% CI 0.77 to 26.2; participants = 60; studies= 1). We downgraded the quality of evidence related to this last effect estimate by three levels, from high to very low due to very serious limitations of design and serious imprecision of the effect (wide confidence interval).

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

Wahab 2008 assessed this outcome and detailed the proportion of participants who presented with an increase of serum lipids only in the isotretinoin group (3/30); the study also reported mild nausea and abdominal discomfort (3/30) only for the azithromycin group.

Secondary outcome: Dropout rates

There were no dropouts in the Wahab 2008 study.

7. Oral isotretinoin versus oral erythromycin

We found one RCT (Jones 1983b) for the comparison.

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

Jones 1983b assessed the outcome but did not provide any specific numerical data.

Primary outcome: Frequency of serious adverse effects

There was no serious adverse event in the study by Jones 1983b, which involved 90 participants with moderate and severe acne and compared isotretinoin 0.5 mg/kg/day for 16 weeks (Group A, n = not provided) with erythromycin 1 g/kg/day for 24 weeks (Group B, n = not provided) and isotretinoin 0.5 mg/kg/day for 16 weeks plus erythromycin 1 g/kg/day for 24 weeks (Group C, n = not provided). The quality of this evidence was low due to very serious limitations of design, more specifically unclear risk of selection bias and high risk of reporting bias.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

Jones 1983b assessed the outcome but did not provide any specific numerical data.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

Jones 1983b assessed the outcome but did not provide any specific numerical data.

Secondary outcome: Dropout rates

Jones 1983b did not report detailed data related to dropouts from each intervention group. Authors just cited the withdrawal of four participants (from a total of 90) due to side effects.

8. Oral isotretinoin versus oral minocycline

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

There were no available data for this outcome.

Primary outcome: Frequency of serious adverse effects

There was no report of any serious adverse event among participants of the included trial for this comparison (Pigatto 1986) (n = 24), which had involved participants with severe acne. The quality of the evidence was low due to very serious limitations of design in the study, more specifically unclear risk of selection, performance and detection bias and high risk of reporting bias.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

There were no available data for this outcome.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

One trial assessed this outcome and compared isotretinoin 1 mg/kg/d for 10 weeks followed by 0.5 mg/Kg/d for 10 weeks (n = 12) versus minocycline 100 mg/day followed by 50 mg/day for severe acne (n = 12) (Pigatto 1986). The proportion of participants who presented any less serious adverse effects was 67% higher in the isotretinoin group (RR 1.67, 95% CI 1.03 to 2.69; participants = 24; studies = 1). The quality of the evidence was very low due to very serious limitations of design (the study presented high risk of reporting bias and unclear risk of selection, performance, and detection bias) and imprecision of the effect (wide confidence interval).

Additionally, we presented the data on the frequency of each less serious adverse event reported by all included RCTs in Table 3; Table 4. For Pigatto 1986, data for each less serious adverse effect are in Table 3.

Secondary outcome: Dropout rates

There were no dropouts in the Pigatto 1986 study.

9. Oral isotretinoin versus oral tetracycline

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

The sole included RCT for this comparison, which enrolled people with severe acne, measured the improvement in acne severity assessed by a decrease in the number of cysts (Lester 1985). At the end of the therapy phase (16 weeks), participants on isotretinoin 1.0 to 2.0 mg/kg/day had a greater reduction in mean cysts count than those on tetracycline 0.5 g to 1 g/day but the confidence interval was wide and included 1 showing uncertainty (MD -2.80, 95% CI -7.90 to 2.30; participants = 30; studies = 1). After 24 weeks, on the follow-up assessment, isotretinoin-treated participants again had a greater decrease in the number of cysts than did the tetracycline-treated group (MD -5.3, 95% CI -9.80 to -0.80; participants = 30; studies =1). The quality of evidence from both time points of measurement was very low due to very serious limitations in the study design (high risk of attrition bias and unclear risk of selection, performance and detection bias) and serious indirectness related to the outcome, as the trial measured the primary efficacy outcome of this review by assessing the clearance of cysts only, not of all inflammatory types of acne lesions (papules plus pustules, nodules, and cysts). Besides these reasons to downgrade the quality of both effects to very low, there was also serious imprecision (95% confidence intervals were wide).

Primary outcome: Frequency of serious adverse effects

Lester 1985 was the only included RCT in this comparison and did not detect any serious adverse event among participants with severe acne (n = 30). The quality of the evidence was low due to very serious limitations of design in Lester 1985, more specifically unclear risk of selection, performance, detection and other bias, and also high risk of attrition bias.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

There were no available data for this outcome.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

One trial assessed this outcome and compared oral isotretinoin 1.0 to 2.0 mg/Kg/day with tetracycline 0.5 g to 1 g/day for 16 weeks in participants with severe acne (Lester 1985). There was twice the risk of a less serious adverse effect among participants in the isotretinoin group (RR 2.07, 95% CI 1.22 to 3.51; participants = 30; studies = 1). The quality of evidence was downgraded to very low due to very serious limitations in the study design (high risk of attrition bias and unclear risk of selection, performance and detection bias) and serious imprecision (wide confidence interval). We entered data related to each less serious adverse event reported by the trial, in Table 3.

Secondary outcome: Dropout rate

Lester 1985 reported two dropouts due to poor control of the disease in the tetracycline group (2/15) and none in the isotretinoin group (0/15). Participants in the isotretinoin group had a lower risk of dropout but we are uncertain about this result because the confidence interval was wide and included 1 (RR 0.20, 95% CI 0.01 to 3.97; participants = 30; studies = 1) (Table 4). The quality of the evidence was very low due to very serious limitations of design in the trial (high risk of attrition bias and unclear risk of selection bias), besides serious imprecision of the effect (the wide confidence interval of the effect included the clinically important difference of 25%).

10. Oral isotretinoin versus oral dapsone

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

One included trial for this comparison assessed the outcome by measuring the reduction in lesion counts, but only in pustules, nodules, and cysts, not in all inflammatory lesion counts (Prendiville 1988). The RCT compared oral isotretinoin 40 mg/day versus oral dapsone 100 mg/day during 16 weeks for participants with severe acne. The report did not provide the exact values of the lesion counts at each time point of measurement. Authors just stated that participants on isotretinoin group had a lower number of lesions at 20 weeks, 28 weeks, and 36 weeks than the people in

the dapsone group, with P values less than 0.05 at these three time points of measurement.

Primary outcome: Frequency of serious adverse effects

There were no serious adverse effects in participants of Prendiville 1988 (n = 40), which had addressed the comparison above in participants with severe acne. The quality of the evidence was low due to serious limitations of design in the trial, more specifically high risk of performance, attrition and reporting bias, and unclear risk of selection, detection and other bias.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

One RCT planned to assess this outcome but did not report the respective results of the comparison at any time point (Prendiville 1988).

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

There were no available data for this outcome.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

One trial assessed this outcome and compared oral isotretinoin 40 mg/day versus oral dapsone 100 mg/day for 16 weeks (Prendiville 1988) among participants with severe acne. The authors did not provide numeric data, but stated that all participants in the isotretinoin group presented at least one less serious mucocutaneous adverse event (cheilitis was the most notable). There was a hypersensitivity reaction (morbiliform eruption and abnormal liver function tests) in one participant in the dapsone group.

Secondary outcome: Dropout rates

Prendiville 1988 assessed this outcome, and the effect was equal for both interventions, oral isotretinoin 40 mg/day versus oral dapsone 100 mg/day, during 16 weeks, for participants with severe acne. Three participants on isotretinoin (3/20) and three in the dapsone group (3/20) dropped out of the study (RR 1.00, 95% CI 0.23 to 4.37; participants = 40; studies = 1). The quality of the evidence was downgraded by three levels due to very serious limitation of design in the trial (unclear risk of selection and detection bias and high risk of performance and attrition bias), besides serious imprecision (the effect had a wide confidence interval). Nonattendance or noncompliance were the reasons for dropouts in 1/20 in the dapsone group and 3/20 in the isotretinoin group. There was one dropout in the dapsone group due to dissatisfaction with treatment and another one due to hypersensitivity reaction. The effects related to the reasons for dropout are presented in Table 4.

11. Oral isotretinoin versus oral etretinate

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

There were no available data for this outcome.

Primary outcome: Frequency of serious adverse effects

Goldstein 1982 did not report any serious adverse event among all participants with severe acne (n = 56). The quality of the evidence was moderate due to serious limitations of design in the trial, more specifically unclear risk of selection, detection and attrition bias.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

There were no available data for this outcome.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

One trial assessed this outcome and compared isotretinoin 1 mg/kg/d for eight weeks (n = 28) versus etretinate 1 mg/kg/day for eight weeks in 28 participants with severe acne (Goldstein 1982). There was no difference between both interventions regarding the frequency of less serious adverse effects (RR 1.00, 95% CI 0.93 to 1.07; participants = 56; studies = 1). We considered the quality of evidence as being moderate due to serious limitations of design; the study had unclear bias for selection, detection, and attrition. We also presented data from each less serious adverse effect reported by the trial in Table 3.

Secondary outcome: Dropout rate

Goldstein 1982 reported six dropouts among 58 participants with severe acne. The loss to follow-up occurred during the follow-up period. However, the number of dropouts by intervention group was not reported.

12. Different doses/therapeutic regimens of oral isotretinoin

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (after at least 16 weeks)

Three studies assessed this outcome (Corlin 1984, Lee 2011, Strauss 1984). However, the data were heterogeneous (with multiple different comparisons of doses and therapeutic regimens in addition to different ways for the measurement of the outcome), and it was not possible to pool them in meta-analysis.

In Corlin 1984, the decrease in total inflammatory lesion count (papules, pustules, and nodules) was 79% (mean number of lesions: 83 to 17), 80% (94 to 19) and 84% (105 to 17), respectively, for 0.05 mg/kg/daily (41 participants), 0.1 mg/kg/daily (54 participants) and 0.2 mg/kg/daily (59 participants) of oral isotretinoin after 20 weeks. Participants had severe acne. Neither standard deviation, P values or confidence intervals were available. The quality of the evidence was low due to very serious limitations of design in the RCT, more specifically high risk of performance and attrition bias and unclear risk of selection, detection, and other bias.

In Lee 2011, three doses were compared during 24 weeks in participants with moderate acne: (a) continuous (daily) low dose (0.25 to 0.4 mg/kg/day); (b) continuous conventional dose (0.5 to 0.7 mg/kg/day) and (c) intermittent regimen (i.e. there was no daily intake of the drug; the participant took the medicine only in some prespecified periods during the whole treatment) (0.5 to 0.7 mg/kg/day, first week in every four weeks). After 24 weeks, mean inflammatory lesion counts were lower in the continuous (daily) low dose regimen (MD 3.72 lesions, 95% CI 2.13 to 5.31; participants = 49; studies = 1) and continuous (daily) conventional dose (MD 3.87 lesions, 95% CI 2.31 to 5.43; participants = 49; studies = 1), when both were compared with the intermittent regimen. For both effects at 24 weeks, we downgraded the quality of evidence by two levels, from high to low, due to very serious limitations of design in Lee 2011 (unclear risk of bias regarding allocation concealment and high risk of performance and attrition bias). When comparing both continuous (daily intake) regimen groups, there was a greater effect with conventional dose regimen, but we are uncertain about this result because the confidence interval was wide and included 0 (MD 0.15 lesion, 95% CI -1.09 to 1.39; participants = 49; studies = 1). For this last measure at 24 weeks, the quality of the evidence was very low: besides the very serious limitations of design in Lee 2011, there was also the serious imprecision of the effect (the 95% confidence interval included the null effect and was wide).

In Strauss 1984, 150 participants with severe acne were included and the improvement in lesion count was defined as a 95% decrease in total inflammatory lesion count (greater than 4 mm) after 20 weeks. The compared doses were 0.1 mg/kg/d, 0.5 mg/kg/d and 1 mg/kg/d. Among participants of the group treated with the dose of 0.1 mg/kg/day, 58% achieved the 95% improvement in the total counting of facial and truncal inflammatory lesions (4 mm or greater in diameter), versus 80%, and 90% in both groups treated with higher doses (0.5 mg and 1 mg/kg/day, respectively). A reliable estimate of effect for the three different single pairwise comparisons was not possible due to lack of accurate denominators, as exact number of dropouts at the time point of this assessment was not clearly reported. The quality of the evidence was low due to very serious limitations of design in the study (high risk of attrition and reporting bias and unclear risk of selection, performance, and detection bias).

Primary outcome: Frequency of serious adverse effects

There was no report of any serious adverse event in 14 RCTs on different doses/regimens of oral isotretinoin (n= 906). The quality of the evidence was low due to very serious limitations of design in the studies (Agarwal 2011; Ahmad 2015; Akman 2007; Corlin 1984; Cumurcu 2009; Dhaked 2016; Farrell 1980; Jones 1983a; Kapadia 2005; King 1982; Lee 2011; Shetti 2013; Strauss 1984; Van der Meeren 1983). These studies involved people with all severities of acne (mild, moderate, and severe), and the follow-up of the outcome was the same as the duration of the therapy (ranged from 12 to 32 weeks, mean 20.9 weeks) plus the follow-up after treatment ended (ranged from 0 to 48 weeks, mean 18.3 weeks).

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

There were no available data for this outcome.

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

Five trials assessed this outcome (Ahmad 2015; Akman 2007; Dhaked 2016; Kapadia 2005; Lee 2011). However, the data were heterogeneous regarding the different doses and regimens of oral isotretinoin, and it was not possible to pool them in meta-analyses.

Akman 2007 compared the effects of three different regimens of oral isotretinoin in participants with moderate and severe acne: (a) conventional dose of 0.5 mg/kg/d for 10 days of each month, for six months; (b) 0.5 mg/kg/d for one month, followed by 0.5 mg/kg/d for the first 10 days of each month for five months; (c) 0.5 mg/kg/d for six months. Authors used the FDA Global Grade, as described in (Cunliffe 2003), to assess acne improvement. They only reported a significant decrease of the acne grade in each treatment group at the end of the therapy phase (P < 0.001), with more higher grades of acne severity after cessation of oral isotretinoin in the group with the intermittent dose (conventional dose of 0.5 mg/kg/d for 10 days of each month, for six months) than in the group with conventional dose daily (0.5 mg/kg/d, for six months) at the end of the 12-month follow-up period (P = 0.002). The report did not provide the exact values of the acne grade in each intervention group for the measurements cited above.

Ahmad 2015 compared single (group 1) versus twice (group 2) daily doses of isotretinoin in participants with mild, moderate, and severe acne. The administered dose was from 0.5 to 1.0 mg/kg/d in both intervention groups during a mean period of 22 weeks. In the first month of therapy, participants received only half of the programmed maintenance dose to avoid exacerbation of the disease. The Global Acne Scoring (GAS) system was used to objectively classify acne cases in the study into mild (score 1 to 18), moderate (score 19 to 30), severe (score 31 to 38), and very severe (score > 39). The median GAS significantly decreased from 34 to 0 (P < 0.001) in group 1 and from 31 to 0 after treatment in group 2 (P < 0.001). Authors reported that there was no difference of effect between single and twice daily doses of isotretinoin at the end of therapy, with a P value of 0.8. More detailed numerical data for this effect were not provided.

Dhaked 2016 analysed isotretinoin 20 mg alternate days versus isotretinoin 20 mg/daily for 24 weeks in participants with moderate and severe acne. The lower dose (20 mg alternate days) improved acne severity 5% less than 20 mg/daily at the end of the therapy by the assessment of the number of participants who achieved an excellent treatment response (> 90% reduction in the lesion counts) (RR 0.95%; 95% CI 0.91 to 1.01; participants = 234; studies = 1); however, the confidence interval did include 1 showing uncertainty. We downgraded the quality of this evidence by two levels, from high to low, due to very serious limitations of design in the trial (unclear risk of selection, performance, and detection bias and high risk of attrition bias). At the 12-week follow-up period after the end of the therapy, the proportion of participants who maintained the excellent response to isotretinoin therapy was 18% lower in the 20 mg alternate days group (RR 0.82, 95% CI 0.72 to 0.92; participants = 234; studies = 1). The quality of the evidence was very low: there were very serious limitations of design in the RCT (as we have already cited above) and serious imprecision (the 95% confidence interval of the effect included the clinically important difference of 25% between interventions).

Kapadia 2005 compared isotretinoin 20 mg/day versus 40 mg/day for 24 weeks in participants with moderate to severe acne. The proportion of participants with complete clearing, excellent (> 80% clearing) or good (> 50% clearing) was 80% (24/30) with 20 mg/day and 86% (26/30) with 40 mg/day at all time points of measurement (8, 16 and 24 weeks). Participants receiving the higher daily dose of oral isotretinoin achieved a 8% greater improvement in acne severity than the group who received 20 mg/day in these assessments but the confidence interval included 1 showing uncertainty (RR 0.92, 95% CI 0.74 to 1.16; participants = 60; studies = 1). We considered the quality of the evidence as being low due to the very serious limitation of design in Kapadia 2005 (unclear risk of selection, performance, and detection bias; and high risk of reporting bias).

Lee 2011 studied three low dose isotretinoin regimens for moderate acne during 24 weeks: (a) continuous - daily drug intake - low dose (0.25 to 0.4 mg/kg/day); (b) continuous - daily drug intake - conventional dose (0.5 to 0.7 mg/kg/day); and (c) intermittent - stopping and starting intake often over a month - conventional dose (0.5 to 0.7 mg/kg/day for the first week in every four weeks). Authors used the Global Acne Grading System (GAGS), which classifies acne into mild (score 1 to 18), moderate (score 19 to 30), severe (score 31 to 38), and very severe (score > 39), to assess the improvement in acne severity according to physician's evaluation. The study provided mean values of the score in each intervention group at each time point of assessment of the outcome. Participants on therapy with the intermittent regimen had higher mean values of GAGS scores at the end of the treatment than participants on either continuous low dose (MD 1.57, 95% CI 0.12 to 3.02; participants = 60; studies = 1) or continuous conventional dose (MD 1.75, 95% CI 0.13 to 3.37; participants = 49; studies = 1). Treatment with continuous low doses of oral isotretinoin produced a higher mean final value of GAGS scores, i.e. it was less effective than therapy with continuous conventional doses, but the confidence interval did included zero showing some uncertainty (MD 0.18, 95% CI -1.44 to 1.80; participants = 49; studies = 1). The quality of the evidence from these three measures of effect was very low due to very serious limitations of design in the RCT (unclear risk of bias regarding allocation concealment and high risk of performance and attrition bias) and serious imprecision of the effect, which had a wide confidence interval. One year after the end of the therapy phase, participants on intermittent oral isotretinoin had higher mean values of GAGS scores than those participants who received either the continuous low dose regimen (MD 6.35, 95% CI 1.52 to 11.18; participants = 49; studies = 1) or the continuous conventional dose regimen (MD 7.93, 95% 3.33 to 12.53; participants = 49; studies = 1). Both analyses were of low-quality due to the very serious limitations of design in the trial, which we have already described above. Participants who were in the continuous low dose intervention group presented higher mean values of GAGS scores than those ones in the continuous conventional dose group at the 12 months follow-up measurement after the end of the treatment but the confidence interval included 0 showing uncertainty (MD 1.58, 95% CI -2.71 to 5.87; participants = 49; studies = 1). We downgraded the quality of this evidence to very low due to the very serious limitations of design in Lee 2011 and the imprecision related to the wide confidence interval of the effect.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

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Secondary outcome: Frequency of less serious adverse effects

Thirteen trials assessed this outcome (Agarwal 2011; Ahmad 2015; Akman 2007; Corlin 1984; Cumurcu 2009; Dhaked 2016; Farrell 1980; Jones 1983a; Kapadia 2005; Lee 2011; Shetti 2013; Strauss 1984; Van der Meeren 1983). The data were heterogeneous regarding ways for the assessment of the outcome and also the many different doses and therapeutic regimens of oral isotretinoin. Therefore, we could not pool them in meta-analyses. The numbers in detail for each less serious adverse event reported in each study are in Table 6. We have briefly described in each of the following paragraphs the results of this outcome by study, with the respective information about the severity of acne in the participants. The follow-up of the outcome was the duration of the therapy (ranged from 12 to 32 weeks, mean 21.3 weeks) plus the follow-up after treatment ended (ranged from 0 to 48 weeks, mean 19.8 weeks). It was not clear in any of the 13 studies how long treatment was given until the measure of the outcome, as all of them reported only the number of participants which developed each one of the less serious adverse effects during the entire follow-up.

Agarwal 2011 compared four therapeutic regimens, of 16 weeks, for participants with mild, moderate, and severe acne: (a) continuous, 1 mg/kg/d; (b) alternate days, 1 mg/kg/d; (c) intermittent, 1 mg/kg/d for one week of each month; and (d) alternate days, 20 mg/d. Data related to the estimates of effect for the overall frequency of less serious adverse effects were not reported. The numbers for each less serious adverse event reported by the authors are presented in Table 6.

Ahmad 2015 compared single versus divided daily doses of oral isotretinoin (0.5 to 1.0 mg/kg/d) in participants with mild, moderate, and severe acne for a mean period of 22 weeks. During the initial month, only half of the anticipated maintenance dose was given to avoid acne exacerbation. The rate of less serious clinical adverse effects was higher (P = 0.04) with the single dose, including dry chapped lips, dry skin, eczema, epistaxis, dry eyes, gastrointestinal upset, angular stomatitis, back pain, ingrowing nail, cough, headache, pyogenic granuloma, and white hair. The report of the study did not provide more detailed information for this outcome.

Akman 2007 compared two different intermittent regimens with the traditional therapy regimen for moderate and severe acne: (a) conventional dose of 0.5 mg/kg/d for 10 days of each month, for six months; (b) 0.5 mg/kg/d for one month, followed by 0.5 mg/kg/d for the first 10 days of each month for five months; and (c) 0.5 mg/kg/d for six months. Authors reported that the frequency of each less serious clinical adverse event was higher in group (c). However, the report did not provide data related to the effect estimate of the overall frequency of less serious adverse effects. Regarding data of each less serious adverse event individually, we present the numbers in Table 6.

Corlin 1984 compared doses of 0.05 mg/kg/daily (64 participants), 0.1 mg/kg/daily (62 participants) and 0.2 mg/kg/daily (65 participants) oral isotretinoin, for 20 weeks, for severe acne. There was no report of data related to the estimate of the effect for the overall frequency of less serious adverse effects. We presented estimates of effect related to each less serious adverse event in Table 6.

Cumurcu 2009 compared conventional dose (> 0.5 mg/kg/day) with low dose (< 0.5 mg/kg/day) for 12 weeks. There was no report of data related to the overall frequency of less serious adverse effects. The numbers for each less serious adverse event, specifically ocular adverse effects, are presented in Table 6.

Dhaked 2016 analysed the comparison of isotretinoin 20 mg alternate days versus 20 mg/daily for moderate and severe acne for 24 weeks. There were no data related to overall frequency of less serious adverse effects; authors presented only estimates of effect related to each less serious adverse event. We presented these estimates of effect in Table 6.

Farrell 1980 compared doses of 0.1 mg/kg/d, 0.5 mg/kg/d and 1 mg/kg/d for 12 weeks, and the authors reported that there was no significant difference between treatment groups regarding incidence of clinical adverse effects. However, the report did not individualise the data of less serious adverse effects by intervention group. Also, there was no information regarding the overall frequency of less serious adverse effects for each intervention group.

Jones 1983a compared doses of 0.1 mg/kg/d, 0.5 mg/kg/d and 1.0 mg/kg/d for 16 weeks for moderate to severe acne, and there was no report of the overall incidence of less serious adverse effects in each group. We presented data of each less serious adverse event from this study in Table 6.

Kapadia 2005 compared doses of 20 mg/day and 40 mg/day for 24 weeks for moderate and severe acne, but the report of the study cited data regarding less serious adverse effects per intervention group only for mood changes. There was a higher incidence of mood changes in the group taking 40 mg/day. The numbers in detail for this specific less serious adverse event are presented in Table 6.

Lee 2011 compared three different therapeutic regimens for moderate acne, for 24 weeks: (a) continuous - daily intake - low dose (0.25 to 0.4 mg/kg/day); (b) continuous - daily drug intake - conventional dose (0.5 to 0.7 mg/kg/day); and (c) intermittent - stopping and starting intake often over a month - conventional dose (0.5 to 0.7 mg/kg/day for the first week in every four weeks). We made pairwise comparisons between the three treatment groups and participants receiving the intermittent conventional dose regimen had a 53% reduction in the risk of less serious adverse effects in the comparison with those ones on the continuous conventional dose group (RR 0.47; 95% CI 0.26 to 0.83; participants = 60; studies = 1). The risk of less serious adverse effects was 31% lower in continuous low dose group while compared to continuous conventional dose group (RR 0.69; 95% CI 0.48 to 1.00; participants = 60; studies = 1). In the comparison with participants on intermittent conventional dose, the group who received continuous low dose isotretinoin had a risk 32% higher for less serious adverse effects but we are uncertain about this result because the confidence interval included 1 (RR 0.68; 95% CI 0.35 to 1.30; participants = 60; studies = 1). The quality of the evidence for the last three effects was very low due to serious imprecision of the effects, which had wide confidence intervals, and very serious limitations of design in the study (unclear risk of bias for selection and high risk of bias for performance and attrition). In an additional analysis of each less serious adverse event, the risk of dry, chapped lips was 53% lower with intermittent conventional dose when compared with continuous conventional doses. More

numbers in detail for each less serious adverse event are presented in Table 6.

Shetti 2013 compared low dose continuous oral isotretinoin with low dose intermittent oral isotretinoin for participants with moderate to severe acne. The study did not provide details of dose or duration of therapy. Also there was not an adequate report of numerical data related to less serious adverse effects.

Strauss 1984 compared doses of 0.1 mg/kg/d, 0.5 mg/kg/d and 1 mg/kg/d, for 20 weeks, for severe acne. There was no report of data related to the overall incidence of less serious adverse effects in each intervention group. We presented data from each less serious adverse event in Table 6.

Van der Meeren 1983 compared doses of 0.5 and 1.0 mg/kg/d for 12 weeks, for participants with severe acne. There was no difference between intervention groups regarding the overall frequency of less serious adverse effects (RR 1.00; 95 % CI 0.94 to 1.07; participants = 58; studies = 1). The quality of evidence was low due to very serious limitations of design in the study, which had unclear risk of bias for selection, performance, and detection and high risk of bias for attrition. Authors also reported that the average number of less serious adverse effects per participant was significantly higher (P = 0.002) with 1.0 mg/kg/d (6.4 events/participant versus 5.3 events/participant in the group with 0.5 mg/kg/d). The standard deviations for this assessment were not provided. Data from each less serious adverse event are presented in Table 6.

Secondary outcome: Dropout rates

Twelve trials assessed this outcome (Agarwal 2011; Ahmad 2015; Akman 2007; Corlin 1984; Cumurcu 2009; Dhaked 2016; Farrell 1980; Jones 1983a; Kapadia 2005; Lee 2011; Strauss 1984; Van der Meeren 1983). However, the data were heterogeneous (due to the large range of different doses and regimens which the studies had analysed) and it was not possible to pool them in meta-analyses.

In Agarwal 2011, by analysis of the six pairwise comparisons between the four intervention groups, ((a) continuous, 1 mg/kg/d; (b) alternate days, 1 mg/kg/d; (c) intermittent, 1 mg/kg/d for one week of each month; and (d) alternate days, 20 mg/d), there was no difference between them regarding dropout rates. All six estimates of effect are represented in Table 5, with the groups which had lower dropout rates in bold when there was a difference in the effect. We considered all these analyses as being of very low-quality due to the very serious limitations of design in Agarwal 2011 (high risk of performance, detection, and attrition bias) and serious imprecision of all six effects (wide confidence intervals). The study included participants with any degree of acne severity.

Ahmad 2015 and Kapadia 2005 reported no dropouts.

We made three pairwise comparisons involving the intervention groups of Akman 2007 ((a) conventional dose of 0.5 mg/kg/d for 10 days of each month, for six months; (b) 0.5 mg/kg/d for one month, followed by 0.5 mg/kg/d for the first 10 days of each month for five months; and (c) 0.5 mg/kg/d for six months). There was no difference between them regarding overall dropout rates. All three estimates of effect are presented in Table 5, and the groups which had lower dropout rates in each comparison are in bold when there was a difference in the effect. We considered the quality of the evidence from these three comparisons as being very low due to serious imprecision of the effects (wide confidence intervals) and very serious limitations of design in the study (unclear risk of bias for selection, performance, and detection, besides high risk of bias for attrition).

Corlin 1984 compared three daily doses (0.05 mg/kg, 0.1 mg/kg and 0.2 mg/kg) for 20 weeks in participants with severe acne. From analysis of the three possible pairwise comparisons between intervention groups, overall dropout rates were higher in the group on 0.05 mg/kg/daily when compared with both, 0.1 mg/kg/daily (RR 2.79; 95 % CI 1.35 to 5.75; participants = 191; studies = 1) and 0.2 mg/kg/daily (RR 3.89; 95 % CI 1.70 to 8.92; participants = 191; studies = 1). The quality of evidence for both effects was very low due to very serious limitations of design in the study (unclear risk of selection and detection bias and high risk of performance and attrition bias) and serious imprecision (both effects had a wide confidence interval). All three estimates of effect related to overall dropout rates, as other data regarding analysis of reasons for dropouts, are presented in Table 5.

There was no difference between participants receiving conventional daily dose (> 0.5 mg/kg) and those in the low daily dose group (< 0.5 mg/kg), both for 90 days, regarding overall dropout rates in Cumurcu 2009 (RR 1.04; 95% CI 0.07 to 15.74; participants = 26; studies = 1). The quality of the evidence was very low due to very serious limitations of design in the study (unclear risk of selection, performance, and detection bias and high risk of attrition and reporting bias) and serious imprecision of the effect (wide confidence intervals). Additional data from analysis of reasons for dropouts in this study are presented in Table 5.

In the study by Dhaked 2016, which compared isotretinoin 20 mg alternate days versus isotretinoin 20 mg/daily for moderate and severe acne for 24 weeks, there was twice the risk of dropout among participants on therapy with 20 mg alternate days; however, the confidence interval was wide and included 1 so we are uncertain about this result (RR 2.00, 95% CI 0.37 to 10.71; participants = 234; studies = 1). The quality of the evidence was very low due to the serious imprecision of the effect (wide confidence intervals) and the very serious limitations of design in the RCT, more specifically unclear risk of selection, performance, and detection bias and high risk of attrition bias.

Farrell 1980 reported two dropouts (2/14): one participant discontinued treatment due to hair loss and scalp desquamation (with no information about the intervention assigned) and one participant from isotretinoin 0.1 mg/kg/day (lowest dose) had a marked flare and was excluded.

Jones 1983a did not report detailed data related to dropouts from each one of the three intervention groups.

With data from the study by Lee 2011, which involved participants with moderate acne, we evaluated overall dropout rates by comparison of the three pairwise interventions: (a) continuous - daily intake - low dose (0.25 to 0.4 mg/kg/day); (b) continuous - daily drug intake - conventional dose (0.5 to 0.7 mg/kg/day); and (c) intermittent - stopping and starting intake often over a month - conventional dose (0.5 to 0.7 mg/kg/day for the first week in every four weeks). The quality of the evidence was very low due to serious imprecision of the three estimates of effect (which are presented in Table 5, with the groups which had lower dropout rates in bold when there was a difference in the effect) and very

serious limitations of design in the study, which had unclear risk of bias for selection and high risk of bias for performance and attrition. Also in Table 5, we presented data for the reasons for dropout in Lee 2011.

From Strauss 1984, we analysed overall dropout rates between the three intervention groups (0.1 mg/kg/d, 0.5 mg/kg/d, and 1 mg/kg/d, for 20 weeks, for severe acne) by pairwise comparisons. The three estimates of effect are presented in Table 5, with the groups which had lower dropout rates in bold when there was difference in the effect. We considered the quality of the evidence as being very low, as all three estimates of effect had wide confidence intervals (serious imprecision) and the study had very serious limitations of design (unclear risk of selection, performance, and detection bias and high risk of attrition and reporting bias).

Van der Meeren 1983 involved participants with severe acne and compared doses of 0.5 and 1.0 mg/kg/d for 12 weeks. Overall dropout rates were higher among participants receiving 1.0 mg/kg/day group but we are uncertain about this result as the confidence interval included 1 (RR 1.16; 95% CI 0.28 to 4.73; participants = 58; studies = 1). The quality of the evidence was very low due to serious imprecision of the effect (wide confidence intervals) and very serious limitations of design in the study, which had unclear risk of bias for selection, performance, and detection and high risk of bias for attrition. Additional data related to reasons for dropouts from Van der Meeren 1983 are presented in Table 5.

13. Standard oral isotretinoin versus other formulations of oral isotretinoin

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (after at least 16 weeks)

Two trials assessed this outcome (Strauss 2001; Webster 2014). In both studies, authors stated that the other formulations of oral isotretinoin had as their main advantage the fact that they were not food-dependent. The food-dependency of absorption is an attribute of standard isotretinoin. Strauss 2001 compared standard isotretinoin 0.85 to 1.18 mg/kg/d with micronised isotretinoin 0.32 to 0.4 mg/kg/d (for 20 weeks, for participants with severe acne). The decrease in mean total inflammatory lesion count was greater with the standard formulation (MD -1.5 lesion, 95% CI -2.96 to -0.04; participants = 492; studies = 1). We downgraded the quality of this evidence from high to very low (by three levels) due to very serious limitations of design in the study (high risk of attrition and reporting bias) and imprecision of the effect (wide confidence intervals). Webster 2014 compared isotretinoin-Lidose 1 mg/kg/d for 20 weeks with standard isotretinoin 0.5 mg/kg/d for the first 8 weeks, followed by 1 mg/kg/d until week 20, for participants with severe acne. There was no significant difference between the groups in terms of mean absolute decrease of facial and truncal nodule counts (16.4 with standard isotretinoin versus 16.8 with isotretinoin-Lidose; 95% CI = -0,22 to 0.64). The authors reported that 81% (332/410) of participants receiving standard isotretinoin obtained a 90% improvement in nodule counts versus 76.9% (310/403) of participants in the isotretinoin-Lidose group, but there was not a significant difference between the effects (RR 1.05, 95% CI 0.98 to 1.13; participants = 742; studies = 1). We considered this evidence as being of very low-quality (downgrade of three levels) due to very serious limitations of design in Webster 2014 (high risk of attrition bias and unclear risk of selection bias) and

serious indirectness, since the study analysed the primary efficacy outcome of this review by assessing a decrease in nodules only, not in all inflammatory types of acne lesions (papules plus pustules, nodules, and cysts).

Primary outcome: Frequency of serious adverse effects

Two studies assessed this outcome (Strauss 2001; Webster 2014). Strauss 2001 (n = 602) reported six serious adverse effects; however, they were considered as "remotely related" (two cases of appendicitis with standard isotretinoin) or unrelated to isotretinoin use (one accident and one worsened diabetes with standard isotretinoin, and one terminated pregnancy and one accident with micronised isotretinoin). The quality of the evidence was low due to very serious limitations of design in Strauss 2001, more specifically high risk of attrition and reporting bias and unclear risk of selection, performance, detection, and other bias. Webster 2014 (n = 925) reported one serious psychiatric adverse event (substance abuse) with isotretinoin-Lidose. The quality of this last analysis was low due to very serious limitations of design in the trial, more specifically high risk of attrition bias and unclear risk of selection bias.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

One trial assessed this outcome (Strauss 2001). Strauss 2001 found no difference in effects between both groups (after 20 weeks) in the proportion of participants with complete clearing or excellent improvement (almost clear) in acne severity: 91% (221/241) with standard isotretinoin and 90% (228/251) with micronised isotretinoin (RR 1.01, 95% CI 0.96 to 1.07; participants = 492; studies = 1) at 12 to 20 weeks after treatment. We downgraded the quality of this analysis by two levels, from high to low, due to the very serious limitations of design in the study (high risk of attrition and reporting bias).

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

Two trials assessed this outcome in participants with severe acne who received isotretinoin during 20 weeks (Strauss 2001; Webster 2014). There was no difference between the effect of standard isotretinoin and the other formulations, with high rates of participants with complete clearing or excellent improvement (almost clear) in acne severity after the therapy in both studies (RR 1.06, 95% CI 1.00 to 1.11; participants = 1274; studies = 2; I^2= 0%) (Analysis 3.1). The quality of this evidence was downgraded two levels, from high to low, due to the very serious limitations of design in both studies (high risk of attrition and reporting bias in Strauss 2001, and high risk of attrition bias in Webster 2014).

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

There were no available data for this outcome.

Secondary outcome: Frequency of less serious adverse effects

Two studies assessed this outcome (Strauss 2001; Webster 2014). In Strauss 2001, the overall frequency of less serious adverse effects during a 20-week therapy phase was similar for both formulations (micronised and standard isotretinoin) in participants with severe acne (RR 1.01; 95% CI 0.99 to 1.03; participants = 600; studies =1). The quality of the evidence was low due to

very serious limitations of design in the study (unclear risk of selection, performance, and detection bias, besides high risk of attrition and reporting bias). Webster 2014 reported a 4% lower risk of less serious adverse effects with standard isotretinoin in the comparison with isotretinoin-Lidose, for 20 weeks, for severe acne but the confidence interval included 1 (RR 0.96; 95% CI 0.91 to 1.02; participants = 925; studies = 1). The quality of evidence was low due to very serious limitations of design in the study (unclear risk of selection bias and high risk of attrition bias). We did not pool data from these studies due to substantial statistical heterogeneity (I² = 52%). Data related to each clinical or laboratory related less serious adverse event from both studies are in Table 3.

Secondary outcome: Dropout rates

Two studies, which compared different formulations of oral isotretinoin against the standard formulation during a 20-week therapy period, assessed the outcome (Strauss 2001; Webster 2014). Results from both were pooled in meta-analysis. The overall dropout rates were equal for standard isotretinoin and other formulations (RR 1.00, 95% CI 0.74 to 1.34; participants = 1527; studies = 2; I² = 37%) (Analysis 3.2), but there was heterogeneity. By analysing results from each study separately, there was 16% greater overall dropout rates with micronised isotretinoin than with standard isotretinoin but the confidence interval included 1 showing uncertainty (RR 1.16, 95% CI 0.83 to 1.63; participants = 600; studies = 1) (Strauss 2001); and a 14% lower risk of dropout with standard isotretinoin in the comparison with isotretinoin-Lidose, again with the confidence interval including 1 showing uncertainty (RR 0.86, 95% CI 0.63 to 1.19; participants = 925; studies = 1) (Webster 2014). Dropout rates due to adverse effects were 11% lower with standard isotretinoin than with other formulations but we are uncertain about this result as the confidence interval included 1 (RR 0.89, 95 % CI 0.56 to 1.43; participants = 1527; studies = 2; I² = 0%) (Analysis 3.2). Together, rates of dropouts due to loss to follow-up, non-compliance, or withdrawal of consent were 10% higher among participants on standard isotretinoin but since the confidence interval includes 1 we are uncertain of this result (RR 1.10, 95% CI 0.82 to 1.48; participants = 1527; studies = 2; I² = 0%) (Analysis 3.2). We downgraded the quality of evidence for all these five effects cited above from high to very low (by three levels) due to the very serious limitations of design in both studies (high risk of attrition and reporting bias in Strauss 2001, and high risk of attrition bias in Webster 2014) and the serious imprecision of the effects, which presented wide confidence intervals. Numbers in detail for dropouts are presented in Table 4.

14. Oral isotretinoin versus placebo

Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks)

There were no available data for this outcome.

Primary outcome: Frequency of serious adverse effects

No serious adverse effects were detected in participants from both included RCTs which compared oral isotretinoin with placebo: Peck 1982 (n = 33) and Rademaker 2013b (n = 60). The quality of the evidence was low due to very serious limitations of design in both trials: high risk of reporting bias, and also unclear risk of selection, performance, detection, and other bias in Peck 1982; high risk

of attrition bias and unclear risk of selection and other bias in Rademaker 2013b.

Secondary outcome: Improvement in acne severity assessed by participant's self-assessment of acne severity

One trial assessed this outcome (Rademaker 2013b). The study only reported that there was a statistical difference in favour of the isotretinoin group after 16 weeks (P = 0.03).

Secondary outcome: Improvement in acne severity assessed by physician's global evaluation

There were no available data for this outcome.

Secondary outcome: Changes in quality of life (QoL) assessed using a validated instrument

One trial assessed this outcome and compared oral isotretinoin 5 mg/day with placebo for 16 weeks in participants with low-grade acne (Rademaker 2013b). Investigators used the Dermatology Life Quality Index (DLQI), a validated questionnaire in which higher scores meant a worse quality of life, to assess the outcome. There was a greater decrease in mean DLQI score with isotretinoin after 16 weeks of therapy (MD -2.70, 95% CI -4.13 to -1.27; participants = 58; studies = 1). We downgraded the quality of this evidence from high to very low (three levels) due to very serious limitations of design in the study (high risk of attrition bias and unclear risk of selection bias) and serious imprecision of the effect (wide confidence intervals).

Secondary outcome: Frequency of less serious adverse effects

Two trials assessed this outcome (Peck 1982; Rademaker 2013b). Peck 1982 compared oral isotretinoin at a minimum of 0.5 mg/kg/d with placebo. At the monthly visit, participants who did not improve or had a mild worsening of acne had their doses of isotretinoin or placebo increased by 0.5 mg/kg/day. When there was intense worsening of acne in participants on placebo at this same time point of measurement, the investigators followed the study protocol and moved the participants to the isotretinoin group. There were no numerical details of the frequency of each adverse event observed at the first double-blind phase. Authors only reported the occurrence of mucocutaneous alterations, arthralgia, decreased appetite, fatigue, sunburn, raised liver function tests, and hypertriglyceridaemia among participants who received isotretinoin.

In Rademaker 2013b, there was a 4.31 times higher risk of a less serious adverse event among participants with low-grade acne receiving oral isotretinoin in comparison with participants in the placebo group after 16 weeks but the confidence interval was very wide and included 1 showing great uncertainty (RR 4.31; 95% CI 0.45 to 41.09; participants = 60; studies = 1). The quality of evidence was very low due to very serious limitations of design in the study (high risk of attrition bias and unclear risk of selection bias) and serious imprecision of the effect (wide confidence interval). The numbers in detail for each less serious adverse event are presented in Table 3.

Secondary outcome: Dropout rates

Two studies assessed this outcome (Peck 1982; Rademaker 2013b). Peck 1982 reported no dropouts. Rademaker 2013b reported 14 dropouts in overall and did not specify the number of dropouts by group. The reasons were loss to follow-up (n = 5), adverse effects

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(n = 2), not specified (n = 1), and temporary exclusion due to minor protocol violations (n = 8).

DISCUSSION

Summary of main results

This systematic review provided a comprehensive analysis of the best available evidence on efficacy and safety of oral isotretinoin for acne. We addressed concerns regarding external and internal validity of the 31 included RCTs in 3836 people. We considered oral isotretinoin versus oral antibiotics plus topical agents as the main comparison in this review.

Study participants ranged in age from 12 years to 55 years and in acne severity from mild to severe, although most participants had severe acne. There were twice as many male than female participants. Study duration was not clearly reported in most studies; based on those that did, the mean duration was 23 months.

Most of the included studies compared different doses or regimens of oral isotretinoin (a further two studies assessed standard oral isotretinoin against different formulations of oral isotretinoin), and about a quarter compared isotretinoin against antibiotics (with or without topical treatments). Two studies compared isotretinoin against placebo, one against a retinoid, and two assessed oral isotretinoin with versus without topical agents.

For our main comparison, there were only three RCTs (Gollnick 2001; Oprica 2007; Tan 2014), which involved 400 people with moderate and severe acne. None of the three trials had reported data specifically related to severe recalcitrant acne. From meta-analysis of the data from these three studies, we found the following very low-quality evidence related to the assessment of our primary outcomes, which had a very short-term follow-up (20 to 24 weeks of therapy) (outcome assessment was immediately at the end of treatment):

1. there was no difference between oral isotretinoin and oral antibiotics plus topical treatments regarding efficacy in clearing acne inflammatory lesions during therapy phase; and
2. isotretinoin led to one participant developing Stevens-Johnson syndrome, whereas no participants experienced serious adverse effects in the oral antibiotics plus topical treatment group (Summary of findings for the main comparison).

However, we are uncertain of these conclusions due to the very low-quality of this evidence, so these results neither support nor refute the common recommendation that oral isotretinoin is the most effective available acne treatment if administered for a mean period of 20 weeks. Our findings did not directly challenge recent acne therapy guidelines, where isotretinoin is a first-line medication for moderate to severe acne that does not respond to systemic antibiotic therapy plus topical therapy (Gollnick 2016; Nast 2010; Thiboutot 2009; Zaenglein 2016).

Findings related to two secondary efficacy outcomes of our review (improvement of acne at the end of the treatment measured by physician global evaluation of acne severity and frequency of less serious adverse effects) showed there may be higher efficacy of oral isotretinoin in the comparison with antibiotics plus topical agents, but more adverse effects of a less serious nature, such as severe or persistent skin symptoms, or both (e.g. dry lips, dry skin,

and cheilitis), and systemic events (e.g. vomiting and nausea) (low-quality evidence).

Due to lack of data from RCTs in the current literature, our review could not provide evidence related to either of our primary efficacy outcomes, or any other of our outcomes, in long-term follow-up.

Also, as none of the three included RCTs was restricted to participants with severe recalcitrant acne, uncertainties are still present regarding oral isotretinoin in improving acne severity and quality of life during the therapy phase and, especially, in long-term follow-up for this subset of acne participants.

When different doses/regimens of oral isotretinoin were assessed, three studies comparing different doses of isotretinoin measured the primary outcome 'Improvement in acne severity assessed by a decrease in total inflammatory lesion count'; this was done immediately after 20 to 24 weeks of therapy.

Two of these studies (304 participants with severe acne) compared three different doses and observed greater improvement with the higher dose (low-quality evidence). The third study (60 participants with moderate acne) compared three different doses and therapeutic regimens and showed that continuous (daily) low dose and continuous (daily) conventional dose improved acne more (low-quality evidence for both effects) than the intermittent regimen. Conventional dose reduced inflammatory lesion counts more than low dose; however, we are uncertain of this result because it was based on very low-quality evidence.

In the trials of different doses/regimens of oral isotretinoin, participants had moderate to (mainly) severe acne, although a small number had mild acne. There were no serious adverse effects in 14 trials (906 participants) that assessed safety outcomes (low-quality evidence); treatment duration lasted 12 to 32 weeks, with follow-up up to 48 weeks after treatment stopped. Severity of acne measured by a doctor was not assessed in this comparison. Thirteen trials (858 participants) analysed frequency of less serious adverse effects, such as skin dryness, hair loss, and pruritus. However, assessment of this outcome was very heterogeneous among the studies and this precluded evidence synthesis; this means we cannot draw certain conclusions (low- to very low-quality evidence, where assessed).

None of the 31 included RCTs reported birth defects but potential teratogenic effects are recognised as a limitation to use of oral isotretinoin.

Serious adverse effects reported by nonRCTs

Additionally, we made a qualitative synthesis from nonRCTs (cohort and case-control) with a focus on serious adverse effects, to assess serious adverse effects and controversies regarding isotretinoin safety, especially psychiatric outcomes and inflammatory bowel disease. Due to the low frequency of these outcomes, the inclusion of observational studies might constitute the best approach to explore them. These two serious safety outcomes have been the cause of concern among people with acne, clinicians, and decision-makers around the world. Numerous personal injury lawsuits, usually involving high costs and especially in the United States, have already claimed the association of either psychiatric or inflammatory bowel disease with oral isotretinoin use (Williams 2012).

Psychiatric disease

Among the uncertainties about the use of oral isotretinoin for acne, the UK DUETs highlights the possible association between oral isotretinoin and depression and suicidal behaviour in acne patients (DUETs 2010). This review found eight nonrandomised comparative studies (Azoulay 2008; Chia 2005; Cohen 2007; Jick 2000; Kaymak 2009; McGrath 2010; Ng 2002; Sundstrom 2010) that evaluated psychiatric safety issues in participants with acne who had used oral isotretinoin. Table 2 presents data from these nonRCT studies and also a qualitative synthesis we conducted by applying an extension for nonrandomised studies to the Cochrane's 'Risk of bias' tool, according to the report by Turner 2013. Interestingly, in one of eight nonRCTs included in this review, there was a significant reduction of the level of depression within the oral isotretinoin group when compared with those on topical therapy (Kaymak 2009). One retrospective case-control study found that exposure to isotretinoin within five months immediately prior to the first diagnosis or hospitalisation for depression was significantly higher than in a five-month control period (Azoulay 2008). However, most of the nonRCTs did not find a significant difference in the frequency of depression between oral isotretinoin and other active oral or topical treatment (Chia 2005; Cohen 2007; Jick 2000; McGrath 2010; Ng 2002; Sundstrom 2010). Among these eight nonRCTs, two assessed frequency of suicide and did not find a significant difference between the groups (Jick 2000; Sundstrom 2010). All the nonRCTs, the cohorts and case-control studies assessing depressive outcomes, were at high risk of bias for at least one criteria of the internal validity assessment. This fact reduced the quality rating of this body of evidence to very low, as nonRCTs start as low-quality evidence according to the approach of The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (Guyatt 2011).

Inflammatory bowel disease

There was no case of Inflammatory bowel (IBD) disease reported in the 26 RCTs included in this review. From the additional search for nonrandomised studies on adverse effects, and also from references from our searching for RCTs, we found six nonrandomised controlled studies on oral isotretinoin and the risk of inflammatory bowel disease (Alhusayen 2013; Bernstein 2009; Crockett 2010; Etminan 2013; Racine 2014; Rashtak 2014). Among these studies, Crockett 2010 found a significant association between oral isotretinoin and ulcerative colitis (but not Crohn's disease), and Alhusayen 2013 detected an association between oral isotretinoin and IBD in participants aged 12 to 19 years only after a prespecified subgroup analysis by age. However, in all other four studies (Bernstein 2009; Etminan 2013; Racine 2014; Rashtak 2014), there was no increased occurrence of IBD associated with the use of oral isotretinoin. Instead, in Rashtak 2014, there was a decreased risk of IBD with isotretinoin exposure; and in Racine 2014, isotretinoin use was associated with a lower risk of ulcerative colitis. We did not assess risk of bias, nor the quality of evidence for these studies on oral isotretinoin and IBD.

We did not find reports of any other serious adverse effect among nonrandomised studies analysed within the additional screening process.

Overall completeness and applicability of evidence

Our review has limitations in terms of its external validity, and these relate to the following:

1. scarcity of data related to some types of participants, such as very young adolescents (our results related to people from 12 to 55 years) and people with truncal or recalcitrant acne;

2. few studies addressing both our primary efficacy outcomes, "improvement in acne severity assessed by a decrease in total inflammatory lesion count", and participant-reported outcomes, such as "improvement in acne severity" assessed by the participant's self-assessment, as well as "changes in quality of life";

3. very few studies focused on our main comparison, oral antibiotics plus topical agents versus oral isotretinoin, and also there was low-quality data from studies on the comparison of different doses or regimens of oral isotretinoin; and

4. most of the evidence was supported by data from short-term follow-up.

The included studies overall had a very short follow-up period (the mean being 26.5 weeks after the end of the therapy phase), precluding a long-term evaluation of efficacy outcomes.

Approximately a third of included studies addressed our primary outcome "improvement in acne severity". The secondary efficacy outcome, "improvement in acne severity", evaluated by participant self-assessment, was measured in only four included RCTs, and only two studies assessed changes in quality of life using a validated instrument.

Daily low dose and intermittent regimens of therapy with oral isotretinoin, which might be safer for patients, have been frequently adopted to treat not only severe, but also moderate and mild acne (Zaenglein 2016). We found 14 RCTs that compared different doses or regimens of oral isotretinoin. Once again, it was not possible to pool the data and produce more robust evidence to answer this question. There was either insufficient reporting of data or great heterogeneity regarding doses and regimens, to an extent that grouping their data would not produce clinically sensible results. Only one from these 14 studies provided data on our primary efficacy outcome in an adequate way to make possible a measurement of the effect (Lee 2011), and also only one of these 14 RCTs included participants with mild acne (Agarwal 2011).

According to the UK DUETs (DUETs 2009), one of the concerns raised by professionals dealing with acne is the true benefit of early intervention with oral isotretinoin versus alternative treatments for moderate or mild acne. As a result of the lack of evidence derived from RCTs, this review could not provide an answer to this question either.

Regarding the frequency of less serious adverse effects, there was considerable heterogeneity in the means of monitoring, assessing, and measuring the clinical and laboratory adverse effects among included RCTs. This fact precluded pooling of data from specific types of less serious adverse effects, such as the mucocutaneous alterations or arthralgia, for example. The available data could not provide any evidence related to long-term adverse effects that were possibly related to oral isotretinoin, another concern that is very often raised among acne patients (DUETs 2007). Although all but two of the included studies assessed the frequency of serious (our primary safety outcome) or less serious (our secondary safety outcome) adverse effects in the short-term, and all but three of the studies addressed dropout rates, the quality of the evidence meant we could not draw firm conclusions.

Furthermore, we could not provide any evidence on the effect of oral isotretinoin in specific subgroups, such as very young adolescents or people with truncal acne or more severe recalcitrant disease (including severe recalcitrant nodular acne), i.e. those that represented subgroups that seem to have the poorest response to the drug and are more likely to relapse (Nast 2010). Also, all included RCTs were carried out in dermatology clinics, which could limit the extension of findings to different settings, such as those visiting general clinicians.

According to the UK Database of Uncertainties about the Effects of Treatments (DUETs), one of the gaps in scientific knowledge about oral isotretinoin for acne is the comparison between the use of low dose rather than standard dose (DUETs 2011). Also, alternatives to the daily prescription of oral isotretinoin for acne have become more frequent in clinical practice due to the serious safety concerns related to the drug which have been specially discussed in the last decade in both the general and scientific media. In this review, we analysed different doses/therapeutic regimens of oral isotretinoin. Two studies (both from the 1980s, out of 12 RCTs that were from the 80s; these older studies evaluated and presented efficacy and safety outcomes in a very heterogeneous way) compared different daily doses during 20 weeks for participants with severe acne. However, these studies could not provide a reliable measurement of the effect due to both large attrition bias and lack of numerical data (Corlin 1984; Strauss 1984). In a more recent trial involving 60 people, Lee 2011 compared three different therapeutic regimens for 24 weeks (continuous low dose (0.25 to 0.4 mg/kg/day), continuous conventional dose (0.5 to 0.7 mg/kg/day) and intermittent dose (0.5 to 0.7 mg/kg/day, first week in every 4 weeks)); the study found low- and very low-quality evidence, respectively, of: 1) higher decreases in inflammatory lesion counts after 24 weeks with both continuous regimens (conventional and low dose) when each one of them were compared with the intermittent regimen; and 2) greater effect of continuous conventional dose than continuous low dose in reducing total inflammatory lesion count at 24 weeks of therapy.

Quality of the evidence

For our seven different primary and secondary outcomes, the quality of evidence ranged from moderate to very low. A downgrade of at least one level, from high to moderate quality according to GRADE, was present in all effects we analysed due to serious limitations of design in the included studies. This review included 31 RCTs, which involved a total of 3836 participants, and all these trials presented unclear or high risk of bias for at least two of the seven domains of risk of bias analysed by Cochrane's 'Risk of bias' tool (Figure 3). Over half the trials were at high risk of attrition bias, and presented an important potential impact of missing data on effect estimates. Additionally, for most outcomes, we downgraded by one more level the quality of the evidence, from low to very low, due to serious imprecision of the effects caused by the wide confidence intervals which included the clinically relevant difference of 25% between interventions as well as no clinically relevant difference between the interventions. Due to indirectness, we downgraded by one level the evidence related to our primary efficacy outcome and the main comparison of the review, oral isotretinoin versus oral antibiotic plus topical agents: in two of the three included RCTs, the outcome was assessed by counting only one or two types of inflammatory acne lesions, not all of them (Summary of findings for the main comparison). It was not

possible to address publication bias in our review due to the low number of studies contributing to each of our estimates of effect; no measurement in this review has included data from more than three RCTs. The very low-quality body of evidence identified by this review did not allow a robust and definitive conclusion about the true efficacy and safety of oral isotretinoin, i.e. we still have uncertainty about all the effects of oral isotretinoin for acne.

Potential biases in the review process

Potential bias might emerge from any differences between our previous published protocol (where we prespecified the research question and inclusion criteria for studies) and this review, but we clearly described these minor deviations from our protocol in the Differences between protocol and review section. The application of the GRADE system (Guyatt 2011) to evaluate the quality of evidence related to each effect measured by our review was not prespecified in our protocol. In fact, Cochrane methodology did not incorporate GRADE assessments until after our protocol publication. To avoid any potential bias related to study selection, we had all articles written in other languages translated to English during the screening process, and before the decision regarding eligibility. Two of us independently screened references and assessed the studies for eligibility, which also occurred in the processes of data extraction and evaluation of risk of bias of the included studies. A third opinion from a different author resolved disagreements during the study selection, data extraction, and 'Risk of bias' assessment. Despite not having designed a funnel plot to assess the likelihood of publication bias of the included studies, we adopted other procedures to avoid any potential bias in our review process due to this issue, such as performing a comprehensive search for ongoing studies and handsearching conference proceedings. We also made efforts to obtain unpublished protocols and additional data from all of our included RCTs, especially from those ones for which we detected a high risk of reporting bias. Potential bias could rise from our results and assessments of quality related to included RCTs that had poor reporting of data. When relevant data were missing or poorly presented, we clearly described this within our review sections. Also, the absence of planned subgroup analyses to investigate heterogeneity in our review could be seen as a source of bias. However, as we have explained in the Differences between protocol and review section, the scarcity of data from included studies did not allow us to perform subgroup analyses regarding severity of acne, treatment duration, level of improvement in acne severity, age, and gender.

Agreements and disagreements with other studies or reviews

We identified only one non-Cochrane systematic review (Lehmann 2001), which had assessed the efficacy and safety of oral isotretinoin for acne in clinical trials. In Lehmann 2001, authors stated that methodological limitations, multiple treatments, and heterogeneity regarding assessment of outcomes precluded quantitative data synthesis from the trials on oral isotretinoin versus other anti-acne therapies, placebo, or itself in different doses, and this fact limited their conclusions. We have also found the same limitations in our analysis of our included RCTs that were also analysed by Lehmann. The review by Lehmann 2001, however, presented only a narrative summary of the results from trials and did not provide estimates of effect measures related to outcomes from the trials. None of the trials included in the review by Lehmann

2001 reported birth defects, and this finding is consistent with our findings. The review, a publication on the management of acne from a governmental agency, was available for historical reference only, since it was never updated. Lehmann 2001 was systematically reviewed, but lacked risk of bias assessment for each included study and clear criteria for quality of evidence assessment. Also, there were no prespecified outcomes; the searches for clinical trials did not address studies in languages other than English, and nonrandomised controlled clinical trials were included.

A Cochrane review, Garner 2012, assessed the efficacy and safety of oral isotretinoin in comparison with oral minocycline for acne and, consistent with our review, found that isotretinoin was equivalent to minocycline plus topical azelaic acid in reducing acne inflammatory lesion counts after 24 weeks of treatment. Garner 2012 also found isotretinoin was associated with less serious adverse effects than minocycline after four weeks of therapy. We also found four guidelines on acne management published in the last ten years (Gollnick 2016; Nast 2010; Thiboutot 2009; Zaenglein 2016). These studies did not perform a systematic and thorough extraction of data, nor assessment of quality of the evidence which supported their recommendations, as we have done in applying the GRADE guidelines (Guyatt 2011) in this review.

Four Cochrane reviews on interventions for acne (Arowojolu 2012; Barbaric 2016; Cao 2015; Garner 2012) commented on the considerable heterogeneity in measurement of efficacy outcomes related to acne among the available randomised trials, consistent with our findings. These reviews detected few studies which evaluated participant-reported outcomes and quality of life, a fact which we have also noted.

We retrieved three systematic reviews of the literature (Kontaxakis 2009; Magin 2005; Marqueling 2005) which addressed the concern of the association between oral isotretinoin for acne and psychiatric symptoms. The three studies concluded that, based on the best available evidence, it was not possible to establish a definitive causal relationship. This is consistent with the findings of our additional search for serious adverse effects in nonRCTs studies (nonrandomised clinical trials, cohorts, and case-control), but we are uncertain of the validity of this data as it is very low-quality evidence. However, none of these reviews reported prespecified outcomes, nor performed quality assessments of the evidence according to clear and well-defined criteria. In Magin 2005, the search was restricted to studies in English. There was no clear description of the study selection process in the reviews by Kontaxakis 2009 and Magin 2005. We found two meta-analyses of population studies on oral isotretinoin and inflammatory bowel disease (IBD) (Etminan 2013; Lee 2016). Both had addressed the same six studies we retrieved in our review and concluded that there was no evidence of any association between oral isotretinoin and occurrence of IBD. Lee 2016 had restricted searching and selection to articles in English. In Etminan 2013, the searches for studies in databases were restricted to the period from 2000 through May 2012. Both studies (Etminan 2013; Lee 2016) did not report prespecified outcomes.

Despite consensus recommendation for avoidance of the use of topical anti-acne treatment together with isotretinoin (Gollnick 2016), as this may potentiate the occurrence of mucocutaneous side effects of oral isotretinoin, two of our included RCTs analysed benefits and harms of oral isotretinoin together with anti-acne topical agents to treat moderate and severe acne (Dhir 2008; Faghihi 2014). Neither of these two studies assessed our primary efficacy outcome. There was no serious adverse event in participants from either trial (low-quality evidence).

Systemic antibiotics as monotherapy are not recommended and also do not seem to be a usual option in clinical practice (Gollnick 2016; Nast 2010; Thiboutot 2009; Zaenglein 2016). However, five included trials of this review, with 244 people, compared oral isotretinoin to tetracycline (Lester 1985), minocycline (Pigatto 1986), dapsone (Prendiville 1988), azithromycin (Wahab 2008), and erythromycin (Jones 1983b); four of them did not provide data for our primary efficacy outcome. From one RCT, which involved 30 participants (Lester 1985), we found very low-quality evidence that isotretinoin produced a greater improvement in acne severity than tetracycline on follow-up assessment at 16 and 24 weeks, after a 16 weeks of therapy. Regarding harms, there were no serious adverse effects among participants on either oral isotretinoin or oral antibiotics in these five trials (low-quality evidence).

The classical indication for the use of oral isotretinoin since its launch on the market remains in moderate to severe acne that does not respond to the combination of oral antibiotic plus topical agents. The superiority of oral isotretinoin in achieving a prolonged remission, and even a cure, of more severe cases is a well-accepted concept among dermatologists around the world (Gollnick 2016; Nast 2010; Thiboutot 2009; Zaenglein 2016). Due to design limitations in the three RCTs that investigated the main comparison of our review (Gollnick 2001; Oprica 2007; Tan 2014), our findings demonstrate a lack of high-quality RCT support for this view in acne management. Our findings do not challenge this view either, and our findings do not challenge current treatment approaches in acne.

AUTHORS' CONCLUSIONS

Implications for practice

The current recommendation of clinical guidelines that oral isotretinoin should be the first-line treatment for moderate to severe acne unresponsive to previous therapies, being more effective than the use of oral antibiotics plus topical agents, underpins current dermatological practice. The findings of this review do not challenge that recommendation. However, the low- or very low-quality evidence means that the clinical trials in this area are not able to more precisely define the role of isotretinoin in practice. Unfortunately, due to the scarcity of data, and mainly short-term follow-up of the randomised controlled trials (RCTs), this review does not provide a definitive evidence-based conclusion about the efficacy and safety of oral isotretinoin in the two most clinically important comparisons for acne treatment (oral isotretinoin compared with oral antibiotics plus topical agents for acne, and different doses/regimens of oral isotretinoin).

Regarding the best dose regimen, together with daily or intermittent use of oral isotretinoin, the three included studies were too heterogeneous with respect to isotretinoin doses.

Due to very low-quality evidence, RCTs do not provide certainty about how much oral isotretinoin improves acne severity assessed by a decrease in total inflammatory lesion count or whether isotretinoin increases the frequency of serious adverse effects when compared with oral antibiotics plus topical agents for acne. Based on low-quality evidence, isotretinoin may slightly improve acne

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severity assessed by physician's global evaluation, but it may lead to more less-serious adverse effects, such as local events (severe or persistent skin symptoms, or both, such as dry lips, dry skin, and cheilitis) and systemic events (vomiting and nausea).

When using different doses/regimens of oral isotretinoin, there was low-quality evidence that a higher continuous dose may improve acne severity when compared to a lower or intermittent dose, with no serious adverse effects found. Severity of acne measured by a doctor was not assessed in this comparison. It was not possible to synthesise evidence regarding the frequency of less serious adverse effects due to heterogeneity in the assessment of this outcome, so we are uncertain if there are differences between the dosing groups. Events reported included skin dryness, hair loss, and pruritus (low- to very low-quality evidence, where assessed).

We have scarce RCT evidence about the effects of oral isotretinoin against the following: placebo, oral etretinate, and oral isotretinoin associated with topical agents.

The very low-quality of the evidence (from all RCTs and nonRCTs) did not allow a definitive conclusion about a higher risk of psychiatric outcomes, including suicide attempts and inflammatory bowel disease associated with oral isotretinoin use.

Implications for research

Although we have not identified strong RCT evidence to support the current role of oral isotretinoin in clinical practice, we have not identified any RCT evidence which challenges current practice. Due to the lack of evidence, some questions related to the use of oral isotretinoin for acne still need to be clarified in further studies that fulfil the following characteristics:

- more robust sample sizes to allow: the observation of rare, but serious adverse effects; and subgroup analyses considering issues such as severity of acne (mild, moderate, and severe), affected areas (face or trunk, or both), age and gender;
- longer duration and follow-up to assess long-term effects (benefits and harms);
- standardisation of the best primary outcome, especially regarding the time points of outcome measurements; and
- adherence to the CONSORT guideline providing recommendations for clinical trials in order to improve the quality of research and guide decision making (Schulz 2010).

With the aim of providing reliable physician guidelines and a robust evidence-based support for daily clinical practice in acne therapy, future randomised clinical trials on oral isotretinoin for acne should focus on treatment of acne when there is insufficient response to therapy with oral antibiotics plus topical agents. To achieve more reliable results, trials should restrict their inclusion criteria to participants with moderate to severe acne from all ages (enabling subgroup analysis, such as assessment of very young adolescents), and genders; and assess the efficacy and safety of both therapies monthly during the treatment and for at least a one-year follow-up period. Future studies should be conducted in multiple settings, to ensure applicability of findings.

Assessment of different doses/regimens constitutes another important area of research related to oral isotretinoin for acne. In this case, randomised trials with a high number of participants presenting any degree of acne severity would be important to make clear the optimal dose/regimen, while taking into account safety concerns related to oral isotretinoin. RCTs on different doses/regimens of oral isotretinoin would also clarify issues regarding the best total cumulative dose according to acne severity.

Primary efficacy outcomes in further RCTs on oral isotretinoin must be based on the improvement of total inflammatory lesion counts, a more objective measure of clearing from acne than investigator's assessments of improvement measured by scales or by their subjective impressions. As acne has an important psychosocial impact, participant's assessment of the disease improvement and changes in quality of life should also be among efficacy outcomes in future trials on oral isotretinoin for acne. In addition, the nature and frequencies of adverse effects must be assessed and reported in a clear and pre-standardised way, following directions from the CONSORT Statement (Ioannidis 2004; Schulz 2010). Also, the use of a uniform terminology in the evaluation and report of safety outcomes in acne trials, as recommended in MedDRA (Medical Dictionary for Regulatory Activities) (MedDRA 2016), should be adopted in future RCTs on oral isotretinoin for acne, as another effort to facilitate extraction, pooling, and replication of data from these studies. This applies, especially, to data related to less serious adverse effects of oral isotretinoin.

According to the recommendations of the CONSORT Statement (Schulz 2010), a clear description of the efforts to ensure random and concealed allocation of participants in further RCTs on oral isotretinoin for acne may reduce much of the downgrading of evidence found in our review. Also, an adequate and detailed report of all prespecified outcomes in the published protocol study can minimise the risk of reporting bias in future RCTs. The peculiar nature of mucocutaneous adverse effects related to oral isotretinoin use promotes difficulties in blinding of participants, personnel, and outcome assessors in clinical trials, a fact which is well recognised among acne researchers.

However, these concerns may not be used as a rationale for an absence of blinding of outcome assessment in further trials. Future technology, such as a specific computer software which makes the assessment of core acne outcomes more objective, may help (Min 2013). Also, future RCTs on acne should describe in detail all missing data, with the reasons for losses, besides adopting an adequate intention-to-treat analysis.

Nowadays, there are research groups working on the well recognized and well described issue of lack of standardised outcome measures and methodological practices in RCTs on acne therapy (Arowojolu 2012; Barbaric 2016; Cao 2015; Garner 2012). The Cochrane Skin Group Outcomes Research Initiative (CSG-COUSIN, Schmitt 2016) and the Acne Core Outcomes Research Network (ACORN) (ACORN 2013) may guide acne outcome assessments in RCTs and help to increase the quality of the evidence from future research on acne therapy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agarwal 2011

Methods	Parallel design, randomised controlled trial
Participants	120 participants from a single centre, Department of Skin, STD, and Leprosy in SMS Medical College and Hospital, Jaipur - India.
	Inclusion criteria: patients with mild (few to several papules/pustules with no nodule), moderate (several to many papules/pustules with few to several nodules), or severe acne vulgaris (numerous and/or extensive papules/pustules with many nodules).
	Exclusion criteria: pregnant females, married females desiring to get pregnant or using temporary methods of contraception, patients having family and/or personal history of hyperlipidaemia or diabetes, and those having drug-induced acne.
	Age: for all participants, mean 18.95 years (range 14 - 26, median 19)
	Gender: male - 66 participants; female - 46 participants
	Duration of acne: not provided
	Acne severity: mild - 37 participants; moderate - 38 participants; severe - 37 participants
Interventions	Four different treatment regimens each consisting of 30 participants and lasting 16 weeks.
	• Group A was prescribed isotretinoin 1 mg/kg/day;
	• Group B was prescribed 1 mg/kg alternate day;
	• Group C was prescribed 1 mg/kg/day for one week/four weeks;
	• Group D was prescribed a fixed low dose regimen of 20 mg every alternate day.
	Along with oral isotretinoin, all participants were also given oral azithromycin 500 mg once a day 1 hour before meals for three days a week for three weeks. All participants were also advised to apply topical 1% clindamycin phosphate cream twice daily.
Outcomes	• Improvements in acne severity were recorded at two-weekly intervals for 24 weeks by measuring total acne load, which was calculated on the basis of Definition Severity Index (Lidén 1980).
	• Laboratory assessments (complete blood cell counts, liver function tests, and serum lipid profile) done initially and repeated at four-weekly intervals for 16 weeks*.
	• Frequency of side effects were recorded at two-weekly intervals for 24 weeks*.
	• Failure of treatment, which was defined as no improvement in lesions, requiring subsequent increase in isotretinoin dosage, or even additional treatment at the end of 16 weeks of treatment.

Agarwal 2011 *(Continued)*

- Relapse of acne considered as the emergence of near pretreatment severity of acne in the treated participant within eight weeks of post-therapy follow-up.

* Indicates outcomes which matched those prespecified for this review

Funding body	None stated
Notes	Age, gender, and acne severity data were provided only for the whole 112 participants who completed the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised by stratified randomisation method..." Comment: Despite the mention of stratified randomisation in the report, authors clarified by personal communication to us (email) that they actually adopted a simple (rather than stratified) randomisation process in each stratum (mild, moderate, and severe). Participants in each stratum picked one of the shuffled cards, which were in four different colours. Each one of the four available colours were linked to one of the four intervention groups
Allocation concealment (selection bias)	Low risk	Comment: By personal communication to us, authors described a pharmacy-controlled randomisation (an independent pharmacy prepared the drug containers, which were of identical appearance for all interventions groups, as were the capsules, all from the same brand). It was likely the allocation was concealed via the randomisation method used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: By personal communication to us, authors described an open design.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: By personal communication to us, authors described an open design, with no blinding of outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 120 patients with a mean age of 18.95 years (range 14 - 26, median 19) were included in the present prospective study... For final result analysis, there were 112 patients as described in the flowchart." Comment: The level of loss to follow-up could be a source of bias. Furthermore, the trial reported a 'per-protocol' analysis, which did not consider data from loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section.
Other bias	High risk	Quote: "Along with oral isotretinoin, all patients were also given oral azithromycin 500 mg once a day 1 hour before meals for three days a week for three weeks. All the patients were also advised to apply topical 1% clindamycin phosphate cream twice daily." Comment: There was a high risk of bias due to an inappropriate administration of a co-intervention. Concomitant treatment with an oral antibiotic plus a topical antibiotic applied to all four intervention groups might underestimate the potential higher risk of acne flare (an adverse effect) on the first weeks of therapy among participants on higher isotretinoin doses.

Ahmad 2015

Methods	Parallel design, randomised clinical trial
Participants	58 participants from a single centre, Department of Dermatology and Venereology, Faculty of Medicine, Minia University, Minia, Egypt
	Inclusion criteria: participants stopped any acne treatment 1 week before starting oral isotretinoin
	Exclusion criteria: female participants who are or might become pregnant during treatment, lactating mothers, participants with pre-existing liver disease, abnormal liver function test, or hyperlipidaemia, participants with acne conglobata and acne fulminans
	Age: 12 to 39 years (median 20 years; mean and SD of 22.12 ± 7.05)
	Gender: 15 males, 43 females
	Duration of acne: not available
	Acne severity: mild (6), moderate (13), severe (31), very severe (11)
Interventions	All participants received oral isotretinoin at a dose of 0.5 – 1.0 mg/kg/day. During the initial month of treatment, only half of the anticipated maintenance dose was given to avoid acne exacerbation, as previously recommended.
	• Group I (n = 26): full dose of oral isotretinoin once daily after breakfast
	• Group II (n = 32): twice daily divided dose of oral isotretinoin after meals (breakfast and dinner)
	The median starting dose during the first month of treatment was 30 mg/day (mean = 28.4 ± 4.8), whereas the median maintenance dose thereafter was 60 mg/day (mean = 55.6 ± 10.9). Participants received a median total cumulative dose of 126.1 mg/kg body weight (mean = 126 ± 22.5) and the median duration of treatment was 22 weeks (mean = 21.40 ± 3.73).
Outcomes	• Global acne scoring (GAS) system was used to objectively classify acne cases included in the study into mild (score 1–18), moderate (score 19–30), severe (score 31–38), and very severe (score >39)[*].
	• Participants' tolerability.
	• Adverse effects - The National Cancer Institute Common Terminology Criteria for Adverse Events were used to delineate laboratory adverse effects[*].
	Serum cholesterol, triglycerides, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were evaluated before and 3 months after starting treatment.
	[*] Indicates outcomes which matched those prespecified for this review
Funding body	No information available
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: The trial did not provide any information about allocation concealment

Ahmad 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: The study compared single versus divided daily dose of oral isotretinoin and did not use a placebo for blinding purpose
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: The study compared single versus divided daily dose of oral isotretinoin and did not use a placebo for blinding purpose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There were no losses
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Low risk	Comment: No other risk of bias was found

Akman 2007

Methods	Parallel design, randomised controlled trial
Participants	66 participants from multiple centres in Turkey (number of centres was not stated) Inclusion criteria: acne with the FDA global grade 2 (moderate) and 3–4 (severe); participants with acne who had not responded to conventional antibiotic therapy or who had rapidly relapsed after conventional treatment Exclusion criteria: acne conglobata, acne fulminans, or systemic disorders requiring any treatment Age: by group, mean ± standard deviation (years). • Group 1 (n = 22): 22.73 ± 5.5 • Group 2 (n = 19): 19.95 ± 7.3 • Group 3 (n = 19): 19.95 ± 4,8 Gender: 23 male/37 female • Group 1: 8/14 • Group 2 : 10/9 • Group 3 : 5/14 Duration of acne: not provided Acne severity: 29 moderate/31 severe • Group 1: 11/11 • Group 2: 10/9 • Group 3: 8/11
Interventions	• isotretinoin 0.5 mg/kg/day for 10 days of each month, for six months (n = 22) • isotretinoin 0.5 mg/kg/day for one month, followed by 0.5 mg/kg/day for the first 10 days of each month for 5 months (n = 19) • isotretinoin 0.5 mg/kg/day for six months (n = 19)

Akman 2007 *(Continued)*

Outcomes	• Acne grading, assessed by FDA global grade (Cunliffe 2003), at the baseline, afterwards, every month during therapy, and every 3 months for a 12-month follow-up period. Only facial lesions were taken into consideration[*].
	• Side effects at weeks 2, 4, 8, 12, 16, 20, and 24[*]. Each side effect was evaluated by physicians on a 4-point scale as none (0), mild (1), moderate (2) or severe (3).
	• Side effects scored by the participants using a 10 cm visual analogue scale (VAS), ranging from none to extremely noticeable on a weekly basis during the treatment
	• Liver function tests and fasting lipids evaluated at the baseline, and afterwards, monthly during the treatment[*]
	[*] Indicates outcomes which matched those prespecified for this review
Funding body	Akdeniz University Scientific Research Projects Unit
Notes	Age, gender, and acne severity data were provided only for participants who completed the study in each group. Besides this, there was a difference in the numerical data of males and females in each group between the results section of the main text and Table 1 presented in the report. Authors provided the correct data to us by personal communication (email).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "This was a multicenter, randomised and controlled study consisting of 66 patients... Six patients failed to continue the follow-up." Comment: The level of loss to follow-up could lead to a considerable attrition bias. Furthermore, the trial presented a 'per-protocol' analysis, which did not consider data from loss to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however there was an adequate report of outcomes listed in methods section
Other bias	Low risk	Comment: There were no other apparent sources of bias

Corlin 1984

Methods	Parallel design, randomised controlled trial
Participants	191 participants from multiple centres (14 Departments of Dermatology) in Germany

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Oral isotretinoin for acne (Review)

Corlin 1984 *(Continued)*

Inclusion criteria: diagnosis of severe papulopustular acne which was untreatable with ordinary methods

Exclusion criteria: not stated

Age: 21 years (mean) – range 14 to 42 years

Gender: 148 male/43 female

Duration of acne: not provided

Acne severity: all participants had severe papulopustular acne

Interventions	- Intervention 1 (n = 64): oral isotretinoin 0.05 mg/kg/day - Intervention 2 (n = 62): oral isotretinoin 0.1 mg/kg/day - Intervention 3 (n = 65): oral isotretinoin 0.2 mg/kg/day All three interventions were given for 20 weeks.
Outcomes	- Lesion count of all acne lesions, inflammatory and non-inflammatory[*] - Intensity of seborrhoea graded by a scale - Adverse effects[*] - Laboratory measurements[*] All clinical outcome measurements were recorded at baseline, every 2 weeks and, after 3 months, every 4 weeks until the end of the treatment. Laboratory parameters were assessed at baseline, 4, 12, and 20 weeks. [*] Indicates outcomes which matched those prespecified for this review
Funding body	Hoffmann-La Roche AG
Notes	Both reports of this study were in German and data were extracted by a German member of the Cochrane Collaboration indicated by Cochrane Skin Group One author worked at Hoffmann-La Roche AG, Grenzach-Wyhlen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: The study had an open design, with participants and personnel aware of the treatment arm to which participants were allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The study had an open design. However, there was no information regarding blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: The trial reported a 'per-protocol' analysis for clinical efficacy outcomes. All randomised participants (191) were considered in the analysis of laboratory alterations and adverse effects. However there was a considerable level of losses to follow-up, which could underestimate differences regarding

Corlin 1984 *(Continued)*

		adverse effects between groups, as participants who were lost-to follow up earlier could have a higher number of adverse effects if they had received the interventions during the whole period of therapy (20 weeks).
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was sponsored and promoted by a pharmaceutical company

Cumurcu 2009

Methods	Parallel design, randomised controlled trial
Participants	51 participants from a single centre, Department of Dermatology, Gaziosmanpasa, a University School of Medicine in Turkey
	Inclusion criteria: participants with acne vulgaris who had laboratory and routine physical examination results within the normal limits
	Exclusion criteria: systemic hypertension; coronary arterial disease; familial hyperlipidaemia; diabetes mellitus; renal or hepatic functional disorders; severe osteoporosis or severe pulmonary, gastrointestinal, or hematologic problems; having dry eyes, intolerance to contact lenses, or clinical blepharoconjunctivitis during the pretreatment ophthalmologic assessment
	Age: mean ± standard deviation (years)
	• Group 1 (n = 26): 26.92 ± 5.42 • Group 2 (n = 25): 28.52 ± 7.22
	Gender: 20 male/31 female
	• Group 1: 10/10 • Group 2: 15/16
	Duration of acne: not provided
	Acne severity: not provided
Interventions	• Group 1 (n = 26): oral isotretinoin, in a high dose regimen, > 0.5 mg/kg/day • Group 2 (n =25): oral isotretinoin, in a low dose-regimen, < 0.5 mg/kg/day
	Duration of treatment not stated
Outcomes	• Tear film stability evaluated by fluorescein break-up time test (BUT) • Tear basal secretion assessed by anaesthetised Schirmer's I-test • Conjunctival *Staphylococcus aureus* colonization assessed by cultures of samples taken from the lower palpebral fornix of the conjunctiva • Ocular adverse effects related to oral isotretinoin detected by a complete bilateral ophthalmologic examination[*] • Subjective ocular complaints (photophobia, burning, itching, scratching) reported by participants[*]
	All outcomes were measured at baseline, at days 45 and 90 of treatment, and at follow-up, 30 days after the end of treatment, but subjective ocular complaints were detected at the end of the trial and at follow-up
	[*] Indicates outcomes which matched those prespecified for this review

Cumurcu 2009 *(Continued)*

Funding body	None stated

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Forty-nine of the 51 patients completed the study. Two patients dropped out of the study: one patient in Group 1 because of blurred vision, and one patient in Group 2 for unrelated reasons". Comment: Analysis included those lost to follow-up during the study and incomplete outcome data were balanced in numbers across groups. However, there was no balance in reasons for missing outcomes across intervention groups and this could be a source of bias, as all outcomes of the trial had a very low frequency.
Selective reporting (reporting bias)	High risk	Quote: "Subjective complaints (photophobia, burning, itching, scratching) were significantly higher in Group 1 compared with baseline (P < 0.05). However, 1 month after the discontinuation of treatment, the difference between the groups was not significant (P > 0.05)". Comment: No protocol available and one outcome, subjective complaints, was reported incompletely, so that it could not be entered in a meta-analysis (only the P value was reported).
Other bias	Low risk	Comment: There were no other apparent sources of bias

De 2011

Methods	Parallel design, randomised controlled trial
Participants	41 participants from Postgraduate Institute of Medical Education and Research, Chandigarh, India. Inclusion criteria: participants with severe grade 4 acne according to the FDA global score Exclusion criteria: not provided Age: not provided Gender: not provided Duration of acne: not provided

De 2011 *(Continued)*

	Acne severity: severe
Interventions	• Group A (n = 21): daily low dose isotretinoin (0.3 mg/kg/day) and azithromycin pulse (500 mg daily on three consecutive days fortnightly) • Group B (n = 20): standard dose isotretinoin (0.5 mg/kg/day) in a total cumulative dose of 120 mg/kg Participants in both groups received interventions for eight months
Outcomes	• Improvement in severity of acne assessed by participants themselves using a 10-point visual analogue scale (VAS) on each visit, fortnightly for the first two follow-ups, and subsequently monthly until treatment completion* • Occurrence of any side effects assessed on each visit, with assessments of liver function tests and lipidogram only every 2 months* * Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	Only a preliminary report of this study was available as a conference proceeding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: The high level of loss to follow-up in the study could lead to a considerable attrition bias (33% in Group A and 45% in Group B)
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Low risk	Comment: There were no other apparent sources of bias

Dhaked 2016

Methods	Parallel design, randomised controlled trial
Participants	240 participants from a single centre, the outpatient clinic in the dermatology department of SMS Medical College, Jaipur - India

Dhaked 2016 *(Continued)*

Inclusion criteria: patients with moderate (several to many papules/pustules with few to several nodules) and severe acne vulgaris (numerous and/or extensive papules/pustules with many nodules), involving all body sites

Exclusion criteria: pregnant women, women desiring to get pregnant or using temporary methods of contraception, patients having family and/or personal history of hyperlipidaemia or diabetes, and those having drug-induced acne.

Age: for all participants, mean 18.88 years (standard deviation 2.46, range 15-30, median 18.51)

Gender: male - 189 participants; female - 45 participants

Duration of acne: < 1 year - 66 participants; 1 to 3 years - 113 participants; > 3 years - 55 participants

Acne severity: moderate - 118 participants; severe - 116 participants

Interventions	• Group A (120 participants): 20 mg of oral isotretinoin daily for 24 weeks • Group B (120 participants): 20 mg of oral isotretinoin every alternate day for 24 weeks All participants were also advised to apply topical 1% clindamycin phosphate cream twice daily and white petroleum jelly on lips, when required
Outcomes	• Improvement in acne severity assessed by mean total acne load (TAL), on the basis of Definition Severity Index (Lidén 1980) • Improvement in acne severity evaluated by mean percentage decrease in TAL • Improvement in acne severity assessed by treatment response according to a response criterion, which was as follows: 1+ = poor response (< 30% reduction in the lesion counts); 2+ = fair response (30%–60% reduction in the lesion counts); 3+ = good response (60%–90% reduction in the lesion counts); and 4+ = excellent response (> 90% reduction in the lesion counts)[*] • Laboratory assessments (complete blood cell counts, liver function tests, and serum lipid profile) done initially and repeated at four and eight weeks thereafter[*] • Frequency of adverse effects[*] • Relapse of acne, considered as the emergence of near pretreatment severity of acne in the treated participant within twelve weeks of post-therapy follow-up Authors evaluated adverse effects, total acne load (TAL), and treatment response according to mean percentage decrease in TAL at an interval of: two weeks, during the 24-week therapy; six weeks, for the 12 weeks after completion of treatment. [*] Indicates outcomes which matched those prespecified for this review
Funding body	None
Notes	Age, gender, and acne severity data were provided only for the whole 112 participants who completed the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: The study did not provide any information to permit judgement

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Dhaked 2016 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Out of 240 patients, six patients were lost to follow up during the study period. For final result analysis, there were 234 patients (Group A, 118 and Group B, 116)." Comment: The trial reported a 'per-protocol' analysis, which did not consider data from loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Low risk	Comment: There were no other apparent sources of bias

Dhir 2008

Methods	Parallel design, randomised controlled trial Duration of trial: from November 2004 to April 2006
Participants	60 participants from a single centre, the Department of Dermatology, Indian Naval Health Service (IN-HS) Asvini, Mumbai, India Inclusion criteria: clinically diagnosed cases of nodulocystic acne Exclusion criteria: being pregnant or breastfeeding; having abnormal lipid profiles, significant hepatic dysfunction, or an underlying psychiatric disorder Age: 81.5% (49) participants: 16-25 years Gender: 44 males/16 females - Group I: 21/9 - Group II: 23/7 Duration of acne: not provided Acne severity: all included participants had nodulocystic acne
Interventions	- Group I (n = 30) – oral isotretinoin 20 mg twice a day along with topical clindamycin (1%) during the daytime and adapalene (0.1%) at bedtime for 24 weeks - Group II (n = 30) - oral isotretinoin 20 mg twice a day for 24 weeks
Outcomes	- Clinical evaluation assessed by the mean scores of acne lesions at each time point. Scoring was calculated by the sum of the following values: (i) For Comedones/Papules/Pustules (for each): \> 20 lesions - 4 15-19 lesions - 3 11-14 lesions - 2 < 10 lesions - 1 (ii) Nodules/Cysts (for each) \> 10 lesions - 4 6-10 lesions - 3 < 6 lesions - 2

- Physician's global assessment as given below*:
  - (a) Clear: 100% reduction in pretreatment score
  - (b) Excellent: 75-99% reduction in pretreatment score
  - (c) Good: 50-74% reduction in pretreatment score
  - (d) Moderate: 25-49% reduction in pretreatment score
  - (e) Poor: 0-24% reduction in pretreatment score.
- Frequency of clinical and laboratory side effects*

Participants were examined every four weeks. Clinical scoring and side effects were recorded at each visit during both therapy phase and follow-up period (six months).

* Indicates outcomes which matched those prespecified for this review

Funding body	None stated
Notes	Age data were not presented as means or a closed range for each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This is an open label..." Comment: Participants and personnel were not blinded; they were aware of the treatment arm to which participants were allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "This is an open label..." Comment: The study had an open design. However, there was no information regarding blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Out of the 60 patients who were included in the study, 50 completed the treatment while five patients dropped out from each group." Comment: The trial reported a 'per-protocol' analysis, which did not consider data from loss to follow-up. Also, the report did not detail reasons for missing data.
Selective reporting (reporting bias)	High risk	Quote: "Patients were examined every four weeks and clinical scoring and side effects were recorded at each visit. This was supplemented by the physician's global assessment as..." Comment: No protocol available and a selective choice of data for an outcome might have occurred, since physician's global assessment of improvement in acne severity was performed every four weeks, during the therapy phase, but only data from the assessment at visit 6 (24 weeks, end of treatment) were reported.
Other bias	Low risk	Comment: There were no other apparent sources of bias

Faghihi 2014

Methods	Parallel design, randomised controlled trial
	Duration of the trial: from September 2012 until September 2013
Participants	58 participants from a single dermatologic clinic, located at Al-Zahra General Hospital, Isfahan, Iran
	Inclusion criteria: having moderate to severe facial acne vulgaris
	Exclusion criteria: acne secondary to other problems; pregnancy or intention of pregnancy; breastfeeding; other dermatological diseases of the face; G6PD deficiency; history of having taking any medication that could interact with dapsone (e.g. trimethoprim-sulfametoxazol) or isotretinoin (e.g. tetracyclines, methotrexate and vitamin A supplements) within the previous 3 months; and known hypersensitivity to the study medication
	Age: for all participants, ranged from 18 to 25 years
	Age: by group, mean ± standard deviation (years)
	• Group A (n = 29): 20.3 ± 3.2 • Group B (n = 29): 20.1 ± 2.9
	Gender: 25 male/33 female
	• Group A (n = 29): 13 male/16 female • Group B (n = 29): 12 male/17 female
	Duration of acne: 3.19 (mean) ± 1.8 (standard deviation) years; 2 to 5 years (range)
	Acne severity: moderate to severe
Interventions	Group A (n = 29): oral isotretinoin, 20 mg once a day plus 5% dapsone gel applied on the face twice daily, both for 8 weeks
	Group B (n = 29): oral isotretinoin, 20 mg once a day plus vehicle neutral gel applied on the face twice daily, both for 8 weeks
Outcomes	• Assessment of lesion count (sum of inflammatory and non-inflammatory lesions) by manually counting for both the treatment site and control site at baseline and on each follow-up visit (weeks 4, 8 and 12) • Severity of acne assessed by the Global Acne Assessment Scale (GAAS) (Ziana 2006), a 5-point scale which starts with the value 0 (clear) and goes until 5 (very severe); measurements happened at baseline and the end of the study[*] • Assessment of any possible side effects on each visit at weeks 4, 8 and 12[*]
	[*] Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study

Faghihi 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "During the study period, only a caregiver who was not involved in the experiment was aware of the contents of the tubes; the patients and the examiner were blind to the topical compounds." Comment: There was a description of who was masked during the conduct of the trial, despite no description of an evaluation of the success of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "During the study period, only a caregiver who was not involved in the experiment was aware of the contents of the tubes; the patients and the examiner were blind to the topical compounds." Comment: There was an explicit report of blinding of outcome assessment, despite having not reported an evaluation of the success of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "...and all the participants completed the study." Comment: As there were no missing data, the authors had probably performed a real intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Comment: There was an available protocol on a clinical trials registry and all outcomes listed in methods section of the protocol were adequately reported in the final publication
Other bias	Low risk	Comment: There were no other apparent sources of bias

Farrell 1980

Methods	Parallel design, randomised controlled trial
Participants	16 participants from a single centre, the Department of Dermatology, University of Iowa College of Medicine, Iowa City, United States of America Inclusion criteria: severe acne vulgaris with refractoriness to conventional therapy; and presence of a minimum of ten or more deep cystic nodules, each having a greatest diameter of 4 mm or more Exclusion criteria: abnormal laboratory profile Age: 16 to 31 years Gender: male Duration of acne: not provided Acne severity: severe
Interventions	• Intervention 1 (n = 5): oral isotretinoin 0.1 mg/kg/day • Intervention 2 (n = 5): oral isotretinoin 0.5 mg/kg/day • Intervention 3 (n = 4): oral isotretinoin 1.0 mg/kg/day All interventions were given for 12 weeks
Outcomes	• Changes from baseline in sebum production and composition measured from forehead skin by routine procedures employed in the laboratory of the study (Downing 1968; Strauss 1961) • Counting and measurement of the greatest diameters of all nodulocystic lesions larger than 4 mm in diameter in a designed area on the face, chest, and/or back on each visit • Frequency of side effects evaluated clinically and by a questionnaire*

Farrell 1980 *(Continued)*

The three above outcomes were assessed weekly for the first 8 weeks of treatment and then at 2-week intervals for the last 4 weeks of treatment and for an 8-week post treatment period.

Laboratory assessments (haemogram, urinalysis, and blood chemistries) evaluated at baseline, 2, 4, 8, and 12 weeks of therapy and at 8 weeks after therapy was discontinued*.

* Indicates outcomes which matched those prespecified for this review

Funding body	Hoffman-La Roche Inc., and a research grant (RO-1-AM-22083-02) from the United States Public Health Service
Notes	The number of participants stated for each intervention group refers to participants who completed the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to a treatment schedule according to a computer-generated randomised code..." Comment: The trial described an adequate method for the random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...in a double-blind study." "...the drug was dispensed by an individual not involved in patients evaluation. Therefore, neither the physicians involved in the clinical evaluation nor the patients were aware of individual assignment to the three dose groups". "At the end of the study when the code was broken...". Comment: There was a description of who was masked during the conduct of the trial, despite no description of any evaluation of the success of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Therefore, neither the physicians involved in the clinical evaluation nor the patients were aware of individual assignment to the three dose groups". Comment: This statement did not clarify whether all outcome assessors were blinded. It was not clear in the report if all the outcome assessments and the clinical evaluation of participants were done by the same people from the study staff.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Fourteen of the sixteen patients completed the study according to protocol." "As stated earlier, this patient was then dropped from the double-blind study, and no further data from this case are included in sub-sequent weeks." Comment: The trial reported a 'per-protocol' analysis, which did not consider data from loss to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section

Farrell 1980 *(Continued)*

Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was sponsored and promoted by a pharmaceutical company

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Goldstein 1982

Methods	Parallel design, randomised controlled trial
Participants	56 participants from multiple centres, three Departments of Dermatology, in United States of America
	Inclusion criteria: male participants with severe, treatment-resistant nodulocystic acne; good general health; and to have at least ten inflammatory acne nodules or cysts, 4 mm or more in diameter, on the face, back, or chest
	Exclusion criteria: not stated
	Age: for all participants, ranged from 14 to 54 years (mean: 23.4 years)
	Gender: 100% male
	Duration of acne: average period of 8 years (range: 2 to 26 years)
	Acne severity: severe
Interventions	• Intervention 1: (n = 28) oral isotretinoin 1.0 mg/kg/day
	• Intervention 2: (n = 28) oral etretinate 1.0 mg/kg/day
	Both drugs were administered in two divided doses daily, for 8 weeks
Outcomes	• Percentage change in lesion counts of the face, chest, and back, limited to inflammatory nodules, 4 mm or greater in diameter
	• Changes from baseline in sebum excretion production (Strauss 1961)
	• Frequency of any side effects evaluated subjectively[*]
	The three outcomes above were assessed at each visit and performed at baseline, 2, 4, and 8 weeks of therapy and at 4 and 8 weeks post-therapy
	Laboratory alterations assessed by: urinalysis, complete blood count, and blood chemistry determinations repeated after 1, 2, and 8 weeks of therapy; semen analyses, including determination of sperm count, motility, and morphology, performed at baseline and the end of therapy and 8 weeks later[*]
	Frequency of ophthalmologic alterations assessed by examination, including dilated slit-lamp and determination of ocular tension, done on each participant at baseline and after completion of drug therapy[*]
	[*] Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation

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Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A multicenter double-blind study..." "The capsules were coded and dispensed in such a fashion that neither the patients nor the examining physician knew which retinoid was being administered". Comment: There was a description of who was masked during the conduct of the trial, despite no description of any evaluation of the success of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...neither the patients nor the examining physician knew which retinoid was being administered". Comment: This statement did not clarify whether all outcome assessors were blinded. It was not clear in the report if all the outcome assessments and the clinical evaluation of participants were done by the same people from the study staff
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All fifty-six patients completed the 8-week course of drug therapy, and fifty-one of these completed the 8-week follow-up period." Comment: The report did not provide detailed numbers and reasons for missing data in each intervention group
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Low risk	Comment: There were no other apparent sources of bias

Gollnick 2001

Methods	Parallel design, randomised controlled trial
Participants	85 participants from 10 centres in Germany, Austria and Switzerland Inclusion criteria: • Phase 1: male participants over 16 years of age with severe inflammatory/nodular forms of facial acne (acne conglobata, acne papulopustulosa nodosa and acne nodulocystica); severity of the acne being at least grade 4 using Cunliffe's classification (Leeds scale); having at least 2 deep inflammatory lesions (nodes, cysts or nodules) and other papules and pustules • Phase 2: very good therapeutic improvement during the whole period of study phase 1 for immediate subsequent admission; very good clinical improvement achieved prematurely, before completing the 6 months of study phase 1, for early transference to study phase 2 Exclusion criteria: women, participants with milder (comedonal or papulopustular acne) or more severe (acne fulminans, acne tetrade) forms of acne, photosensitive participants, and participants with contraindications to isotretinoin or minocycline, and those hypersensitive to the excipients contained in the azelaic acid cream Age: for all participants, mean/range (years): 19/15 - 31 • Group 1: 19/16 - 31 • Group 2: 19/15 - 27 Gender: 100% male Duration of acne: mean/range (years): 4/0 - 14

Gollnick 2001 *(Continued)*

- Group 1: 4/ 0 - 14
- Group 2: 3/0 - 10

Acne severity: 100% severe

Interventions	AA/Mino group (n = 50):
	• 6-month study phase 1: 20% azelaic acid cream, twice daily to affected areas, plus oral minocycline, 50 mg, twice daily
	• 3-month study phase 2 (maintenance treatment period): 20% azelaic acid cream twice daily
	Iso group (n = 35):
	• 6-month study phase 1: oral isotretinoin - initial dose (month 1) was 0.8 mg/kg, decreasing in month 2 to 0.7 mg/kg, in month 3 to 0.5-0.7 mg/kg and in months 4-6 to 0.5 mg/kg per day
	• 3-month study phase 2 (maintenance treatment period): no therapy
Outcomes	Primary efficacy outcome:
	• Changes in the number of facial papules, pustules and deep inflammatory acne lesions assessed at every examination[*]
	Secondary efficacy outcomes:
	• The investigator's and the participant's subjective global assessment of the therapeutic result (classified as "very good, good, moderate, no improvement, deterioration") measured at each examination[*]
	Other outcomes:
	• Degree of seborrhoea assessed at each examination
	• Adverse effects (clinical and laboratory) and subjective complaints evaluated at each participant examination and documented by nature, severity, and duration at every visit[*]
	Patient examinations were done for all participants at baseline and at monthly intervals over the 6-month treatment period in study phase 1.
	In study phase 2, participants of the initial AA/mino group were examined at monthly intervals over the 3-month maintenance treatment period, but the participants of the initial Iso group were examined only once (after completion of the second 3-month study phase).
	[*] Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias)	High risk	Quote: "...the study design was essentially open label..."

Gollnick 2001 *(Continued)*

All outcomes		Comment: Participants and personnel were not blinded; they were aware of the treatment arm to which participants were allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...the study design was essentially open label..." Comment: The study had an open design. However, there was no information regarding blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 85 eligible patients recruited to the study, 77 completed the first study phase (90.6%). Eight patients (6 from the AA/Mino group, 2 from the Iso group) dropped out of the study because of poor compliance, adverse reactions, lack of efficacy, infringement of the study protocol or for other reasons. All 85 patients were included in the analysis of the efficacy." Comment: The level of loss to follow-up could lead to a considerable attrition bias. Reasons for attrition were described, but there was imbalance of missing data between intervention groups
Selective reporting (reporting bias)	High risk	Comment: No protocol available; data from participants subjective global assessment of improvement after therapy were not reported, despite having been listed in the methods section
Other bias	Low risk	Comment: There were no other apparent sources of bias

Jones 1983a

Methods	Parallel design, randomised controlled trial
Participants	76 participants from two centres, Departments of Dermatology from the General Infirmary and from St James's University Hospital, both at Leeds, United Kingdom
	Inclusion criteria: failure to respond to long-term oral antibiotic therapy; partial response to antibiotics, but rapid relapse on cessation of such therapy
	Exclusion criteria: not stated
	Age: mean ± standard deviation (years)
	• Group 1: 23.7 ± 1.1
	• Group 2: 24.3 ±1.3
	• Group 3: 24.6 ± 1.7
	Gender: 45 male/31 female
	• Group 1: 11/11
	• Group 2: 17/13
	• Group 3: 17/7
	Duration of acne: not provided
	Acne severity: moderate to severe
Interventions	• Intervention 1 (n = 22): oral isotretinoin 0.1 mg/kg/day
	• Intervention 2 (n = 30): oral isotretinoin 0.5 mg/kg/day
	• Intervention 3 (n = 24): oral isotretinoin 1.0 mg/kg/day
	All interventions were administered for 16 weeks

Jones 1983a *(Continued)*

Outcomes	• Percentual changes from baseline in sebum excretion rate measured by a gravimetric method (Strauss 1961)
	• Clinical improvement assessed as percentage change in acne severity on face, back, and chest - evaluated by a 0-10 acne grading scale (Burton 1971; Cunliffe 1981) - and in the acne lesion count (sum of inflammatory and non-inflammatory lesions of the face)
	• Clinical and laboratory (biochemical) side effects*
	Outcomes were estimated at all visits: initial, at 4-week intervals during 16 weeks, and at 32 weeks (after the follow-up period).
	* Indicates outcomes which matched those prespecified for this review
Funding body	Roche Products Limited
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "A double-blind dose-response study on seventy-six patients is now reported..." Comment: There was no description of who was blinded and also no description of efforts to ensure blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "A double-blind dose-response study on seventy-six patients is now reported..." Comment: There was no description of who was blinded and also no effort to ensure blinding was described
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Thirteen patients (nine relapses, four failures) received further treatment prior to the 32 weeks and were withdraw from the study at that point. Five patients failed to attend during the follow-up period for a variety of reasons." "...the drug schedule had to be altered in only three patients. These three patients were excluded from the study." Comment: There was no clear description of missing data for each group in the report. However, the level of loss to follow-up could lead to a considerable attrition bias
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was sponsored and promoted by a pharmaceutical company

Jones 1983b

Methods	Parallel design, randomised controlled trial
Participants	90 participants from Leeds Dermatological Research Foundation, Department of Dermatology, The General Infirmary at Leeds, United Kingdom
	Inclusion criteria: participants with moderate to moderately severe acne
	Exclusion criteria: not stated
	Age: not provided
	Gender: not provided
	Duration of acne: not provided
	Acne severity: moderate to moderately severe
Interventions	• Group 1 (n = ? - not provided): isotretinoin 0.5 mg/kg/day
	• Group 2 (n = ? - not provided): erythromycin 1 g/kg/day
	• Group 3 (n = ? - not provided): isotretinoin 0.5 mg/kg/day plus erytromycin 1 g/kg/day
	Participants received isotretinoin for 16 weeks and erythromycin for 24 weeks
Outcomes	• Improvement in acne grade*, facial lesion count* and sebum excretion rate
	• Incidence of clinical side effects* and biochemical abnormalities*
	Assessments occurred every 4 - 8 weeks; follow-up continued every 8 - 12 weeks off therapy.
	* Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Ninety patients have been studied and randomly allocated on a double-blind basis..." "The appropriate placebos were given in the first two groups." Comment: There was a description of an appropriate method to ensure blinding, despite not having described clearly who was blinded, or any evaluation of the success of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Ninety patients have been studied and randomly allocated on a double-blind basis..." "The appropriate placebos were given in the first two groups."

Jones 1983b *(Continued)*

		Comment: There was a description of an appropriate method to ensure blinding, despite not having described clearly who was blinded, or any evaluation of the success of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: The report did not provide detailed numbers and reasons for missing data in each intervention group
Selective reporting (reporting bias)	High risk	Quote: "The group receiving antibiotic alone showed less improvement (50%) than the other two groups (70 %) at the end of the treatment period. The combination therapy showed no significant difference from the 13-cis-retinoic group alone." Comment: There was no clearly and detailed report of the number of participants enrolled in each group. Also, authors did not describe which type of efficacy outcome measurement (acne grade or facial lesion count) had the particular difference in acne improvement cited in the report
Other bias	Low risk	Comment: There were no other apparent sources of bias

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Kapadia 2005

Methods	Parallel design, randomised controlled trial
Participants	60 participants from 3 medical centres, in Karachi, Pakistan Inclusion criteria: not provided Exclusion criteria: not provided Age: not provided Gender: not provided Duration of acne: not provided Acne severity: moderate to severe
Interventions	• Group 1 (n = 30): oral isotretinoin 20 mg/daily • Group 2 (n = 30): oral isotretinoin 40 mg/daily Interventions were administered for 24 weeks
Outcomes	• Improvement in acne severity evaluated by physician assessment, on the basis of global acne grading system, as 1: excellent (> 80% clearing of lesions); 2: good (> 50% clearing of lesions); 3: moderate (30 – 50% clearing of lesions); 4: slight: (< 30% clearing of lesions); and 5: no change[*] • Frequency of any clinical or laboratory side effect appeared during the trial[*] Assessments were done at baseline and every 8 weeks till 24 weeks. Laboratorial investigations were performed at baseline and at the end of the study. [*] Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	
Risk of bias	

Kapadia 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "None of the patients were lost to follow- up" Comment: An intention-to-treat analysis was probably done
Selective reporting (reporting bias)	High risk	Comment: No protocol available and not all detected adverse effects had frequencies reported separately for each intervention group
Other bias	Low risk	Comment: There were no other apparent sources of bias

King 1982

Methods	Parallel design; randomised controlled trial
Participants	48 participants from two centres, Departments of Dermatology from the General Infirmary and from St James's University Hospital, both at Leeds, United Kingdom
	Inclusion criteria: failure to respond to conventional therapy, including several courses of antibiotics
	Exclusion criteria: not stated
	Age: for all participants, mean age was 25 years
	Gender: 24 male/24 female
	Duration of acne: not provided
	Acne severity: not provided
Interventions	• Intervention 1 (n = 13): oral isotretinoin 0.1 mg/kg/day • Intervention 2 (n = 21): oral isotretinoin 0.5 mg/kg/day • Intervention 3 (n = 14): oral isotretinoin 1.0 mg/kg/day All interventions were administered for 16 weeks
Outcomes	• Clinical improvement assessed as percentage change in acne severity on face, back and chest - evaluated by a 0-10 acne grading scale (Burton 1971; Cunliffe 1981) • Changes from baseline in sebum excretion rate measured by a gravimetric method (Strauss 1961) • Changes from baseline in production rate of free fatty acids assessed by the method described in Dole 1960

King 1982 *(Continued)*

- Changes in skin micro-organisms population assessed by the collection of skin samples from the right cheek using the scrub technique (Williamson 1965) and the determination of the number of bacterial colony-forming units present per cm^2 skin by the method of Miles & Mistra (Miles 1938)

Funding body	Roche Products Limited
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate and microbial population". Comment: There was no description of who was blinded and also no description of efforts to ensure blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate and microbial population". Comment: There was no description of who was blinded and also no description of efforts to ensure blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There was no information regarding missing data
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was sponsored and promoted by a pharmaceutical company

Lee 2011

Methods	Parallel design, randomised controlled trial
Participants	60 participants from a single centre, the Department of Dermatology, Chung-Ang University Hospital, Seoul, Korea Inclusion criteria: moderate acne which had not responded to antibiotic therapy or which had rapidly relapsed after antibiotic therapy Exclusion criteria: severe acne types, such as conglobata or fulminans; other systemic diseases; history of oral isotretinoin or oral contraceptive use previously or concurrently; pregnancy and lactation; and history of other acne treatment in the preceding 3 months Age: all participants, ranged from 16 to 33 years Age: by group, mean ± standard deviation (years)

Lee 2011 *(Continued)*

- Group A: 20,8 ± 2,7
- Group B: 23,6 ± 3,4
- Group C: 22,4 ± 4,5

Gender: 20 male/40 female

Duration of acne: mean ± standard deviation (years)

- Group A: 5,8 ± 1,9
- Group B: 6,8 ± 2,5
- Group C: 6,4 ± 3,1

Acne severity: moderate acne

Interventions	- Group A (n = 20): oral isotretinoin 0,5-0,7mg/kg/daily (continuous conventional dose) - Group B (n = 20): oral isotretinoin 0,25-0,4mg/kg/daily (continuous low dose) - Group C (n = 20): oral isotretinoin 0,5-0,7mg/kg/daily for 1 week out of every 4 weeks (intermittent conventional dose) Interventions were administered for 24 weeks
Outcomes	Improvement in acne severity assessed by: - The global acne grading system score (GAGS) (Demircay 2008; Doshi 1997) measured at baseline and each visit (every 4 weeks during the treatment period and 1 year after the end of therapy, the follow-up visit) - Changes from baseline of non-inflammatory (comedones) and inflammatory (papules, pustules and nodules) lesion counts counted at 0, 12, and 24 weeks*· - Degree of satisfaction on a four-point scale (4, very satisfied; 3, satisfied; 2, slightly satisfied; 1, dissatisfied) evaluated at the end of the study - Relapse rates assessed at the follow-up visit and defined as deterioration to moderate or more severe acne based on the GAGS global score - Frequency of side effects recorded at each visit* - Frequency of laboratory alterations evaluated by performing full blood cell counts, liver function tests (AST, ALT, and direct and total bilirubin) and lipid profiles (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides) at 0, 12, and 24 weeks* * Indicates outcomes which matched those prespecified for this review
Funding body	A Chung-Ang University Research grant in 2010
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned to treatment groups in a 1 : 1 : 1 ratio using a computer-generated randomisation schedule." Comment: The trial described an adequate method for the random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias)	High risk	Quote: "It was not possible to blind either the patient or the therapist, but the examiner was blinded to group assignment during collection of the data."

Lee 2011 *(Continued)*

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "This was a 24-week, prospective, randomised, controlled, open with blinded assessment trial". "It was not possible to blind either the patient or the therapist, but the examiner was blinded to group assignment during collection of the data." Comment: There was a clear description of blinded outcome assessment during the conduct of the trial, despite no description of any evaluation of the success of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Analyses were done according to intention-to-treat principle..." Comment: Despite having cited the term "intention-to-treat", the study presented a level of loss to follow-up (20%, 15%, and 20%, respectively, in Groups A, B and C) which could have led to a considerable attrition bias. Reasons for attrition were described and there was a imbalance between intervention groups.
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Low risk	Comment: There were no other apparent sources of bias

Leheta 2011

Methods	Parallel design, randomised controlled trial
Participants	60 participants from Faculty of Medicine, Cairo University, Cairo, Egypt and Faculty of Medicine, Alexandria University, Alexandria, Egypt Inclusion criteria: participants with mild to moderate acne Exclusion criteria: not provided Age: not provided Gender: not provided Duration of acne: not provided Acne severity: mild to moderate acne
Interventions	• Group A (n = ? - not provided): 0.5 mg/kg/day for to 2 weeks, followed by 1 mg/kg/day for the remaining period of treatment • Group B (n = ? - not provided): 5% benzoyl peroxide gel each morning + 0.1% tretinoin cream each evening, both applied to face • Group C (n = ? - not provided): chemical peeling with TCA 25% every two weeks for eight sessions, then monthly during the follow-up period There was no description of the duration of therapy phase for groups A and B, or of the follow-up period for all groups
Outcomes	• Improvement in acne severity score[*] Time points of outcome measurement not provided [*] Indicates outcomes which matched those prespecified for this review

Leheta 2011 *(Continued)*

Funding body	None stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Selective reporting (reporting bias)	High risk	Quote: "However, there was no statistically significant difference (P = 0.401) between the treatment groups, as regards the acne severity score after treatment, ..." Comment: There was no clearly and detailed report of the number of participants enrolled in each group. Also, the only exact numerical data provided in the results section of the study regarding the comparison between the three intervention groups was the P value cited above.
Other bias	Low risk	Comment: There were no other apparent sources of bias

Lester 1985

Methods	Parallel design, randomised controlled trial
Participants	30 participants from two centres, Departments of Dermatology of Sunnybrook Medical Center and Women's College Hospital, at Toronto, Canada Inclusion criteria: presence of 10 or more deep dermal inflamed cystic nodules, which measured 4 mm or more on their longest diameter; past of minimal responses to treatment with tetracycline; failure to respond to other oral and topic agents, including antibiotics, topical tretinoin, benzoyl peroxide, and prednisone, as well as many other conventional forms of acne therapy. Exclusion criteria: pregnant and women of childbearing potential; significant ocular, hepatic, renal, or hematologic diseases or abnormalities; superficial x-ray therapy within 6 months prior to the study; history of hypersensitivity to tetracycline or to vitamin A and its derivatives Age: for all participants, ranged from 17.1 to 37.7 years Age: by group, mean ± standard deviation/range (years)

Lester 1985 *(Continued)*

- Group 1: 24.3 ± 5.9/17.1-35.4
- Group 2: 26.5 ± 7.2/18.1-37.7

Gender: male/female

- Group 1: 15/0
- Group 2: 14/1

Duration of acne: mean ± standard deviation (years)/range

- Group 1: 8.3 ± 5.9/2-20
- Group 2: 8.9 ± 6.3/2-22

Acne severity: 100% severe

Interventions	- Group 1 (n = 15): oral isotretinoin 1.0 to 2.0 mg/kg/day, taken in divided doses for 16 weeks. Increments of 0.5 mg/kg/day to the maximal dosage permitted at biweekly intervals - Group 2 (n = 15): tetracycline hydrochloride 500 mg/day to 1 g/day, given for 16 weeks. Increments of 250 mg/day to reach the maximal dosage were permitted at biweekly intervals
Outcomes	Clinical efficacy assessments: - Changes from baseline in the number of cysts of 4 mm or greater[*], the sum of their longest diameters and the number of comedones and pustules in face, back, and chest - Signs and symptoms associated with the acne condition, including erythema and pain of the acne lesions, oiliness of the skin, rate of development of new lesions, and healing time of the lesions - Clinical and laboratory safety assessments - Frequency of abnormalities in routine haematology, blood chemistry, urinalysis, ophthalmic examination, and spermatogenesis evaluations[*] - Frequency of adverse reactions related to the test medications according to organ system[*] The ophthalmic examination was done at the end of the treatment period and spermatogenesis evaluations were performed at 12, 20, and 24 weeks. All other outcomes measurements were made at 2, 4, 8, 12, and 16 weeks during drug administration, and at 20 and 24 weeks during the follow-up period. [*] Indicates outcomes which matched those prespecified for this review
Funding body	Hoffman-La Roche Ltd
Notes	Authors declared being from the Clinical Research Unit of Hoffman-La Roche Ltd., Toronto, Ontario, Canada

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The double-blind condition of the trial was preserved by the pharmacists, who dispensed the appropriate test medication at the dosage level prescribed by the investigator. In addition, the objective cyst evaluations were performed by a research nurse independent of consultation with the investigator".

Lester 1985 *(Continued)*

		Comment: It was not clear if the term "double-blind" was a reference to participants and personnel or to investigators (personnel) and independent research nurse (outcome assessor)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...the objective cyst evaluations were performed by a research nurse independent of consultation with the investigator". Comment: There was no description of blinding assessment for all outcomes reported in the study
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Two patients in the tetracycline-treatment group withdrew from the study prematurely due to poor control of their disease". Comment: There was an imbalance in missing outcome data due to 'inefficacy' across the two intervention groups
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was sponsored and promoted by a pharmaceutical company

Oprica 2007

Methods	Parallel design, randomised controlled trial
Participants	52 participants from a single centre, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden Inclusion criteria: male and female participants who had moderate or severe inflammatory acne vulgaris (at least grade 3 on the face, back, or chest according to the Leeds technique); age range 15–35 years Exclusion criteria: papulo-pustular acne with no nodules or very severe forms (acne fulminans); use of oral/topical acne treatments within 8 weeks of the start of treatment; use of drugs that may interfere with tetracycline (i.e. retinoids, anticoagulants, antacids, iron preparations, hepatic enzyme inducers); pregnant women or those who, wanted to become pregnant; breastfeeding mothers; systemic or psychiatric diseases (including drug and alcohol abuse); any dermatological condition that might interfere with the evaluation of acne; acne due to secondary causes; participation in any other clinical trial; hypersensitivity or allergy to the study medication Age: for all participants, ranged from 15 to 35 years Age: by group, median ± SD (years) • Group 1 (n = 25): 19 ± 5.5 • Group 2 (n = 24): 18 ± 6 Gender: male/female • Group 1 (n = 25): 15/10 • Group 2 (n = 24): 17/7 Disease duration: median ± SD (years): • Group 1 (n = 25): 4 ± 4.2 • Group 2 (n = 24): 3 ± 5.4 Acne severity: moderate or severe acne

Oprica 2007 *(Continued)*

Interventions	• Group 1 (tetracycline/adapalene) (n = 25): tetracycline hydrochloride (500 mg twice daily, one hour before meals) plus topical adapalene once a day in a thin film on the affected area, for 24 weeks • Group 2 (oral isotretinoin) (n = 24): oral isotretinoin 1 mg/ kg/day, in two divided doses, for 24 weeks
Outcomes	• Improvement in lesion-counting and acne-grading system described by Burke & Cunliffe (Burke 1984). At each visit (baseline, follow-up visits at 2, 4, 6 months of treatment, and 2 months after cessation of treatment) lesions were counted on the face, back, and chest and categorised into non-inflammatory (open and closed comedones), superficial inflammatory (papules, pustules), and deep inflammatory (nodules)[*] • Participants' perception and assessment regarding the two treatments, evaluated by the Dermatology Life Quality Index (DLQI) (Finlay 1994) completed by all participants before the treatment started and after the end of the therapy phase[*]· • Microbiological assessments of the skin from five areas (forehead, right cheek, left cheek, back, and chest). Samples were taken at each visit • Frequency of alterations in laboratory parameters of participants before the treatment started and after 2, 4, and 6 months of therapy[*]: • * Group 1: complete blood count, and a 12-hour fasting blood chemistry panel; • * Group 2: blood counts, liver enzymes, triglycerides, fasting total cholesterol, low-density lipoproteins, and high-density lipoproteins. • Frequency of possible side effects of the drugs detected by questioning participants at each visit[*] [*] Indicates outcomes which matched those prespecified for this review
Funding body	Edward Welander and Finsen Foundations; F. Hoffman-La Roche Ltd Co
Notes	There was no report of demographic data for all initially randomised participants (52)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were assigned randomly to one of 2 treatment groups, using a computer-generated randomisation code..." Comment: The trial described an adequate method for the random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "...randomisation code known only to a person not involved in the trial." Comment: There was an adequate concealment of the allocation sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "In our open study, both treatments improved the clinical condition". Comment: Participants and personnel were not blinded; they were aware of the treatment arm to which participants were allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "In our open study, both treatments improved the clinical condition". Comment: The study had an open design. However, there was no information regarding blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 52 patients were randomised; 26 to receive TET/ADA and 26 to receive ISO. Of these, 3 patients abandoned the study after randomisation and were not included in further analyses. Overall, 7 patients in the ISO group and 6 patients in the TET/ADA group abandoned the study at different times. The therapy was regarded as completed due to a very good clinical response before the end of 6 months in one patient from the ISO group."

Oprica 2007 *(Continued)*

		"Analysis of clinical efficacy parameters was performed on the intention-to-treat population, which included all patients who had at least one post-base-line evaluation. For patients who prematurely discontinued the treatment, the last observations were carried forward."
		Comment: Despite having cited the term "intention-to-treat", actually authors performed a "per protocol" analysis, since analysis did not included data from all initially randomised participants
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was sponsored and promoted by a pharmaceutical company

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Peck 1982

Methods	Parallel design, randomised controlled trial
Participants	33 participants from a single centre, the Clinical Center of the National Institutes of Health, at Bethesda, United States
	Inclusion criteria: having at least ten inflamed deep derma or subcutaneous acne cysts or nodules of at least 4 mm diameter; history of minimal response to treatment with oral and topical antibiotics, oral vitamin A, topical vitamin A acid, topical benzoyl peroxide, x-irradiation, oral contraceptives, oral dapsone, intralesional injections of corticosteroids, oral prednisone, surgical drainage, applications of liquid nitrogen, photochemotherapy with psoralen and long wave ultraviolet light, and other acne therapies
	Exclusion criteria: pregnant women and fertile women who refused to use birth control measures
	Age, gender and duration of acne: not provided
	Acne severity: not stated if moderate or severe, only reported as cystic acne
Interventions	• Group 1 (n = 16): oral isotretinoin at a minimum of 0.5 mg/kg/day for a minimum period of 4 months in the first double-blind phase of the study. Additional courses of isotretinoin could be given after an 8-week rest period between courses if it was thought that the participant could benefit from further treatment
	• Group 2 (n = 17): placebo for a minimum period of 1 month
	At the monthly visit, "if there had been no change or only a slight worsening of the acne, then the dose of isotretinoin or placebo was increased by 0.5 mg/kg/day. If there had been a marked worsening, the protocol permitted a cross-over to active drug if the patient had been taking placebo."
Outcomes	• Primary efficacy outcome: * Improvement in the number of cysts assessed by lesion counts • Secondary outcomes: * Improvement in the number of papules and pustules assessed by lesion count (lesions were counted at baseline, monthly until 15 months, and at the follow-up evaluation, after 40 months from the start of the therapy) • Reduction in sebum production assessed by quantitative analyses of samples obtained according to the method described previously by Strauss and Pochi (Strauss 1961) Clinical and laboratory side effects evaluated at baseline and monthly intervals during and after treatment[*] [*] Indicates outcomes which matched those prespecified for this review

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Peck 1982 *(Continued)*

Funding body	Hoffman-La Roche Inc.
Notes	We considered for our review only the first four weeks of the study: after this time point, switching of participants from placebo group to isotretinoin group had started.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly assigned... according to a computer-generated code." Comment: The trial described an adequate method for the random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "If there had been a marked worsening, according to predetermined criteria, then the double-blind code was broken." "...or an equivalent number of placebo capsules identical in appearance. The capsules were dispensed to the patients by a third party ..." Comment: Despite having described efforts to keep blinding of participants and personnel during the first study phase ("double-blind"), there was no explicit reporting of who was and was not blinded across participants, personnel, and outcome assessors
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: It was not clear in the report whether the person who had done the outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: An intention-to-treat analysis was probably done, as there was no dropout for the first four weeks of the study which were considered for our analysis (after this time point, switching of participants from placebo group to isotretinoin group had started)
Selective reporting (reporting bias)	High risk	Quote: "In four matched pairs, the average sebum production was 0.25 mg lipids/10 cm^2/3 hr, with a range of 0.19 to 0.35, taken from 12 to 16 weeks on therapy". Comment: No protocol available and the report in the results section suggested that not all participants from each group had been assessed for one outcome (reduction in sebum production); selective choice of subsets of data for this outcome, which was listed in the methods section, might have occurred
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as a pharmaceutical company promoted it

Pigatto 1986

Methods	Parallel design, randomised controlled trial
Participants	24 participants from two departments (2nd Department of Dermatology and 3rd Department of Medicine) of only one centre, the School of Medicine, University of Milan, Italy

Pigatto 1986 *(Continued)*

Inclusion criteria: male participants with severe cystic acne vulgaris

Exclusion criteria: overweight; people assumed to be consuming more than 5 g of alcohol daily or smoking more than 15 cigarettes daily; use of any drug which could have interfered with lipid metabolism; abnormal liver function tests and altered glucose tolerance tests

Age: for all participants, mean age was 23 years (standard deviation ± 3 years), with range from 20 to 29 years

Gender: all participants were male

Duration of acne: not provided

Acne severity: severe cystic acne

Interventions	- Group 1 (n = 12): oral isotretinoin 1.0 mg/kg/daily for 10 weeks and 0.5 mg/kg/daily for another 10 weeks - Group 2 (n = 12): minocycline 100 mg/day for 10 weeks and then reduced to 50 mg daily for 10 weeks
Outcomes	- Number and diameter of cysts measured at baseline and every two weeks - Clinical side effects and adverse reactions[*] Laboratory analysis: hematology, blood chemistry, and urinalysis were measured at baseline, monthly, and at change of doses[*] Laboratory parameters of the lipid metabolism assessed at baseline, monthly, and at change of doses[*] . [*] Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There was no mention to missing data in the report
Selective reporting (reporting bias)	High risk	Quote: "Laboratory examinations were done monthly and at the change of doses."

Pigatto 1986 *(Continued)*

		Comment: No protocol available. Measurements of lipid metabolism parameters were reported only at baseline, 10 weeks, and 20 weeks: selective choice of data for this outcome might have occurred
Other bias	Low risk	Comment: There were no other apparent sources of bias

Prendiville 1988

Methods	Parallel design, randomised controlled trial
Participants	40 participants from two centres: Ealing Hospital at Middlesex and St John's Hospital for Diseases of the Skin at London, United Kingdom
	Inclusion criteria: not provided
	Exclusion criteria: not provided
	Age: for all participants, ranged from 16 to 31 years
	Gender: 100% male
	Duration of acne: not provided
	Acne severity: severe
Interventions	• Group 1 (n = 20): dapsone 100 mg/daily • Group 2 (n = 20): 13-cis-retinoic acid (oral isotretinoin) 40 mg/daily Interventions were administered for 16 weeks
Outcomes	• Reduction in lesion counts (only pustules, nodules and cysts) on the face, anterior neck, and trunk (chest and back)[*] • Improvement in photographic evaluation assessed by grading slide from each participants at each visit using the acne grading scale (0-10) proposed by Cunliffe (Cunliffe 1981). Colour slides were produced from a standard set of photographs taken of the face and neck, chest, and back • Subjective improvement assessed by each participant by a visual analogue scale ranging from – 5 to + 5[*] • Sebum excretion rate measured from forehead skin by a gravimetric method (Cunliffe 1969; Cunliffe 1975; Pochi 1991) • Analysis of aerobic and anaerobic skin surface microflora assessed by samples taken from the participants' forehead using the 'scrub' technique (Williamson 1965)[*] • Laboratory and clinical side effects[*] • Reasons for withdrawal[*] Assessments for all outcomes were made at 0, 4, 8, 16, 20, 28, and 36 weeks Indicates outcomes which matched those prespecified for this review
Funding body	Roche Products Limited
Notes	
Risk of bias	

Bias	Authors' judgement	Support for judgement

Prendiville 1988 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "In view of the mucocutaneous side-effects of 13-cis retinoic acid which make double-blind assessment of this drug impossible, our study was conducted on a single-blind basis". "Each slide was graded blind using the acne grading scale (0-10)". Comment: Participants and personnel were not blinded; they were aware of the treatment arm to which participants were allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...our study was conducted on a single-blind basis." "Each slide was graded blind using the acne grading scale (0-10)". Comment: The blinding of outcome assessment was clearly stated only for one of the five outcomes of the study
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Six patients failed to complete the study, three in each group. Four patients, one on dapsone and three on 13-cis retinoic acid were withdrawn because of non-attendance or failure to take medication as directed". Comment: Reasons for attrition were described and there was imbalance of missing data between intervention groups
Selective reporting (reporting bias)	High risk	Comment: No protocol available. Besides this, one outcome, subjective improvement assessed by each participant by a visual analogue scale, was not reported using the measures prespecified on the methods section (only P values at each time point of measurement were reported)
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was promoted by a pharmaceutical company

Rademaker 2013b

Methods	Parallel design, randomised controlled trial
Participants	60 participants from three private dermatological practices in metropolitan New Zealand Inclusion criteria: participants from both gender, aged 25-55 years of age, with low-grade adult acne, which was defined as three or more acne lesions month on the face, for at least three months Exclusion criteria: having acne greater than grade 2, by the Modified Leeds Acne Assessment Scale (Burke 1984); pregnancy (or unwilling to use contraception methods), breast-feeding, any significant systemic illness, BMI over 35, use of any systemic medication likely to influence the participant's acne (including systemic glucocorticoids or antibiotics), use of any topical or systemic anti-acne products in the preceding four weeks; oestrogen and/or progesterone therapy (including levonorgestrel-releasing intrauterine device) which was not on a stable dose for at least 6 months before the start of the study; being on a systemic retinoid in the preceding 6 months Age: for all participants, ranged from 25 to 55 Age: by group, mean ± standard deviation (years) • Group 1 (n = 29): 37.6 ± 7.95

Rademaker 2013b *(Continued)*

- Group 2 (n = 29): 38.5 ± 7.12

Gender: 8 males; 52 female

Duration of acne: not provided

Acne severity: low-grade

Interventions	- Group 1 (n = 29): oral isotretinoin 5 mg/day for 32 weeks - Group 2 (n = 29): placebo for 16 weeks, followed by 16 weeks of oral isotretinoin 5 mg/day (open-label phase)
Outcomes	Primary outcome: - Facial acne lesion count (both inflammatory and non-inflammatory lesions) and changes in quality of life (QoL) assessed by the Dermatology Life Quality Index (DLQI)[*] (Finlay 1994), both measured at week 16 Secondary outcomes: - Facial acne lesion count and DLQI scores at weeks 32 and 42 between groups 1 and 2 and within group 2 at weeks 16 and 32 - Facial erythema assessed by using a 0-3 scale (0-no erythema, 1- slight centrofacial erythema, 2 - pronounced erythema, centrofacial and/or generalised on the face, 3 - severe purple-coloured erythema, centrofacial and or generalised on the face); measurements occurred between treatment groups 1 and 2 at weeks 16, 32 and 42 - Self-assessment of the severity of acne using a linear visual 10 cm scale graded from 0 to 10, with 0 being 'none' and 10, 'very bad acne'; the assessments happened between groups 1 and 2 at weeks 16, 32 and 42[*] - Safety of isotretinoin 5 mg daily determined at the end of each period (weeks 16, 32, and 42). For this assessment, investigators asked the participant if they had experienced any adverse effects and reviewed the participants diary card at each visit to ascertain if any adverse effects had occurred[*] [*] Indicates outcomes which matched those prespecified for this review
Funding body	Douglas Pharmaceuticals
Notes	Despite having enrolled 60 participants, the main report of this study provided demographic data only for 58 participants, which investigators considered as the 'intention to treat population' The main author, Rademaker M, declared being on the speaker bureau for Douglas Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Following written informed consent, patients were randomised to receive either isotretinoin for 32 weeks..." Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This investigator initiated, industry-sponsored study was designed, as a randomised, double-blind, placebo-controlled, parallel group clinical study..." "The placebo capsules were developed to be indistinguishable in smell, taste and appearance from the 5 mg isotretinoin test product."

Rademaker 2013b *(Continued)*

		Comment: There was a description of blinding of participants and personnel during the conduct of the trial, despite no description of any evaluation of the success of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To keep the assessor blinded to adverse effects (e.g. dry lips), the DLQI, patient diary and safety assessments were performed by a study nurse separately to the acne lesion count and erythema scoring." Comment: There was an explicit report of blinding of outcome assessment, despite not having reported an evaluation of the success of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Protocol deviations required exclusion of 12 patients from the PP evaluation at week 16..." Comment: Despite having performed both per protocol and last-observation-carried-forward techniques to analyse data, the high level of missing data at all time points of measurement suggested that an unbiased analysis was unlikely
Selective reporting (reporting bias)	Low risk	Comment: There was an available protocol on a clinical trials registry and all outcomes listed in the methods section of the protocol were adequately reported in the final publication
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was promoted by a pharmaceutical company

Shetti 2013

Methods	Parallel design, randomised controlled trial
Participants	100 participants attending Outpatient Department of Dermatology, District hospital, Mandya Inclusion criteria: participants of either gender, more than 18 years, with moderate to severe acne vulgaris Exclusion criteria: pregnant and lactating women. Age: more than 18 years Gender: of either gender Duration of acne: not provided Acne severity: moderate to severe
Interventions	• Group A (n = 50): low dose continuous oral isotretinoin • Group B (n = 50): low dose intermittent oral isotretinoin Daily dose per kilogram and duration of therapy - not provided
Outcomes	• Improvement in acne severity assessed by Global Acne Grading System (GAGS)* • Occurrence of side effects* Time points of outcome measurements not clearly provided - authors just cited regular time intervals of assessment * Indicates outcomes which matched those prespecified for this review

Shetti 2013 *(Continued)*

Funding body	None stated
Notes	Data above were limited, as we first found only a conference proceeding related to this study. We evaluated a full-text reference in a late stage of our review, after the latest update searches. Additional data from this newer report did not impact conclusions of this review at the late stage; we just incorporated the reference as secondary citation for the study in our review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "An open labeled randomised prospective controlled study of moderate to severe acne vulgaris receiving oral isotretinoin in low dose continuous and low dose intermittent regimen was conducted. " Comment: Participants and personnel were not blinded; they were aware of the treatment arm to which participants were allocated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "An open labeled randomised prospective controlled study of moderate to severe acne vulgaris receiving oral isotretinoin in low dose continuous and low dose intermittent regimen was conducted. " Comment: The study had an open design. There was no information regarding blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Selective reporting (reporting bias)	High risk	Quote: "There was statistically significant difference in GAGS score between group A and group B (P < 0.005). " "Side effects were more frequent with low dose continuous isotretinoin than low dose intermittent isotretinoin regimen". "There was a statistically significant elevation of LDL levels (P < 0.001) in low dose continuous isotretinoin regimen". Comment: There was no detailed and accurate report of numerical data in the results section
Other bias	Low risk	Comment: There were no other apparent sources of bias

Strauss 1984

Methods	Parallel design, randomised controlled trial
Participants	150 participants from three medical centres in United States Inclusion criteria: severe, treatment-resistant, nodulocystic acne and a minimum of ten inflammatory nodulocystic acne lesions at least 4 mm in diameter on the face, back, and chest

Strauss 1984 *(Continued)*

Exclusion criteria: not provided

Age: by group, mean age (years)

- Group 1: 23.3
- Group 2: 23.1
- Group 3: 22.2

Gender: 127 male/14 female

- Group 1: 42/ 4
- Group 2: 38/8
- Group 3: 47/2

Duration of acne: mean (years)

- Group 1: 8,8
- Group 2: 8,5
- Group 3: 7.8

Acne severity: severe

Interventions	- Group 1 (n = 46): oral isotretinoin 0.1 mg/kg/day - Group 2 (n = 46): oral isotretinoin 0.5 mg/kg/day - Group 3 (n = 49): oral isotretinoin 1.0 mg/kg/day Interventions were administered for 20 weeks, but therapy could be stopped when a 70% to 80% reduction in the number of lesions had been obtained
Outcomes	- Changes in baseline counts of all facial and truncal inflammatory lesions, 4 mm or greater in diameter. Assessments were taken during clinical evaluations at 0, 2, 4, 8, 12, 16, and 20 weeks, and at monthly intervals for 2 to 3 months after treatment was discontinued[*] - Incidence of most of the known clinical side effects detected by filling a checklist of symptoms, which was completed by participants at each visit[*] - Percent of participants requiring retreatment with oral isotretinoin assessed at least 8 weeks after the end of the therapy phase and determined if the optimal improvement (less than a 95% reduction in lesions) had not been achieved in the first course Incidence of laboratory abnormalities assessed by tests done at baseline, 4, 8 weeks and at the end of treatment [*] Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	There was no report of demographic data for all initially randomised participants (150)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Assignment of individual dosing schedule was done by a randomised, computer generated code..." Comment: The trial described an adequate method for the random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study

Strauss 1984 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The study was conducted in a double-blind fashion, so that the investigator doing the lesion counts did not know the dosage of drug for any individual". Comment: It was unclear if, besides the investigator, participants and other personnel were also blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The study was conducted in a double-blind fashion, so that the investigator doing the lesion counts did not know the dosage of drug for any individual". Comment: The blinding of outcome assessment was clearly stated only for one outcome of the study
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Data from a few of the patients was not complete and could not be used in the final analysis of the drug trial, but at least forty-six patients were used in the analysis of each group." Comment: Loss to follow-up data were somewhat different in the two reports of the study, but even the minor level of loss to follow-up reported in the primary reference of the study could lead to a considerable attrition bias. Also, the number of withdrawals was different between intervention groups
Selective reporting (reporting bias)	High risk	Quote: "Data for week 2 of isotretinoin treatment have not been presented because the number of patients who returned at that time was relatively small". Comment: No protocol available and selective choice of data for an outcome probably occurred, as week 2 was a predefined time point at the methods section of the main report of the study
Other bias	Low risk	Comment: There were no other apparent sources of bias

Strauss 2001

Methods	Parallel design, randomised controlled trial
Participants	602 participants from multiple centres (17) in United States
	Inclusion criteria: males or non-pregnant; non-nursing females 12 years of age or older; severe recalcitrant nodular acne, with 10 or more nodular lesions (facial and truncal) at least 5 mm in diameter
	Exclusion criteria: use of vitamin A supplements in excess; sensitivity or allergy to parabens. hypersensitivity to vitamin A or its derivatives; use of tetracyclines within 3 days of starting the treatment; recent history of drug or alcohol abuse; any skin disease that might interfere with the evaluation of acne; baseline symptoms of significant depression assessed as severe by the Beck Depression Inventory-II (BDI-II); any previous treatment with etretinate (Tegison) or acitretin (Soriatane); treatment with standard isotretinoin within the previous 180 days; treatment with standard isotretinoin before the last 180 days that was associated with a serious adverse event including significant depression or insomnia to a degree that affected the ability to work or perform daily activities; weight less than 30 kg or greater than 130 kg; and any clinically significant elevation of laboratory values at screening
	Age: for all participants ('per protocol population'), ranged from 12 to 46 years
	Age: by group, mean ± SD/median/range (years)
	• Group 1 (n = 251): 22.2 ± 8.2/20.0/12 - 58
	• Group 2 (n = 241): 21.2 ± 6.5/19.0/13 - 46
	Gender: male/female

Strauss 2001 *(Continued)*

- Group 1 (n = 302): 168/83
- Group 2 (n = 300): 147/94

Duration of acne: not provided

Acne severity: severe

Interventions	• Group 1 (n = 251): micronised isotretinoin, 0.32 to 0.4 mg/kg/day taken once daily at least 2 hours after dinner and matching placebo capsule(s) to be taken with breakfast and dinner • Group 2 (n = 241): standard isotretinoin, 0.85 to 1.18 mg/kg/day, taken in two divided doses with the breakfast and dinner meals along with placebo capsule(s) were given at least 2 hours after dinner Both interventions administered for 20 weeks
Outcomes	Primary efficacy outcome: • Change in the total nodular lesions from baseline to week 20. The percentage of participants with 90% clearance of the total number of baseline nodules (facial and truncal) at week 20 was measured as a supportive efficacy variable Secondary efficacy outcome: • Change in the number of papules plus pustules (facial and trance) from baseline to week 20 • Lesion counts of nodules and papules plus pustules were performed at weeks 8, 16 and 20 of treatment. • Global evaluation (by participant and investigator) at week 20 of treatment assessed by comparisons of photographs taken at baseline and rated on a 6-point scale: 1 = condition worsened; 2 = condition unchanged or minimal response; 3 = fair response; 4 = good response; 5 = excellent response; 6 = cleared[*]. Safety outcomes: • Frequencies of any adverse clinical change from the participant's pretreatment condition, which had occurred during the course of the study and after treatment was started, regardless of relation to treatment[*] • Incidence and severity of 5 commonly described, preselected mucocutaneous adverse effects: (1) dry or peeling skin, (2) dry or bleeding nose (epistaxis), (3) dry or irritated eyes, (4) chapped lips (cheilitis), and (5) rash or erythema of the face[*] • Changes in mood assessments evaluated by a self-report questionnaire and a previously described patient report instrument, the Beck Depression Inventory-II (BDI-II)[*] • Changes in laboratory assessments[*] Safety assessments were made at weeks 0, 2, 4, 8, 12, 16, 20. Laboratory tests were performed during the screening/baseline and either at week 20 or at the end of therapy [*] Indicates outcomes which matched those prespecified for this review.
Funding body	A grant from Roche Laboratories Inc.
Notes	There was no report of demographic data for all initially randomised participants (602) Some authors declared being consultants or employees from Roche Laboratories, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization numbers were based on a 1:1 randomisation and distributed in a block size of two".

Strauss 2001 *(Continued)*

		Comment: The trial did not describe an adequate method for the random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "A comparative, double-blind, double-dummy, multicenter efficacy study of 602 patients…" "Investigators were blinded as to randomisation number generation". Comment: Despite the description of efforts to keep the double-blind design, it was not clear who was blinded. The trial did not report if outcome assessments and clinical evaluation/treatment prescription were done by the same people from the study staff
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Investigators were blinded as to randomisation number generation". Comment: Despite the description of efforts to keep the double-blind design, it was not clear who was blinded. The trial did not report if outcome assessments and clinical evaluation/treatment prescription were done by the same people from the study staff
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote (efficacy outcomes): "The Per Protocol analysis population was defined in the study protocol as patients who were randomised and received at least 12 weeks of the study medication, did not have any major protocol violations, had 80% compliance with the allocated treatment, and had not used Ortho Tri-Cyclen as a method of contraception". Comment (efficacy outcomes): The study adopted a 'per protocol' analysis. From 602 participants initially randomised to each treatment group, 110 (51 originally allocated in group 1 and 59, in group 2) were not included in the analysis in the groups to which they were randomised. This level of loss to follow-up could lead to a considerable attrition bias. Quote (safety outcomes): "All patients who took at least one dose (intent-to-treat [ITT] population) of micronised isotretinoin or standard isotretinoin were included in the safety analysis. " Comment (safety outcomes): In the efficacy report of the same study, a high level of loss to follow-up was stated, making it unlikely that a real ITT analysis for safety outcomes had been performed. The measurement of the effect of differences regarding adverse effects between groups might have been underestimated, since participants who were lost-to follow up earlier could have a higher number of adverse effects if they had received the interventions during the whole period of therapy (20 weeks)
Selective reporting (reporting bias)	High risk	Comment: No protocol available and probably there was a selective choice of data for outcomes. According to the methods section of the efficacy report, lesion counts and participants'/investigators' assessments of global response were done at baseline, 8, 16, and 20 weeks, but only changes between measurements at baseline and at the end of the therapy (at 12 to 20 weeks) were reported
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was promoted by a pharmaceutical company

Tan 2014

Methods	Parallel design, randomised controlled trial
	Duration of the trial: from November 2011 to July 2013
Participants	266 subjects from 29 centres in Canada
	Inclusion criteria: male or female subject of any race, aged 12 to 35 years inclusive; subject weighing between 50 and 110 kg; subject with severe acne (IGA at least 4), which in the opinion of the investigator is appropriate for treatment with oral isotretinoin (severe nodular acne, severe inflammatory acne, recalcitrant acne; all unresponsive to conventional first-line therapies); subject with at least 5 nodules on the face
	Exclusion criteria: subject with clinically abnormal results to blood tests performed at screening; subject with acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), pyoderma faciale, sinus tracks; female subject who is pregnant, nursing or planning a pregnancy during the study; subject with known history of hepatic and/or renal insufficiency, to be confirmed by blood tests; subject with known metabolic or structural bone disease (for 12-17 years old population); subject with bowel disease and/or with hypervitaminosis A; subject who presents with treated or untreated depression or has a history of depression including a family history of major depression; subject with a wash-out period (from baseline for topical treatment on the face) of less than two weeks (corticosteroids, antibiotics, antibacterials, antiseptics, retinoids, other anti-inflammatory drugs or other acne treatments), one week (cosmetic procedures), three months (photodynamic therapy and laser therapy for acne); subject with a wash-out period from baseline for systemic treatment of less than: corticosteroids, antibiotics (4 weeks), progesterone for contraception (3 months); spironolactone (3 months), other acne treatments (6 months), cyproterone acetate (6 months).
	Age: for all participants, ranged from 12 to 35 years
	Age: by group, mean ± standard deviation (years)
	• D+A/BPO Group (n = 133): 19.5 ± 5.0 • ISO Group (n = 133): 19.3 ± 4.5
	Gender:
	• D+A/BPO Group (n = 133): 115 (male)/18 (female) • ISO Group (n = 133): 112 (male)/21 (female)
	- Duration of acne: not provided
	- Acne severity: severe
Interventions	• D+A/BPO Group (n = 133): adapalene 0.1%/benzoyl peroxide 2.5% gel plus doxycycline 200mg once daily for 20 weeks • ISO Group (n = 133): oral isotretinoin once daily (0.5 mg/kg/day for the first 4 weeks with scalation to 1 mg/kg/day for subsequent 16 weeks - mean cumulative dose of 136 mg/kg) plus vehicle gel
Outcomes	Efficacy outcomes:
	• Percent change from baseline in facial nodules, papules/pustules, and total lesion counts (sum of comedones, papules/pustules, and nodules) at weeks 2, 4, 8, 12,16, and 20[*] • Investigator global assessment success rate defined as improvement of at least 2 grades from baseline, measured at weeks 2, 4, 8, 12, 16, and 20[*]
	Safety outcomes:
	• Incidence of clinical adverse effects observed by the investigator or reported by the subject at weeks 2, 4, 8, 12, 16, and 20[*] • Incidence of laboratory adverse effects screened by standard laboratory tests at weeks 4, 16, and 20[*] • Incidence of depression assessed by Major Depression Inventory (MDI/ICD-10) (Bech 2001)[*]

Composite efficacy/safety outcome:

- Overall success, a composite endpoint including efficacy and safety measurements. The composite endpoint was developed and predefined based on precedent of nodule counts as a standard efficacy measure for oral isotretinoin clinical trials, and the safety criteria based on consultation with study investigators

[*] Indicates outcomes which matched those prespecified for this review

Funding body	Galderma
Notes	Authors declared being advisor, consultant, investigator, speaker, or employee of a company with commercial interest in the results of the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Prior to the start of the study, the randomisation list was generated by a statistician. The RANUNI routine of the Statistical Analysis System (SAS; Institute Inc., Cary, NC) was used for the kit number generation. Subjects were randomised in a 1:1 ratio for each group." Comment: The study adopted an adequate method to generate the random sequence
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation list was secured in a locked cabinet and in an electronic file with restricted access to only the designated personnel directly responsible for labelling and handling the study treatments..." Comment: There was an adequate concealment of the allocation sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This phase IIIb, non-inferiority, multicentre, randomised, investigator-blinded, controlled, parallel group study recruited subjects of any race". Comment: The authors reported clearly that participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Investigators did not have access to the randomisation list and study treatments were dispensed by the designated study drug dispenser – someone other than the investigator/rater. Both study drug dispenser and subject were instructed not to discuss the study treatments with the investigator/rater." Comment: There was an explicit report of blinding of outcome assessment, despite not having reported an evaluation of the success of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Three study populations were analysed: safety, intent-to-treat (ITT), and per-protocol (PP) populations. The last observation carried forward method was used to impute missing efficacy values. For the composite endpoint, missing values were considered as unsuccessful." Comment: Since missing data were not equally distributed across groups (regarding both number of missing subjects and reasons for incomplete outcome data), it was unlikely that data analysis was unbiased, even with the use of well recognised methods of data imputation
Selective reporting (reporting bias)	Low risk	Comment: There was an available protocol on a clinical trials registry and outcomes listed in the methods section of the protocol were adequately reported in the final publication

Tan 2014 *(Continued)*

Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was promoted by a pharmaceutical company

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Van der Meeren 1983

Methods	Parallel design, randomised controlled trial
Participants	58 participants from five Departments of Dermatology of University Hospitals, in the Netherlands
	Inclusion criteria: male participants with therapy-resistant acne conglobata and multiple inflamed or hemorrhagic cysts or nodules
	Exclusion criteria: hypertriglyceridaemia; women (because of teratogenic effects in animal experiments)
	Age: mean ± standard deviation (22 ± 6) years, range 15 to 31
	Gender: 100% male
	Duration of acne: mean ± standard deviation (7 ± 5) years
	Acne severity: severe
Interventions	• Group I (n = 27): oral isotretinoin 1.0 mg/kg/daily
	• Group II (n = 31): oral isotretinoin 1.0 mg/kg/daily
	Both groups received the interventions for 12 weeks. After this time point, the dose of oral isotretinoin in both groups could be reduced or increased, but no more than 1.0 mg/kg/daily, until completing 24 weeks of treatment
Outcomes	• Improvement in acne severity evaluated by lesion counts of inflammatory lesions (nodules, papules and pustules) and non-inflammatory lesions (open and closed comedones)*
	• Incidence of seborrhoea clinically evaluated as severe, moderate, slight, and absent
	• Incidence and severity of clinical and laboratory side effects*
	• Remission rates assessed as number of participants with a 90% decrease in total lesion count after the start of therapy phase
	Laboratory assessments were done at baseline, 2, 4, 12, and 24 weeks. All other outcomes were evaluated at each visit, which occurred every 2 weeks
	* Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: The trial did not provide any information about random sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: There was no statement regarding methods of allocation concealment in the study

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Van der Meeren 1983 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: The study did not provide any information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Dry lips and dry skin made the continuation of therapy impossible in 5 patients, 4 of group I and only 1 patient of group II. " Comment: Reasons for attrition were completely described in the Dutch report of the study, and there was an imbalance of missing data and reasons for loss to follow-up across intervention groups during the first 12 weeks of the trial, which we considered in our review
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in the methods section
Other bias	Low risk	Comment: There were no other apparent sources of bias

Wahab 2008

Methods	Parallel design, randomised controlled trial Duration of the trial: from January, 2004 to May, 2007
Participants	60 participants from three medical centres in Dhaka, Bangladesh Inclusion criteria: cases having moderate to severe acne as categorised by the Global Acne Grading Score, GAGS Exclusion criteria: not provided Age: for all participants, range from 15 to 30 years Age: by group, mean ± standard deviation (years) • Group A (n = 30): 21.03 ± 4.21 • Group B (n = 30): 21.50 ± 4. 16 Gender: male/female • Group A (n = 30): 17/13 (high risk of performance and detection bias, besides the absence of allocation concealment) • Group B (n = 30): 16/14 Duration of acne: mean ± standard deviation (months) • Group A (n = 30): 9.57 ± 5.52 • Group B (n = 30): 12.93 ± 6.20 Acne severity: moderate/severe • Group A (n = 30): 20/10 • Group B (n = 30): 25/5

Wahab 2008 *(Continued)*

Interventions	• Group A (n = 30): oral isotretinoin, 0.5 to 1 mg/kg body weight according to severity of the disease, for 5 months
	• Group B (n = 30): azithromycin 500 mg three days a week for 3 months
Outcomes	• Improvement on acne severity evaluated by physician assessment, on the basis of global acne grading score, as excellent: complete clearing of lesions; good: 75% clearing of lesions; good: 50 a 75% clearing of lesions; poor: < 50% clearing of lesions; and no response[*]
	• Relapse during the follow-up period
	• Frequency of recorded side effects[*]
	There were monthly assessments of the outcomes during the treatment phase
	[*] Indicates outcomes which matched those prespecified for this review
Funding body	None stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: The report did not provide any information about random sequence generation. However, after being contacted by email, an author said that they used drawing of lots
Allocation concealment (selection bias)	High risk	Comment: There was no statement regarding methods of allocation concealment in the study. However, after being contacted by email, an author said that no concealment method was used while allocating interventions
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: The study did not provide any information to permit judgement. However, after being contacted by email, an author said that no method was used to ensure blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: The study did not provide any information to permit judgement. However, after being contacted by email, an author said that no method was used to ensure blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There was no statement regarding loss to follow-up or exclusions in the report. However, after being contacted by email, an author said that there were no missing data
Selective reporting (reporting bias)	Low risk	Comment: No protocol available; however, there was an adequate report of outcomes listed in the methods section
Other bias	Low risk	Comment: There were no other apparent sources of bias

Webster 2014

Methods	Parallel design, randomised controlled trial
	Duration of the trial: from September, 2009 to October, 2011
Participants	925 participants from 49 medical study centres in USA and Canada

Webster 2014 *(Continued)*

Inclusion criteria: severe recalcitrant nodular acne, compatible with oral isotretinoin use; 10 or more nodular lesions (including face and trunk); no prior exposure to systemic isotretinoin or other retinoids; age between 12 and 54 years; weight between 40 and 110 kg

Exclusion criteria: pregnancy or high risk of becoming pregnant; breastfeeding or considering breast-feeding during the course of the treatment; skin diseases that could interfere with the evaluation of the study medications; concurrent or previous gastrointestinal disease; known suicidal behaviour; psychosis or psychotic symptoms; carcinoma; liver or kidney disease; pseudotumour cerebri; rheumatoid arthritis or vitamin D depletion disease, and paediatric participants with serum 25-hydroxyvitamin D levels < 20 ng /ml

Age: for all participants, ranged from 12 to 52 years

Age: by group, mean ± standard deviation (years)

- Group 1 (n = 464): 20.8 ± 7.5
- Group 2 (n = 461): 20.7 ± 6.8

Gender: male/female

- Group 1 (n = 464): 277/187
- Group 2 (n = 461): 283/178

- Duration of acne: not provided

- Acne severity: severe

Interventions	- Group 1 (n = 464): isotretinoin-Lidose 1 mg/kg/day for 20 weeks - Group 2 (n = 461): standard isotretinoin 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20

Outcomes

Primary efficacy outcomes: both assessed through lesion counts:

- Change in total nodular facial and truncal lesion count from baseline to week 20
- Percentage of participants who experienced at least 90% reduction in nodular facial and truncal lesion count from baseline to week 20[*]

Secondary efficacy outcome:

- Percentage of participants achieving a grade 0 (clear) or 1 (almost clear) on the 6-point Physician's Global Severity Assessment (PGSA) scale at week 20 (facial lesions only)[*]

Exploratory efficacy outcome:

- Measurement of the Patient Assessment of Efficacy (PAE) at week 20 according to a scale from 0 (patient completely satisfied) to 3 (not satisfied)

Safety assessments:

- Incidence of general adverse effects assessed by physical examinations, vital signs, laboratory tests, adverse event reporting, ophthalmologic testing, audiology testing (not all study sites), and musculoskeletal assessments[*]
- Incidence of psychiatric adverse effects assessed by structured clinical interviews for clinical trials, Patient Health Questionnaire-9, Columbia Suicide Severity Rating Scale, General Anxiety Disorder-7 and psychosis evaluation[*]
- Incidence of bone loss, assessed in a subset of adults and all participants aged 12 to 17 years by dual energy x-ray absorptiometry (DEXA) scans; and changes in bone age, evaluated in all participants aged 12 to 17 years by left hand (wrist) X-rays[*]

[*] Indicates outcomes which matched those prespecified for this review

Webster 2014 *(Continued)*

Funding body	Cipher Pharmaceuticals Inc.
Notes	All authors declared being consultants or employees from a manufacturer of oral isotretinoin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A blocked randomisation regimen, not revealed to the sponsor or investigators, provided an approximately balanced allocation to the 2 treatment groups. Patients were randomised in a 1:1 ration to receive a 30-day supply". Comment: Despite the description of a blocked randomisation process, the trial did not describe an adequate method for the random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "At screening, patients were assigned to receive 1 of the 2 treatment regimens using a centralized randomised system prior to the first dose of medication." Comment: Authors described an adequate method of allocation sequence concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both formulations were over-encapsulated for blinding purposes and were identically packaged. Treatment assignment was concealed to patients, investigators, their staff, and the clinical research team". Comment: There was a description of both who was masked during the conduct of the trial and efforts to keep blinding, despite no description of any evaluation of the success of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Treatment assignment was concealed to patients, investigators, their staff, and the clinical research team". Comment: There was a clear description of blinded outcome assessment during the conduct of the trial, despite no description of any evaluation of the success of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Since missing data were not equally distributed across groups (regarding both number of missing subjects and reasons for incomplete outcome data), it was unlikely that data analysis was unbiased, even with the use of well recognised methods of data imputation
Selective reporting (reporting bias)	Low risk	Comment: There was an available registered protocol and the study final report described all pre-specified outcomes according to the protocol text
Other bias	Unclear risk	Comment: The study might be at risk of inappropriate influence of funders, as it was promoted by a pharmaceutical company

AA: azelaic acid
ADA: adapalene
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BDI-II: Beck Depression Inventory-II
BMI: Body Mass Index
BUT: break-up time test
D+A/BPO: doxycycline plus adapalene/benzoyl peroxide
DEXA: dual energy x-ray absorptiometry
DLQI: Dermatology Life Quality Index

FDA: US Food and Drug Administration

G6PD: Glucose-6- phosphate dehydrogenase

GAAS: Global Acne Assessment Scale

GAGS:global acne grading system score

GAS: Global acne scoring

IGA: Investigator global assessment

ISO: isotretinoin

kg: kilogram

LDL: low-density lipoproteins

MDI/ICD-10: Major Depression Inventory

mg: miligram

mm: millimetre

PAE: Patient Assessment of Efficacy

PGSA: Physician's Global Severity Assessment

QoL: Quality of life

SD: standard deviation

SMS: Sawai Man Singh

STD: Sexually transmitted disease

TAL: total acne load

TCA: trichloroacetic acid

TET: tetracycline

VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Herane 2009	This RCT studied a gel hydrating cream to manage dryness of the skin related to oral isotretinoin therapy.
Kus 2005	This RCT studied vitamin E to manage dryness of the skin related to oral isotretinoin therapy.
Li 2004	This RCT had an inappropriate comparator intervention (an alternative treatment, Qingfei Liangxue Fa, which is a prescription from traditional Chinese medicine that is used for clearing the lungs and removing fat).
Lin 1999	This RCT included participants with another condition, haemodialysis-related acne, and not acne vulgaris.
Liu 2008	This RCT had an inappropriate comparator intervention (an alternative treatment: encircling acupuncture combined with venesection and cupping).
Shen 2000	This RCT had an inappropriate comparator intervention (an alternative treatment: compound shecao decoction, from traditional Chinese medicine).
Strauss 2000	This RCT had tested another intervention: vitamin E.
Sun 2000	This RCT had an inappropriate comparator intervention (an alternative treatment: An Ti Shu Tong, 20 mg twice daily, from traditional Chinese medicine).
Williams 1992	This RCT had tested another intervention: intranasal mupirocin.

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Faghihi 2017

Methods	Parallel design, randomised controlled trial Duration of the trial: from 2014 to 2015
Participants	66* participants from 1 single study centre at Isfahan, Iran Inclusion criteria: patient consent to participate in the study, no sensitivity to retinoids, no pregnancy, not willing to become pregnant, and absence of hormonal disorders in patients Exclusion criteria: failure of the patient to attend follow-up sessions for any reason, and adoption of other supplementary therapies during the study Age: by group, mean ± standard deviation (years) • Group 1 (n = 36): 22.94 ± 6.25 • Group 2 (n = 30): 23.1 ± 4.66 Gender: male/female • Group 1 (n = 36): 5/31 • Group 2 (n = 30): 8/22 Duration of acne: not provided Acne severity: moderate to severe
Interventions	• Group 1 (n = 36): oral isotretinoin 0.25 mg/kg/day (low dose isotretinoin) for six months • Group 2 (n = 30): oral isotretinoin 0.5 mg/kg/day (conventional dose) for six months
Outcomes	• Acne severity assessed by a dermatologist through the Global Acne Grading System (GAGS) (Adityan 2009) at baseline, at six-month therapy and six months after the end of therapy phase* • Side effects of isotretinoin examined and recorded by a dermatologist at each monthly visit during the six-month therapy* • Participant satisfaction level assessed and recorded at the end of treatment by visual analogue scale (VAS) (Brokelman 2012) for satisfaction* * Indicates outcomes which matched those prespecified for this review
Notes	* Authors cited 60 participants in the abstract section. However, when authors referred to numbers of males and females in each group in the results section of the report, it was clear that there were 66 participants. Authors did not clearly report if there was loss to follow-up.

GAGS: Global Acne Grading System
VAS: visual analogue scale

Characteristics of ongoing studies *[ordered by study ID]*

IRCT201104094310N6

Trial name or title	Comparison of therapeutic effects of oral erythromycin along with low dose oral Isotretinoin and oral erythromycin and low dose flutamide versus doxycyclin in female severe acne vulgaris
Methods	Randomised controlled trial
Participants	Inclusion criteria: females with severe acne Exclusion criteria: pregnancy; breastfeeding; liver disease; hyperlipidaemia; receiving anti-acne drugs; OCP pills; spironolactone in the last 2 months Age: no age limit

	Gender: female
Interventions	• Intervention 1 (control group): 100 ml oral doxycycline every 12 hours during 2 months • Intervention 2: oral erythromycin (400 ml/BID) and oral isotretinoin (20 ml every 48 hours) during 2 months • Intervention 3: oral erythromycin (400 ml/BID) and flutamide (65 ml oral a day) during 2 months
Outcomes	• Decrease of acne lesions Time point: onset of study and days 30 and 60 Method of measurement: observation
Starting date	20 September 2013
Contact information	m.golmohammadi@arums.ac.ir
Notes	

IRCT2013110315246N1

Trial name or title	Acne cure rate in patients hyperandrogenism with two drugs of decuttane and cyptroterone compound
Methods	Randomised controlled trial
Participants	Inclusion criteria: female; age between 14-45 years old; besides acne, hirsutism (Ferriman & Gallwey score greater than or equal to 4) and Ludwing grade one or higher female androgenetic alopecia; absence of contraindications to treatment with tablets decuttane and cyproterone compound based on questionnaire; not planning a pregnancy or breast-feeding; individual participants signed a consent form Exclusion criteria: drug allergy; pregnancy or lactation; uncooperative patient or patient's consent to continue reading
Interventions	• Intervention 1: decuttane - isotretinoin 20 mg daily + azithromycin 250 mg capsules three times a week, erythromycin solution of 4% once a day, oil-free sunscreen and Tcc soap three months • Intervention 2: cyproterone compound + azithromycin 250 mg capsules three times a week, erythromycin solution of 4% once a day, oil-free sunscreen and Tcc soap three months
Outcomes	• Improvement of acne vulgaris lesions. Timepoint: baseline, three months and one month after the end of treatment. Method of measurement: indices were calculated based on the Total Acne Lesion Count (TLC) and acne severity index (ASI) for each participant • Side effects of the drug. Timepoint: every 6 weeks. Method of measurement: clinical evaluation - liver function test and lipid profile
Starting date	18 April 2012
Contact information	kioumars_jamshidi@med.mui.ac.ir
Notes	

ASI: acne severity index
BID: twice (two times) a day
OCP: oral contraceptive
Tcc: triclocarban

TLC: Total Acne Lesion Count

DATA AND ANALYSES

Comparison 1.   Oral isotretinoin versus any oral antibiotic plus any topical agent

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Improvement in acne severity assessed by a decrease in total inflammatory lesion count, measured in participants who were treated for a minimum period of 16 weeks	3	400	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.96, 1.06]
1.1 Oral isotretinoin versus oral minocycline plus azelaic acid cream	1	85	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.95, 1.05]
1.2 Oral isotretinoin versus doxycycline plus adapalene/benzoyl peroxide gel	1	266	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.98, 1.05]
1.3 Oral isotretinoin versus tetracycline plus topical adapalene	1	49	Risk Ratio (M-H, Random, 95% CI)	4.17 [0.50, 34.66]
2 Frequency of serious adverse effects	3	400	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.98]
2.1 Oral isotretinoin versus oral minocycline plus azelaic acid cream	1	85	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Oral isotretinoin versus tetracycline plus topical adapalene	1	49	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Oral isotretinoin versus doxycycline plus adapalene/benzoyl peroxide gel	1	266	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.12, 72.98]
3 Improvement in acne severity assessed by physician's global evaluation	2	351	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.00, 1.32]
3.1 Very good or good improvement	1	85	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.97, 1.20]
3.2 Decrease of at least two grades from baseline score	1	266	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.09, 1.38]
4 Frequency of less serious adverse effects	2	351	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.42, 1.98]
4.1 Four-week analysis	1	85	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.03, 3.51]
4.2 20-week analysis	1	266	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.39, 1.97]
5 Dropout rates	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 Overall dropout rates	3	403	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.44, 1.09]
5.2 Dropout rates due to adverse effects	3	403	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.30, 2.31]
5.3 Dropout rates due to no improvement or lack of efficacy	2	137	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.03, 2.64]
5.4 Dropout rates due to loss to follow-up or not specified reasons	3	403	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.36, 2.26]

Analysis 1.1. Comparison 1 Oral isotretinoin versus any oral antibiotic plus any topical agent, Outcome 1 Improvement in acne severity assessed by a decrease in total inflammatory lesion count, measured in participants who were treated for a minimum period of 16 weeks.

Study or subgroup	Oral isotretinoin	Oral antib & topical	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.1.1 Oral isotretinoin versus oral minocycline plus azelaic acid cream					
Gollnick 2001	35/35	50/50		45.25%	1[0.95,1.05]
Subtotal (95% CI)	**35**	**50**		**45.25%**	**1[0.95,1.05]**
Total events: 35 (Oral isotretinoin), 50 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.1.2 Oral isotretinoin versus doxycycline plus adapalene/benzoyl peroxide gel					
Tan 2014	131/133	129/133		54.7%	1.02[0.98,1.05]
Subtotal (95% CI)	**133**	**133**		**54.7%**	**1.02[0.98,1.05]**
Total events: 131 (Oral isotretinoin), 129 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
1.1.3 Oral isotretinoin versus tetracycline plus topical adapalene					
Oprica 2007	4/24	1/25		0.05%	4.17[0.5,34.66]
Subtotal (95% CI)	**24**	**25**		**0.05%**	**4.17[0.5,34.66]**
Total events: 4 (Oral isotretinoin), 1 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.32(P=0.19)					
Total (95% CI)	**192**	**208**		**100%**	**1.01[0.96,1.06]**
Total events: 170 (Oral isotretinoin), 180 (Oral antib & topical)					
Heterogeneity: Tau²=0; Chi²=3.69, df=2(P=0.16); I²=45.8%					
Test for overall effect: Z=0.37(P=0.71)					
Test for subgroup differences: Chi²=1.97, df=1 (P=0.37), I²=0%					

Favours oral antib & Top   0.1 0.2   0.5   1   2   5   10   Favours oral isotretinoin

Analysis 1.2.   Comparison 1 Oral isotretinoin versus any oral antibiotic plus any topical agent, Outcome 2 Frequency of serious adverse effects.

Study or subgroup	Oral isotretinoin n/N	Oral antib & topical n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Oral isotretinoin versus oral minocycline plus azelaic acid cream					
Gollnick 2001	0/35	0/50			Not estimable
Subtotal (95% CI)	**35**	**50**			**Not estimable**
Total events: 0 (Oral isotretinoin), 0 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.2.2 Oral isotretinoin versus tetracycline plus topical adapalene					
Oprica 2007	0/24	0/25			Not estimable
Subtotal (95% CI)	**24**	**25**			**Not estimable**
Total events: 0 (Oral isotretinoin), 0 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.2.3 Oral isotretinoin versus doxycycline plus adapalene/benzoyl peroxide gel					
Tan 2014	1/133	0/133		100%	3[0.12,72.98]
Subtotal (95% CI)	**133**	**133**		**100%**	**3[0.12,72.98]**
Total events: 1 (Oral isotretinoin), 0 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
Total (95% CI)	**192**	**208**		**100%**	**3[0.12,72.98]**
Total events: 1 (Oral isotretinoin), 0 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
Test for subgroup differences: Not applicable					

Favours oral isotret   0.001   0.1   1   10   1000   Favours oral antib & top

Analysis 1.3.   Comparison 1 Oral isotretinoin versus any oral antibiotic plus any topical agent, Outcome 3 Improvement in acne severity assessed by physician's global evaluation.

Study or subgroup	Oral isotretinoin n/N	Oral antib & topical n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Very good or good improvement					
Gollnick 2001	34/35	45/50		51.06%	1.08[0.97,1.2]
Subtotal (95% CI)	**35**	**50**		**51.06%**	**1.08[0.97,1.2]**
Total events: 34 (Oral isotretinoin), 45 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.38(P=0.17)					
1.3.2 Decrease of at least two grades from baseline score					
Tan 2014	120/133	98/133		48.94%	1.22[1.09,1.38]
Subtotal (95% CI)	**133**	**133**		**48.94%**	**1.22[1.09,1.38]**
Total events: 120 (Oral isotretinoin), 98 (Oral antib & topical)					

Favours oral antib & top   0.5   0.7   1   1.5   2   Favours oral isotretinoin

Study or subgroup	Oral isotretinoin	Oral antib & topical	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=3.42(P=0)					
Total (95% CI)	168	183		100%	1.15[1,1.32]
Total events: 154 (Oral isotretinoin), 143 (Oral antib & topical)					
Heterogeneity: Tau²=0.01; Chi²=3.14, df=1(P=0.08); I²=68.17%					
Test for overall effect: Z=1.92(P=0.05)					
Test for subgroup differences: Chi²=2.43, df=1 (P=0.12), I²=58.76%					

Favours oral antib & top   0.5   0.7   1   1.5   2   Favours oral isotretinoin

Analysis 1.4. Comparison 1 Oral isotretinoin versus any oral antibiotic plus any topical agent, Outcome 4 Frequency of less serious adverse effects.

Study or subgroup	Oral isotretinoin	Oral antib & topical	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.4.1 Four-week analysis					
Gollnick 2001	16/35	12/50		7.48%	1.9[1.03,3.51]
Subtotal (95% CI)	**35**	**50**		**7.48%**	**1.9[1.03,3.51]**
Total events: 16 (Oral isotretinoin), 12 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.07(P=0.04)					
1.4.2 20-week analysis					
Tan 2014	116/133	70/133		92.52%	1.66[1.39,1.97]
Subtotal (95% CI)	**133**	**133**		**92.52%**	**1.66[1.39,1.97]**
Total events: 116 (Oral isotretinoin), 70 (Oral antib & topical)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.69(P<0.0001)					
Total (95% CI)	**168**	**183**		**100%**	**1.67[1.42,1.98]**
Total events: 132 (Oral isotretinoin), 82 (Oral antib & topical)					
Heterogeneity: Tau²=0; Chi²=0.19, df=1(P=0.66); I²=0%					
Test for overall effect: Z=6.04(P<0.0001)					
Test for subgroup differences: Chi²=0.18, df=1 (P=0.67), I²=0%					

Favours oral isotretinoin   0.2   0.5   1   2   5   Favours oral antib & top

Analysis 1.5. Comparison 1 Oral isotretinoin versus any oral antibiotic plus any topical agent, Outcome 5 Dropout rates.

Study or subgroup	Oral isotretinoin	Oral antib & topical	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.5.1 Overall dropout rates					
Gollnick 2001	2/35	6/50		8.75%	0.48[0.1,2.22]
Oprica 2007	7/26	6/26		23.24%	1.17[0.45,3]

Favours oral isotretinoin   0.01   0.1   1   10   100   Favours oral antib & top

Study or subgroup	Oral isotretinoin n/N	Oral antib & topical n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Tan 2014	17/133	28/133		68.01%	0.61[0.35,1.06]
Subtotal (95% CI)	**194**	**209**		**100%**	**0.69[0.44,1.09]**

Total events: 26 (Oral isotretinoin), 40 (Oral antib & topical)

Heterogeneity: Tau²=0; Chi²=1.62, df=2(P=0.44); I²=0%

Test for overall effect: Z=1.58(P=0.11)

1.5.2 Dropout rates due to adverse effects

Gollnick 2001	0/35	2/50		11.45%	0.28[0.01,5.73]
Oprica 2007	3/26	1/26		21.45%	3[0.33,26.99]
Tan 2014	4/133	6/133		67.1%	0.67[0.19,2.31]
Subtotal (95% CI)	**194**	**209**		**100%**	**0.83[0.3,2.31]**

Total events: 7 (Oral isotretinoin), 9 (Oral antib & topical)

Heterogeneity: Tau²=0; Chi²=1.92, df=2(P=0.38); I²=0%

Test for overall effect: Z=0.35(P=0.73)

1.5.3 Dropout rates due to no improvement or lack of efficacy

Gollnick 2001	0/35	1/50		47.03%	0.47[0.02,11.27]
Oprica 2007	0/26	2/26		52.97%	0.2[0.01,3.97]
Subtotal (95% CI)	**61**	**76**		**100%**	**0.3[0.03,2.64]**

Total events: 0 (Oral isotretinoin), 3 (Oral antib & topical)

Heterogeneity: Tau²=0; Chi²=0.15, df=1(P=0.7); I²=0%

Test for overall effect: Z=1.09(P=0.28)

1.5.4 Dropout rates due to loss to follow-up or not specified reasons

Gollnick 2001	1/35	0/50		8.36%	4.25[0.18,101.39]
Oprica 2007	3/26	3/26		37.13%	1[0.22,4.5]
Tan 2014	4/133	6/133		54.51%	0.67[0.19,2.31]
Subtotal (95% CI)	**194**	**209**		**100%**	**0.9[0.36,2.26]**

Total events: 8 (Oral isotretinoin), 9 (Oral antib & topical)

Heterogeneity: Tau²=0; Chi²=1.17, df=2(P=0.56); I²=0%

Test for overall effect: Z=0.21(P=0.83)

Test for subgroup differences: Chi²=0.97, df=1 (P=0.81), I²=0%

Favours oral isotretinoin	0.01	0.1	1	10	100	Favours oral antib & top

Comparison 2. Oral isotretinoin versus oral isotretinoin plus any topical agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout rates	2	118	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.32, 3.10]

Analysis 2.1. Comparison 2 Oral isotretinoin versus oral isotretinoin plus any topical agent, Outcome 1 Dropout rates.
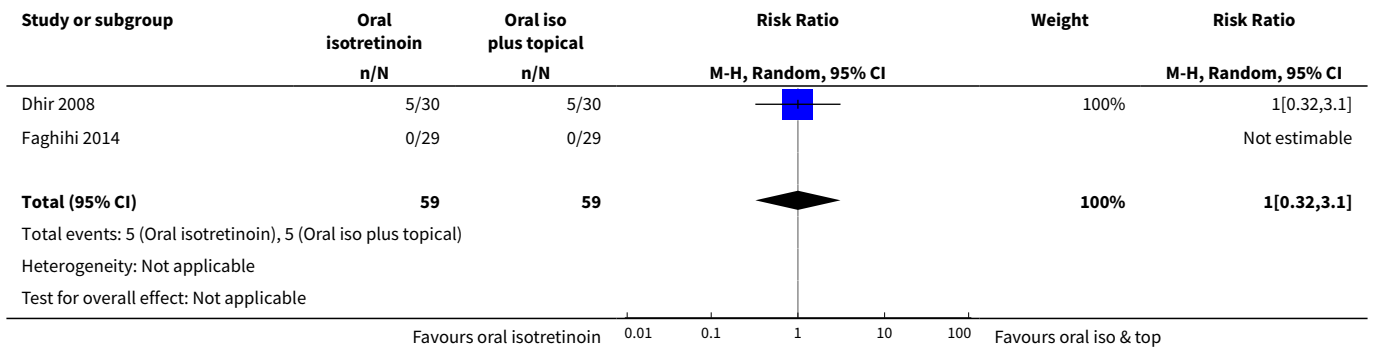
Study or subgroup	Oral isotretinoin	Oral iso plus topical	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Dhir 2008	5/30	5/30		100%	1[0.32,3.1]
Faghihi 2014	0/29	0/29			Not estimable
Total (95% CI)	**59**	**59**		**100%**	**1[0.32,3.1]**
Total events: 5 (Oral isotretinoin), 5 (Oral iso plus topical)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours oral isotretinoin 0.01 0.1 1 10 100 Favours oral iso & top

Comparison 3. Standard oral isotretinoin versus other formulations of oral isotretinoin

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Improvement in acne severity assessed by physician's global evaluation	2	1274	Risk Ratio (M-H, Random, 95% CI)	1.06 [1.00, 1.11]
2 Dropout rates	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Overall dropout rates	2	1527	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.74, 1.34]
2.2 Dropout rates due to adverse effects	2	1527	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.56, 1.43]
2.3 Dropout rates due to loss to follow-up, noncompliance or withdraw of consent	2	1527	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.82, 1.48]

Analysis 3.1. Comparison 3 Standard oral isotretinoin versus other formulations of oral isotretinoin, Outcome 1 Improvement in acne severity assessed by physician's global evaluation.

Study or subgroup	Standard isotretinoin	Other formulations	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Strauss 2001	179/241	176/251		20.35%	1.06[0.95,1.18]
Webster 2014	351/395	326/387		79.65%	1.05[1,1.12]
Total (95% CI)	**636**	**638**		**100%**	**1.06[1,1.11]**
Total events: 530 (Standard isotretinoin), 502 (Other formulations)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.94); I²=0%					
Test for overall effect: Z=2.15(P=0.03)					

Favours other formulation 0.5 0.7 1 1.5 2 Favours standard isotret

Analysis 3.2. Comparison 3 Standard oral isotretinoin versus other formulations of oral isotretinoin, Outcome 2 Dropout rates.

Study or subgroup	Standard isotretinoin	Other formulations	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
3.2.1 Overall dropout rates					
Strauss 2001	59/300	51/302		48.18%	1.16[0.83,1.63]
Webster 2014	60/461	70/464		51.82%	0.86[0.63,1.19]
Subtotal (95% CI)	**761**	**766**		**100%**	**1[0.74,1.34]**
Total events: 119 (Standard isotretinoin), 121 (Other formulations)					
Heterogeneity: Tau²=0.02; Chi²=1.59, df=1(P=0.21); I²=37.23%					
Test for overall effect: Z=0.02(P=0.98)					
3.2.2 Dropout rates due to adverse effects					
Strauss 2001	16/300	16/302		49.28%	1.01[0.51,1.98]
Webster 2014	15/461	19/464		50.72%	0.79[0.41,1.54]
Subtotal (95% CI)	**761**	**766**		**100%**	**0.89[0.56,1.43]**
Total events: 31 (Standard isotretinoin), 35 (Other formulations)					
Heterogeneity: Tau²=0; Chi²=0.24, df=1(P=0.62); I²=0%					
Test for overall effect: Z=0.47(P=0.64)					
3.2.3 Dropout rates due to loss to follow-up, noncompliance or withdraw of consent					
Strauss 2001	43/300	35/302		50.62%	1.24[0.82,1.88]
Webster 2014	39/461	40/464		49.38%	0.98[0.64,1.5]
Subtotal (95% CI)	**761**	**766**		**100%**	**1.1[0.82,1.48]**
Total events: 82 (Standard isotretinoin), 75 (Other formulations)					
Heterogeneity: Tau²=0; Chi²=0.59, df=1(P=0.44); I²=0%					
Test for overall effect: Z=0.65(P=0.52)					
Test for subgroup differences: Chi²=0.6, df=1 (P=0.74), I²=0%					

Favours standard isotret 0.2 0.5 1 2 5 Favours other formulation

ADDITIONAL TABLES

Table 1. Glossary of Medical Terms

Medical term	Explanation
Apoptosis	A programmed cell death where the causes are normal and abnormal biochemical mechanisms occurring inside apoptotic cells. Apoptosis may be a result of the vital cell turnover or a consequence of cancer, neurodegenerative disease, ischaemia or autoimmune disorders
Angular stomatitis	An inflammation which affects the corners of the mouth
Arthralgia	Pain in one or more joints of the body
Blepharoconjunctivitis	The combination of conjunctivitis (inflammation of the conjunctiva, which is the inner surface of the eyelid) with blepharitis (inflammation of the skin in the outer surface of eyelids)
Case-control	A study which consists of recognising individuals who have the outcome (e.g. a specific disease) of interest (cases) and those who do not have that same outcome (controls). The study looks back to find out if individuals (cases and controls) had an exposure of interest. The exposure could be

Table 1. Glossary of Medical Terms *(Continued)*

	a drug or other therapeutic intervention as well as an environmental or behavioural factor. The 2 groups are then compared to see if there is a difference in exposure
Cheilitis	An inflammation of the lips. Cheilitis usually presents with dry lips, cracking or peeling of the lips and flaking of the skin of the lips
Cutaneous	Related to the skin
Dermis	The layer of skin between the epidermis (outer layer of skin) and subcutaneous tissues
Desquamation	The spontaneous detachment of the more superficial layers of the skin
Discoid dermatitis	Also known as 'discoid eczema', 'microbial eczema', 'nummular eczema', 'nummular dermatitis', or 'nummular neurodermatitis', it is one of the many forms of dermatitis and presents with characteristic round or oval-shaped itchy lesions resembling the shape of a coin
Epistaxis	Nasal bleeding
Erector pili muscle	Very small muscles attached to hair follicles contract to make the hair shaft become erect. This may cause ejection of the sebum, which is forced through the hair follicle to the surface
Facial dermatitis	People with this condition present with facial erythema and flaking (especially of the skin around the mouth and nose)
Follicular hyperkeratinisation	A disorder of the cells lining the inside of a hair follicle. These cells usually shed from the skin lining at normal intervals. The dead cells however become cohesive because of an excess of keratin (a natural protein found in the skin), and they do not shed onto the skin's surface, blocking the hair follicle
Hair follicle	A very small cavity in the skin that produces hair
Hyperkeratinisation	An alteration of the skin cell detachment process, which is reduced as a consequence of an excessive production of keratin, the protein present in the most superficial layers of skin
Hypertriglyceridaemia	The elevation of blood concentrations of triglycerides, which may increase risk of stroke and heart attack
Idiopathic intracranial hypertension (IIH)	A neurological condition characterised by increased intracranial pressure (pressure around the brain) in the absence of a tumour or other diseases. The main symptom is headache, but nausea, vomiting, pulsatile tinnitus (buzzing in the ears synchronous with the pulse), double vision, and other visual symptoms may also occur. A consequence of IIH is swelling of the optic disc in the eye, with the possibility of progression to vision loss if IIH is untreated (Binder 2004)
Inflammatory bowel disease (IBD)	A group of inflammatory alterations of the colon and small intestine. The main types of IBD are Crohn's disease and ulcerative colitis. Although very different diseases, both have as symptoms abdominal pain, diarrhoea, vomiting, weight loss, rectal bleeding, and severe internal cramps in the pelvic region. IBD often causes symptoms that may limit quality of life, but it is rarely fatal on its own
Innate and acquired immune responses	Innate immune responses are immediate and nonspecific mechanisms of response to micro-organisms in a generic way, with the aim of protecting the host from invading micro-organisms, such as bacteria and viruses. Acquired immune responses occur later; they are triggered by innate immunity and are specific to a micro-organism or a molecule from a micro-organism. They also enable a stronger response in defence as well as immunological memory
Microcomedones	An early acne lesion that appears with the plugging of a hair follicle by the following: skin cells lining the follicle becoming more cohesive (they are shed and accumulate in the pore instead of flow-

Cochrane
Library

Trusted evidence.
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Table 1.   Glossary of Medical Terms *(Continued)*

	ing out onto the skin); or an excess of sebum and keratin (a natural protein found in the skin) inside the follicle
Micronised	The property of having a very reduced average diameter, measured only by micrometer. Usually this term refers to the process involved in the production of pharmaceutical particles
Mucocutaneous	Related to mucosa and skin
Pharmacokinetic	The analysis of all process which happen in the body since the initial administration of a drug until its total excretion, including its way of action on target tissues
Pilosebaceous unit	A structure consisting of a hair shaft within a hair follicle to which the erector pili muscle and sebaceous glands are attached
Polymorphic	The characteristic of having or passing through some stages of development
Psychosis	A mental state characterised by a detachment from reality. People with psychosis can have hallucinations, delusional beliefs, unusual or bizarre behaviour, personality changes, and thought disorder. Several central nervous system diseases, from both external poisons and internal physiologic illness, are causes of psychosis
Pyogenic granuloma	A benign cell growth of the skin which is composed of numerous small blood vessels. This type of skin lesion usually is smaller than 2,5 cm, appears in a few weeks, and may easily bleed
Sebaceous gland	These are microscopic glands in the skin, usually found in hair-covered areas of the body (greatest abundance on the face and scalp), which are part of the pilosebaceous unit. They secrete an oily/waxy matter (sebum), which lubricates the skin and hair. Sebum is deposited inside the hair follicles and arrives at the skin surface along the hair shaft
Triglycerides	One type of fat which is present in the blood
Xeroderma	Another term for 'dry skin'. Signs and symptoms include scaling, itching, and cracking of the skin
Xerosis	Dryness of the skin

Table 2.   Characteristics of nonrandomised studies (considered for safety analysis)

Study	Methods	Participants	Interventions / Exposures	Outcomes (Psychiatric adverse effects)	Summary Findings (Frequencies of psychiatric adverse effects)	Assessment of the risk of bias (Turner 2013)
Azoulay 2008	Design: Case-control crossover Duration of the study: not provided Period of recruitment: from	Setting: Québec, Canada Initial cohort: 30,496 participants Cases (n = 126): • age, mean ± SD (years): 28.1 ± 9.0	Exposure group: oral isotretinoin use in a five-month period immediately prior to the index date Control group: oral isotretinoin	Incidence of a first diagnosis or hospitalisation for depression in each specific time window Dose response of oral	Adjusted relative risk of depression associated with oral isotretinoin use was 2.68 (95% CI 1.10 to 6.48). There were no statistically significant differences in incidence of depression before and after Canadian label change warning about isotretinoin	Selection bias: High risk Although authors had reported an adjusted analysis for some covariates, the study did not consider either acne severity or time with disease as confounders Performance bias (all outcomes): High risk

Table 2. Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

| | January 1, 1984, and December 31, 2003 | • gender: 37.3% males (n = 47 Inclusion criteria: having been exposed to at least one oral isotretinoin prescription between January 1, 1984, and December 31, 2003 and diagnosed or hospitalised for depression, with an antidepressant prescription in the 30 days following the diagnosis or hospitalisation; being covered by the Régie de l' Assurance Maladie du Québec (RAMQ) drug plan for at least 12 months prior to the date of depression diagnosis (index date); having at least 1 diagnosis of acne vulgaris at any time prior to the index date * Exclusion criteria: having received an antidepressant prescription in the 12 months prior to index date | use out of the 5-month risk period (considering a 2-month wash-out period) prior to the index date | isotretinoin on the incidence of depression Outcomes assessments occurred by linkage of diagnosis codes and antidepressant prescriptions with medical records | possible psychiatric risks There was no significant association between a cumulative dose range and the occurrence of depression | Comment: As the study had a retrospective design, probably personnel and participants were not blinded regarding the exposition/drug Detection bias (all outcomes): Unclear risk Comment: The study did not provide any information regarding blinding of the outcome assessors Attrition bias (all outcomes): Unclear risk Comment: There was no information about missing data or the potential for data to be missing to permit judgment. Selective reporting bias: Low risk Comment: no protocol available; however, there was an adequate report of outcomes listed in methods section Other bias: High-risk The study used an instrument with a poor accuracy to measure outcomes: record linkage across electronic databases. Also, the study had presented only a case-cross-over analysis and this design had a potential risk of bias related to the possibility of carry-over effect in participants of nonexposed groups, despite the 2-month wash-out period |
| Chia 2005 | Design: Prospective cohort Duration of the study: | Setting: United States, two centres at Missouri: Departments of Dermatology at Saint Louis University, Saint Louis, and at University of Mis | Group 1: oral isotretinoin at approximately 1 mg/kg per day, rounded to the | Frequency of CES-D (The Center for Epidemiologic Studies Depression Scale) scores of 17 | 101 subjects completed the study (49 in Group 1; 52 in Group 2). After adjustment for baseline CES-D and participant gender, there was not a significant association between | Selection bias: High-risk Comment: The study analysed the prevalence of CES-D > 16 at follow-up using multiple logistic regression, with baseline CES-D score and gender as covariates in the analysis. How- |

Table 2. Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

not clearly provided	souri, Columbia. Both were outpatient clinics, one urban/hospital affiliated and the other suburban/community affiliated	nearest 20 mg	or higher, which were suggestive of clinically significant depression. The CES-D scale is validated in adolescents and considered more sensitive and less specific than other depression instruments	treatment status (isotretinoin therapy versus conservative therapy) and follow-up CES-D score (prevalence at this time point) suggestive of clinically significant depression (odds ratio (OR), 1.1; 95% CI, 0.23 to 5.6). Also intention-to-treat analysis did not modify this result (OR, 1.3; 95% CI, 0.31 to 5.7)	ever, the incidence of CES-D > 16 at follow-up was not presented using a method for control of confounding. Other potential confounders, such as duration of acne and acne severity, were not considered in the study. Also the two different settings of recruitment (one urban/hospital-affiliated and the other suburban/community- affiliated outpatient clinics) could be a confounding factor, and the analysis did not consider this concern
Period of recruitment: between October 1998 and December 2001	Gender: • Group 1: n = 59 (44 males and 15 females) • Group 2: n = 73 (44 females and 29 males)	Group 2: conservative therapy defined as a topical antibiotic, topical retinoid, and twice-daily administration of an oral antibiotic		CES-D scores of 17 or higher (> 16) at the 3 or 4 months of follow-up suggesting new-onset of depression (incidence measurement) occurred in 4.1% (2 cases) of participants in the oral isotretinoin group, and in 3.8% of participants in the conservative therapy group (RD 0.3; 95% CI, -7.7 to 8.3). The difference between the groups was not statistically significant, even after performing an intention-to-treat analysis	Performance bias (all outcomes): Unclear risk Comment: The study did not provide any information regarding blinding of participants and personnel Detection bias (all outcomes): Unclear risk Comment: The study did not provide any information regarding blinding of the outcome assessors
Factors influencing the choice of treatment: history of previous treatment failure, participant/parent preference, out-of-pocket medical cost, ability/willingness to comply with treatment requirements for frequent visits and phlebotomy, participant/parental concerns about adverse drug effects, and objections to oral contraceptive therapy	The study provided no information regarding duration of acne in enrolled participants Inclusion criteria: male and female participants between the ages of 12 and 19; being presented for treatment of moderate to severe inflammatory and cystic acne Exclusion criteria: history of or current DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) Axis I diagnosis; prior use of or allergy to isotretinoin, and pregnancy	Duration of interventions: not provided	Incidence of suicidal ideation in all participants who scored 17 or higher in CES-D, assessed by interviewing participants with the mood disorders portion of the Structured Clinical Interview for DSM-IV Axis I (major mental disorders) Measurements occurred at baseline and after completing 3 to 4 months of follow-up	No participant had suicidal ideation between participants with CES-D scores > 16 in the isotretinoin group. One subject at baseline presented suicidal ideation in the control group (an incidence of 1.4%)	Attrition bias (all outcomes): Low risk Comment: An intention-to-treat analysis, with adjustments for baseline CES-D and gender, presented the same results of the adjusted analysis that excluded those unavailable for follow-up. Despite the high level of loss to follow-up in the study, there was no potential impact of missing data for all outcomes Selective reporting bias: Low risk Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section Other bias: High risk Comment: The CES-D is a highly sensitive screening

Table 2.   Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

					tool, which could have over-estimated the degree of mood disorder compared with other psychiatric instruments and have exaggerated the adverse effects estimates of the interventions in this study
Cohen 2007	Design: Prospective cohort Duration of the study: not clearly provided Period of recruitment: not provided	Setting: community dermatology practice in Calgary, Canada Oral isotretinoin: n = 100 (41% male) Oral antibiotics: n = 41 (34.1% male) Topical acne therapy: n = 59 (18.6% male) Age – median: • Oral isotretinoin: 21.5 years • Oral antibiotics: 26.0 years • Topical acne therapy: 20 years Duration of acne: not provided Acne severity: percentage of participants with moderate or severe • Oral isotretinoin (n = 100): 96%, 96 participants • Oral antibiotics (n = 41):	Intervention group (n = 100): - oral isotretinoin: dosage not specified Control group (n = 100): • Oral antibiotic (n = 41): drug and dosage not specifie • Topical acne therapy (n = 59): drug and dosage not specified	Change in scores of Zung Depression Status Inventory from baseline in both, intervention and control groups, within 25 to 35 days of the start of acne treatment Percentage of participants having a CES-D (Center for Epidemiologic Studies Depression Scale) score greater than 15 (indicative of clinically significant depression) at baseline and follow-up Incidence of newly detected depression (CES-D > 15) at follow-up in both treatment and control groups	There was no statistically significant difference in Zung scores between both time points of assessment (mean difference 0.00 points; 95% CI -0.6 to 0.6). Also there were no significant differences between groups regarding to the mean change in Zung score (one way ANOVA; df = 1, F = 1.4, P = 0.24) There was a single participant depressed at baseline (who was not depressed on follow-up) and two on follow-up, on the CES-D score, both in the isotretinoin group. Despite this, incidence of newly detected depression was not statistically significant different between isotretinoin and control groups (Fisher' exact test, P = 0.497). Both new incident depression cases were female and had moderate to severe acne. None of them presented past history of depression at baseline assessment	Selection bias: High risk Comment: The study controlled some potential confounding variables and performed a linear regression analysis to adjust the comparison between groups for acne severity, the main potential confounding factor according to authors. However, duration of acne, another important confounding factor for the analysis of the association between oral isotretinoin use for acne and depression, was not even cited within the report Performance bias (all outcomes): High risk Comment: The study had an open design Detection bias (all outcomes): High risk Comment: The study had an open design Attrition bias: (all outcomes): Unclear risk Comment: No information regarding loss to follow-up was provided Selective reporting bias: High risk Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section Other bias: High risk Comment: The CES-D is a highly sensitive screening tool, which could have over-

Table 2.   Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

	58.5%, 24 participants • Topical acne therapy (n = 59): 6.8%, 4 participants Inclusion criteria: being 14 years old, or older, able to provide informed consent, and not currently under pharmacological treatment for depression; not anticipating an alteration in residence during the period of the study; and providing at least two options for follow-up contact Exclusion criteria: not provided	Interviews for assessment of outcomes were 'in person' at baseline, but by telephone call at follow-up, within 25 to 35 days of the start of therapy			estimated the degree of mood disorder compared with other psychiatric instruments and have exaggerated the adverse effects estimates of the interventions in this study. Besides this, the length of the follow-up period was inadequate, since treatment with oral isotretinoin seldom lasts more than 8 weeks. Also, instruments used to assess outcomes were different between both time points of measurement of the study: a clinical interview at baseline, and a telephone interview at follow-up
Jick 2000	Design: Retrospective population based-cohort (record linkage) Duration of the study: not clearly provided Periods of recruitment: not provided for United Kingdom cohort; from 1983 to 1997, Saskatchewan,	Settings: two different centres: province of Saskatchewan, Canada (Canadian Saskatchewan Health Database-CSHD) and United Kingdom (United Kingdom General Practice Research Database-UKGPRD) Saskatchewan cohort: • 7195 oral isotretinoin users; 53% male; 79% aged 10 to 29 years • 13,700 antibiotic users; 43% male;	Current exposure to oral isotretinoin or to antibiotic therapies (tetracycline, erythromycin, clindamycin, minocycline or doxycycline): from the first prescription for acne treatment through 3 months after receiving the last study drug prescription	Prevalence rates of newly diagnosed depression or psychosis (neurotic and psychotic disorders), having person-time as denominator and the number of cases as numerator, assessed by linkage with medical records of diagnosis codes in each computerised database	Saskatchewan database/cohort: • The adjusted relative risk (ARR) estimate for newly diagnosed depression or psychosis was 1.0 (95% CI, 0.7 to 1.3) for current isotretinoin exposure compared with the non-exposed period. The ARR estimates for recent isotretinoin use, current antibiotic use, and recent antibiotic use in participants with acne were 0.9, 1.3, and 0.9, respectively. There was no statistically difference between each one of both exposure	Selection bias: High risk Comment: The study had considered in the analysis some important confounding factors (i.e. age, gender, history of psychiatric disorder) and used multiple logistic regression models. However, there was no report of data related to acne severity, which may be an independent predictor of depression, apart from drug exposure Performance bias (all outcomes): High risk Comment: As the study was a retrospective cohort, probably personnel and participants were not blinded regarding the exposure/drug Detection bias (all outcomes): Unclear risk

Table 2. Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

Canada cohort	75% aged 10 to 29 years	Recent exposure to oral isotretinoin or to antibiotic therapies (tetracycline, erythromycin, clindamycin, minocycline or doxycycline): having received the last study drug prescription 4 to 6 months previously Nonexposed: All other times after finishing treatment with the analised drug (oral isotretinoin or antibiotic) Detailed information regarding dose and duration of exposures/interventions were not provided	• Incidence rates of suicide or attempted suicide, having person-time as denominator and the number of cases of the outcome as numerator, assessed by linkage with medical records of diagnosis codes in each database	group and nonexposed group • For suicide and attempted suicide, the ARR estimate was 0.9 (95% CI, 0.3 to 2.4) when comparing current isotretinoin exposure with the nonexposed period. Also there was no statistically significant difference between each one of the three exposure groups and the nonexposed group. History of psychiatric disorder was associated with higher suicide risk during both isotretinoin and antibiotics therapy from CSHD cohort (ARR 8.0, CI 4.1 to 15.5) GPRD database: • Current isotretinoin use yielded an ARR estimate of 1.8 (95% CI, 0.4 to 5.2) for newly diagnosed depression or psychosis compared with the nonexposed period. The ARR estimates were 1.8, 1.5, and 1.7 for recent isotretinoin use, current antibiotic use, and recent antibiotic use, respectively, and there was no statistically significant difference between each one of these exposure groups compared with the nonexposed period	Comment: The study did not provide any information regarding blinding of the outcome assessors Attrition bias (all outcomes): Low risk Comment: The study had used hazard ratios to measure outcomes (incidence density), which minimise bias due to missing data in both open retrospective cohorts reported Selective reporting outcome: High risk Comment: The study did not provide RR estimates for isotretinoin exposure compared with antibiotic exposure, despite having cited this outcome measurement in methods section Other bias: High risk Comment: The study might be at risk of inappropriate influence of funders, as it was sponsored and promoted by a pharmaceutical company. There was a potential under-ascertainment of psychiatric outcomes, as researchers only performed record linkage with diagnosis codes, and not psychoactive drug prescriptions or interviews. The study used a potentially insensitive instrument to measure outcomes, record linkage across electronic databases. Also, the study had presented only a cohort cross-over analysis of data for each one of both cohorts (CSHD and UKGPRD), since the nonexposed group in each cohort included people who developed one of the psychiatric outcomes assessed 6 months after being exposed either to oral isotretinoin or to antibiotic.
	United Kingdom cohort: • 340 oral isotretinoin users; 58% male; 78% aged 10 to 29 years • 676 oral antibiotic users; 59% male; 78% aged 10 to 29 years Duration of acne: not provided Acne severity: not provided Inclusion criteria: • For both groups, had between 6 months and 5 years of computer-recorded history before, and at least 12 months after, their first isotretinoin or antibiotic prescription for acne, except where death occurred • For antibiotics users group, subjects with acne in whom the condition was diagnosed within the same period (± 6 months) and who fell with-				

Table 2. Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

	in the same as isotretinoin-treated participants, but who were treated with only antibiotic therapies, received within 30 days following the acne diagnosis Exclusion criteria: not provided			• There was only one suicide attempt in the GPRD. The subject was nonexposed In both cohorts (CSHD and UKGPRD): • There was no difference between rates of newly diagnosed depression or psychosis in the first 6 months of isotretinoin use and the rates before therapy. This was an analysis of data from isotretinoin users only (a before-and-after comparison) • Female gender and older age had statistically significant associations with newly diagnosed depression or psychosis	This design had a potential risk of bias related to the possibility of carry-over effects in participants of non-exposed groups in both cohorts who had received oral isotretinoin previously
Kaymak 2009	Design: Prospective nonrandomised controlled trial Duration of the study: not clearly provided Period of recruitment: September 2006 to May 2007 Factors influencing the choice of treatment: previous treatment	Setting: One outpatient dermatology clinic of a university health centre Isotretinoin (study group): n = 37 (11 males and 25 females) Topical treatment (control group): n = 41 (9 males and 20 females) Age - mean ± SD (years): • Isotretinoin group: 20.61 ± 1.87 • Topical treatment group: 20.51 ± 2.01	Isotretinoin group: 0.5 – 0.8 mg/kg/day of oral isotretinoin with food in two divided doses for at least 20 weeks; cumulative dose of 100 mg/kg Topical treatment group: either topical antibiotics or topical retinoids. More detailed information regarding this interven-	Frequency of psychopathology symptoms assessed by two instruments: • The hospital anxiety and depression (HAD), a self-rating scale used to assess the risk and to measure the level of depression	Significantly more participants had BDI scores over 13 (considered as depressive) in the topical treatment group (10/29) compared to the isotretinoin group (4/36) at 4 months time point (P = 0.03) There were also statistically significant differences between the two treatments groups, in favour of isotretinoin, regarding the number of participants with measurements of HAD-D higher than the range of clinically significant depression (> 8) at 2 (P =	Selection bias: Low risk Comment: The study performed an adjusted analysis data for the most important confounding factors while assessing psychiatric outcomes related to oral isotretinoin for acne Performance bias (all outcomes): Unclear risk Comment: The study did not provide any information regarding blinding of participants and personnel Detection bias (all outcomes): Low risk Comment: The author who assessed participant's psychological status was blinded

Table 2. Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

failure, the severity and duration of the acne, participant preference, and participant concerns about adverse drug effects	Duration of acne mean ± SD (years): • Isotretinoin group: 4.86 ± 2.81 • Topical treatment group: 3.93 ± 2.86 Acne severity: participants with severe, moderate or mild acne in both groups. The report did not provide numbers of participants with each one grade of acne severity for each group Inclusion criteria: not provided Exclusion criteria: not provided	tion group was not provided	and anxiety. It contains 14 questions, 7 related to depression (HAD-D) and 7 to anxiety (HAD-A). A validated Turkish version of the full scale (HAD-T) was also used • The Beck depression inventory (BDI), a self-rating scale composed of 21 items, which evaluates the level of depression. Each question is rated from 0 to 3 points. The sum of the points shows the level of depression. A BDI score over 13 was the index for establishing depres-	0.01) and 4 (P = 0.02) months	Attrition bias (all outcomes): High risk Comment: The level of loss to follow-up in the study could lead to attrition bias, especially considering that there was a high imbalance of missing data between the two groups. The trial reported a 'per-protocol' analysis, which did not consider data from loss to follow-up Selective reporting bias: Low risk Comment: no protocol available; however, there was an adequate report of outcomes listed in methods section Other bias:Low risk Comment: There were no other apparent sources of bias

Table 2. Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

			sion diagnosis		
			Change in mean scores of BDI, HAD-D, HAD-A and HAD-T during treatment compared to baseline in both treatment groups		
			Measurements occurred at baseline, 2, and 4 months of follow-up		
McGrath 2010	Design: Prospective nonrandomised controlled trial Duration of the study: not clearly provided Period of recruitment: between September 2006 and September 2007	Setting: • treatment groups: Royal United Hospital, Bath, UK; • control group: matched community sample from: two coeducational schools in South West England; a University campus; and venues at a city centre Gender: • Isotretinoin group: n = 65 (45 males and 20 females) • Oral antibiotic and a topical retinoid group: n = 31 (16 males and 15 females) • Control group: n = 94 (50 males and 44 females)	Isotretinoin group: 0.5 mg/kg/daily for the first 2 weeks, followed by 1 mg/kg/daily until reaching the cumulative dose of 120 mg/kg (participants who did not tolerate the 1 mg/kg/day dose received the next highest dose possible) Oral antibiotic and a topical retinoid group: lymecycline 408 mg daily (or minocycline 100 mg daily in	Occurrence of depression assessed by the Centre for Epidemiological Studies Depression Scale (CES-D) Measurements occurred at baseline, then subsequently at 3 and 6 months, for all participants in both treatment groups. Participants in the matched community control group completed the WHO-QOL-BREF, Centre for Epidemi-	Depression scores over time did not present significant changes in treatment groups ($F_{1.64}$ = 1.06, not significant) and there was no interaction between gender and changes in depression levels (authors included gender as a covariate in the measurements of depression, since scores were higher in women than in men at baseline)	Selection bias: High risk Comment: Despite the analysis of covariance (ANCOVA), controlling for the covariate gender, and the matched healthy control group, the study did not consider other important confounders, such as duration of acne, in the comparison over time between both acne treatment groups Performance bias (all outcomes): High risk Comment: Participants and personnel were not blinded Detection bias (all outcomes): Unclear risk Comment: The study did not provide any information regarding blinding of the outcome assessors Attrition bias (all outcomes): High risk Comment: Authors reported a high level of loss to follow-up: only 43.7% of participants from treatment groups provided useable

Table 2. Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

	Age - mean ± SD (years):	the case of intolerance or inefficacy with previous lymecycline use)plus adapalene cream	ological Studies Depression Scale (CES-D) and visual analogue score only once	data on all three time points of measurements

Age - mean ± SD (years):

- Isotretinoin group: 19.8 ± 3.8
- Oral antibiotic and a topical retinoid group: 19.3 ± 3.9
- Control group: 19.7 (standard deviation not provided)

Duration of acne (years): not provided

Acne severity: not clearly specified

Inclusion criteria:

- treatment groups:
- outpatients commencing treatment for acne at the Royal United Hospital, Bath, UK
- control group:matched healthy community participants from three sources: two coeducational schools in South West England (children aged 14-18 years); adults (aged 18-30 years) from a University campus; and opportunist sampling at venues in a city centre

Exclusion criteria:

the case of intolerance or inefficacy with previous lymecycline use)plus adapalene cream

ological Studies Depression Scale (CES-D) and visual analogue score only once

data on all three time points of measurements

Selective reporting: High risk

Comment: Due to the high level of loss to follow-up, authors carried out data analysis only for the first two time points according to the methods section

Other bias:Low risk

Comment: There were no other apparent sources of bias

Table 2. Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

		• treatment groups: • being under 12 years or over 50 years; pregnant or lactating women; • control group: being under 14 years or over 30 years old, and currently under hospital treatment for acne			

| Ng 2002 | Design: Prospective nonrandomised controlled trial

Duration of the study: not clearly provided

Period of recruitment: between December 1998 and March 2000 | Setting: two private dermatology clinics and a public hospital outpatient dermatology clinic in Melbourne, Australia

Isotretinoin group: n = 174 (58.6% male)

Antibiotic plus topical treatment group: n = 41 (41.5% male)

Age – mean ± SD (years)/range (years):

• Isotretinoin group: 20.2 ± 5.8/15-46
• Antibiotic plus topical treatment group: 20.7 ± 5.8/15 – 38

Duration of acne: not provided

Acne severity: participants with severe or moderate acne in both groups. The report did not provide numbers of participants with each one of the these two grades | Isotretinoin group (n = 174): oral isotretinoin starting at 40 mg/day, increased to a dose of 1.0 mg/kg/day over 1 month according to tolerability, and continued for a total cumulative dose of 120 mg/kg (over 5–6 months)

Antibiotic plus topical treatment group: a standard course of minocycline 100–200 mg/day, titrated according to weight, response and tolerance, and topical treatment consisted of adapalene 0.1% gel, tretinoin | Changes in mean Beck Depression Inventory (BDI) scores during treatment compared to baseline in both groups

Percentage of participants having a BDI score of 10 or greater (indicative of at least a moderate level of depressive symptoms)

Rate of withdrawal from the study because of worsening of mood

Measurements of outcomes occurred at baseline, 1 month, 3 months and at the end of treatment | Changes in mean BDI scores over the therapy course were not significantly different between both treatment groups (P = 0.62)

18 participants from the whole sample had a BDI score of 10 or greater at baseline; the incidence of moderate depressive symptoms in the isotretinoin group remained relatively unchanged during the study and at lower levels than in the antibiotic/topical group

5 participants in the isotretinoin group (n = 174) had dropped out from the study due to depressed mood, 3 males and 2 females. Only in 2 (both male) of these participants, the relationship to isotretinoin use seemed possible. No participant was withdrawn from the antibiotic plus topical group (n = 41) because of mood changes | Selection bias: High risk

Comment: Despite having controlled potential confounding variables and made a linear regression analysis to adjust the comparison between groups, not all important confounding factors were explored by the study analysis. Duration of acne and previous duration of acne treatment were not reported.

Performance bias (all outcomes): High risk

Comment: The study had an open design

Detection bias (all outcomes): High risk

Comment: The study had an open design

Attrition bias:

(all outcomes): High risk

Comment: Despite the intention-to-treat analysis of data, there was an imbalance in dropout rates between the two groups

Selective reporting bias: Low risk

Comment: No protocol available; however, there was an adequate report of outcomes listed in methods section |

Table 2.   Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

	of acne severity for each treatment group Inclusion criteria: participants between 15 and 50 years having moderate to severe acne, and able to comprehend the rating instructions and comply with the study protocol Exclusion criteria: current diagnosis of depression; concomitant use of antidepressants, corticosteroids, anabolic steroids or other depression-inducing medications; pregnancy or breastfeeding	0.05% cream or isotretinoin 0.05% gel	course or 6 months		Other bias: Low risk Comment: There were no other apparent sources of bias	
Sundstrom 2010	Design: Retrospective population-based cohort Duration of the study: not clearly provided Period of recruitment: between 1980 and 1990	Setting: Sweden 5756 participants (3613 males and 2143 females) who were aged 15 to 49 years Duration of acne: not provided Acne severity: severe acne Inclusion criteria: having had at least one course of oral isotretinoin granted by the Medical Products Agency in Sweden during the period of recruitment Exclusion criteria: not provided	Oral isotretinoin administered in a mean dose of 44.5 mg (SD 15.7) for males and 39.2 mg (SD 13.1) for females Duration of intervention: a mean period of 6.0 months (SD 4.0) for males and 6.1 (SD 3.9) for females	Rates of attempted and completed suicides in the different time windows of the cohort compared between themselves (before, during, and after treatment with oral isotretinoin) and with those of the general population, assessed by searching for related events between 1980 and 2001 in the national patient register of	Standardised incidence ratios (comparing the study cohort with the general population) for first suicide attempts and for all attempts rose, respectively, from 0.89 (95% CI, 0.54 to 1.37) and 0.99 (95% CI, 0.65 to 1.44) three years before treatment to 1.36 (95% CI, 0.65 to 2.50) and 1.57 (95% CI, 0.86 to 2.63) in the year preceding treatment. Both ratios were highest within six months after beginning treatment: 1.93 (95% CI, 1.08 to 3.18) for first attempts and 1.78 (95% CI, 1.04 to 2.85) for all attempts. Within three years after treatment, the number of suicide attempts in the cohort was almost the same as the	Selection bias: High risk Comment: Authors considered only age, gender, and calendar year as potential confounding factors while calculating specific rates in the general population control group. The study did not take in account the fact that presence of acne and its severity in the control group (general population) could be a potential confounder Performance bias (all outcomes): High risk Comment: As the study was a retrospective cohort, probably personnel and participants were not blinded for the exposure/drug Detection bias (all outcomes): Unclear risk

Table 2. Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

	in-hospital care and in the cause of death register	number observed in general population, and standardised incidence ratios were 0.97 (95% CI, 0.64 to 1.40) for first attempts and 1.04 (95% CI, 0.74 to 1.43) for all attempts. However, there was a significant increase in the standardised incidence ratio of repeated events (but not of first attempts) 11 years after treatment among female participants of the cohort: 1.36 (95% CI, 1.06 to 1.70) Females who attempted suicide after completing treatment received significantly more than one course in comparison to female participants of the cohort who never attempted treatment There was a statistically significant difference in the chance of committing another suicide attempt between participants who had their first attempt before treatment and those who made a first suicide attempt during treatment or within six months after the finish of the course Treatment with oral isotretinoin reinforced more significantly the suicidal behaviour for participants who committed the first suicide attempt during treatment, or within six months after the end, in comparison with those who first attempted before using oral isotretinoin	Comment: The study did not provide any information regarding blinding of the outcome assessors Attrition bias (all outcomes): Unclear risk Comment: There was no information about missing data or the potential for data to be missing to permit judgment. Selective reporting bias: Low risk Comment: no protocol available; however, there was an adequate report of outcomes listed in methods section Other bias: High risk Comment: The study used a potentially insensitive instrument to measure outcomes, record linkage across electronic databases. Besides this, the exclusion of the outpatients database from the estimate of rates of attempted suicide might had underestimated the primary outcome measurement in all the cohort. Also, authors reported only a single intervention group (there was no comparison within two or more interventions in the cohort), and analysis of data had an internal cross-over pattern, a poorer design if compared with the classical cohort

Table 2.   Characteristics of nonrandomised studies (considered for safety analysis) *(Continued)*

There was an increase in rates of attempted suicide per person-years of follow-up within the isotretinoin Swedish cohort (cohort crossover analysis) from time points of measurement before and after the treatment. For first attempts, the rate difference between the year before treatment and six months following the end of treatment was the highest: 0.86 cases per 1000 person-years (95% CI, -0.78 to 2.50); for all attempts; this rate difference was 0.40 (95% CI, -1.40 to 2.26) per 1000 person-years. The number needed to treat for an additional harmful outcome (first suicide attempt and one additional repeated attempt) was 2300 and 5000 per year, respectively
24 participants had death by suicide (17 males and 7 females) by the end of 2001. The standardised mortality ratio for males who committed suicide within one year after treatment was 1.9 (95% CI, 0.4 to 5.4), and decreased to around one within two years after treatment. For female participants, the highest standardised mortality ratio was 1.8 (95% CI, 0.7 to 3.9), which occurred within 11 years after the treatment

ANCOVA: analysis of covariance

ARR: adjusted relative risk

BDI: Beck depression inventory

CES-D: The Center for Epidemiologic Studies Depression Scale

CSHD: Canadian Saskatchewan Health Database

df: degrees of freedom

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

HAD-A: hospital anxiety and depression - anxiety

HAD-D: hospital anxiety and depression - depression

HAD-T: hospital anxiety and depression - Turkish version

RAMQ: Régie de l' Assurance Maladie du Québec

SD: standard deviation

UKGPRD: United Kingdom (United Kingdom General Practice Research Database)

WHOQOL-BREF: World Health Organization Quality of Life-Brief version

Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies

Adverse effects (AE) outcomes (clinical and laboratory)	Study	Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies		Estimate of effect: risk ratio, 95% CI
		Intervention **Number of participants who experienced the AE/Number of analysed participants**	**Control** **Number of participants who experienced the AE/Number of analysed participants**	
1.Overall incidence - measured at 1st month	Gollnick 2001	Oral isotretinoin 0.5 to 0.8 mg/kg/day for 6 months 16/35	**Oral minocycline (50 mg twice daily) plus topical azelaic acid cream (twice daily) for 6 months*** 12/50	1.90 (1.03 to 3.51)[a]
2. Overall incidence - during the 20-week therapy	Tan 2014	Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel 116/133	**Oral doxycycline 200 mg plus adapalene 0.1% /benzoyl peroxide 2.5% gel (both once daily)** 70/133	1.66 (1.39 to 1.97)[a]
3. Overall incidence - during the 8-week therapy	Faghihi 2014	**Oral isotretinoin, 20 mg once a day plus vehicle neutral gel applied on the face twice daily, both for 8 weeks** 3/29	Oral isotretinoin, 20 mg once a day plus 5% dapsone gel applied on the face twice daily, both for 8 weeks 18/29	0.17 (0.06 to 0.51)[a]
4. Overall incidence - during 20-week therapy	Webster 2014	**Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20** 385/460	Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks 403/464	0.96 (0.91 to 1.02)
5. Overall incidence - during 20-week therapy	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 293/300	Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks 296/300	1.01 (0.99 to 1.03

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Table 3.   Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

6. Overall incidence - during 16-week therapy	Rademaker 2013b	Oral isotretinoin 5 mg once daily 28/29	**Placebo** 26/30	4.31 (0.45 to 41.09)
7. Severe/persistent skin symptoms	Gollnick 2001	Oral isotretinoin 0.5 to 0.8 mg/kg/day for 6 months 7/35	**Oral minocycline (50 mg twice daily) plus topical azelaic acid cream (twice daily) for 6 months** 3/50	3.33 (0.93 to 12.01)
8. Systemic side effects	Gollnick 2001	Oral isotretinoin 0.5 to 0.8 mg/kg/day for 6 months 6/35	**Oral minocycline (50 mg twice daily) plus topical azelaic acid cream (twice daily) for 6 months** 6/50	1.43 (0.50 to 4.07)
9. Melasma-like pigmentation	Dhir 2008	Oral isotretinoin 20 mg twice a day for 24 weeks 5/25	**Oral isotretinoin 20 mg twice a day along with topical clindamycin (1%) during the daytime and adapalene (0.1%) at bedtime for 24 weeks** 3/25	1.66 (0.44 to 6.24)
10. Flare-up (during the first eight weeks of treatment)	Dhir 2008	**Oral isotretinoin 20 mg twice a day for 24 weeks** 3/25	Oral isotretinoin 20 mg twice a day along with topical clindamycin (1%) during the daytime and adapalene (0.1%) at bedtime for 24 weeks 6/25	0.50 (0.14 to 1.78)
11. Dry lips	Tan 2014	Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel 66/133	**Oral doxycycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel (both once daily)** 9/133	7.33 (3.81 to 14.10)[a]
	Rademaker 2013b	Oral isotretinoin 5 mg once daily 18/29	**Placebo** 3/30	14.73 (3.60 to 60.26)
12. Cheilitis	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 28/28	Oral etretinate 1 mg/kg/day for 8 weeks 28/28	1.00 (0.93 to 1.07)
	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 274/300	Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks 271/300	1.01 (0.96 to 1.06)
	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks**	25.00 (1.65 to 379.57)[a]

Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

		12/12	0/12	
	Tan 2014	Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel 32/133	**Oral doxycycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel (both once daily)** 2/133	16.00 (3.91 to 65.42)[a]
13. Cheilitis or dry lips	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/day for 16 weeks 15/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 13/15	4.43 (1.75, 11.23)[a]
14. Xerosis (dry skin)	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 28/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 21/28	1.33 (1.06 to 1.65)[a]
	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/day for 16 weeks 15/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 2/15	6.20 (1.98 to 19.43)[a]
	Strauss 2001	**Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks** 152/300	Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks 159/300	0.96 (0.82 to 1.12)
	Rademaker 2013b	Oral isotretinoin 5 mg once daily 6/29	**Placebo** 4/30	1.70 (0.42 to 6.77)
	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 12/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	25.00 (1.65 to 379.57)[a]
	Tan 2014	Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel 43/133	**Oral doxycycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel (both once daily)** 22/133	1.95 (1.24 to 3.08)[a]
15. Pruritus	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 28/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 16/28	1.73 (1.25 to 2.38)[a]
	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/day for 16 weeks 1/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 0/15	3.00 (0.13 to 68.26)
	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks**	3.00 (0.13 to 67.06)

Table 3.   Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

		1/12	0/12	
16. Rhinitis sicca	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 21/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 16/28	1.31 (0.89 to 1.93)
17. Nasal dryness (dry nose)	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 96/300	Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks 91/300	1.05 (0.83 to 1.34)
	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks 10/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 1/15	10.00 (1.46 to 68.69)[a]
18. Epistaxis	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 14/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 9/28	1.56 (0.81 to 2.99)
	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks 10/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 0/15	21.00 (1.34, 328.86)[a]
	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 122/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 103/300	1.18 (0.96 to 1.46)
	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 8/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	17.00 (1.09 to 265.02)[a]
19. Nasopharyngitis	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 23/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 17/300	1.35 (0.74 to 2.48)
20. Sore mouth	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 12/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 5/28	2.40 (0.97 to 5.92)
21. Dry mouth	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks 3/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 1/15	3.00 (0.35 to 25.68)
	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 4/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	9.00 (0.54 to 150.81)

Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

22. Facial dermatitis	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 18/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 8/28	2.25 (1.18 to 4.30)[a]
23. Dermatitis	Goldstein 1982	**Oral isotretinoin 1 mg/kg/day for 8 weeks** 10/28	Oral etretinate 1 mg/kg/day for 8 weeks 11/28	0.91 (0.46 to 1.79)
	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 46/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 25/300	1.84 (1.16 to 2.91)[a]
24. Skin fragility	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 11/28	Oral etretinate 1 mg/kg/day for 8 weeks 11/28	1.00 (0.5 to 1.92)
25. Localised exfoliation	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 126/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 113/300	1.12 (0.92 to 1.36)
26. Erythema	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks 3/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 0/15	7.00 (0.39 to 124.83)
	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 4/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	9.00 (0.54 to 150.81)
27. Erythematous eruption	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 108/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 86/300	1.26 (0.99 to 1.59)
28. Desquamation	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks 7/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 0/15	15.00 (0.93 to 241.20)
	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 7/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	15.00 (0.95 to 236.42)
29. Fingertip peeling	Goldstein 1982	**Oral isotretinoin 1 mg/kg/day for 8 weeks** 10/28	Oral etretinate 1 mg/kg/day for 8 weeks 18/28	0.56 (0.31 to 0.98)

Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

30. Tender finger tips	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/day for 16 weeks	**Oral tetracycline 0.5 to 1 g/day for 16 weeks**	3.00 (0.13 to 68.26)
		1/15	0/15	
31. Desquamation of palms and soles	Goldstein 1982	**Oral isotretinoin 1 mg/kg/day for 8 weeks**	Oral etretinate 1 mg/kg/day for 8 weeks	0.31 (0.13 to 0.74)[a]
		5/28	16/28	
32. Eczema	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/day for 16 weeks	**Oral tetracycline 0.5 to 1 g/day for 16 weeks**	3.00 (0.13, 68.26)
		1/15	0/15	
33. Fissuring	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/day for 16 weeks	**Oral tetracycline 0.5 to 1 g/day for 16 weeks**	3.00 (0.13 to 68.26)
		1/15	0/15	
34. Crusting of lesions	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/day for 16 weeks	**Oral tetracycline 0.5 to 1 g/day for 16 weeks**	3.00 (0.13 to 68.26)
		1/15	0/15	
35. Morbiliform eruption	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks**	Oral tetracycline 0.5 to 1 g/day for 16 weeks	0.33 (0.01 to 7.58)
		0/15	1/15	
36. Herpes simplex	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks**	Oral tetracycline 0.5 to 1 g/day for 16 weeks	0.33 (0.01 to 7.58)
		0/15	1/15	
37. Flushing	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks	Oral tetracycline 0.5 to 1 g/day for 16 weeks	1.00 (0.07 to 14.55)
		1/15	1/15	
38. Pyogenic granuloma-like lesions	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks**	3.00 (0.13 to 67.06)
		1/12	0/12	
39. Light intolerance	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks**	3.00 (0.13 to 67.06)
		1/12	0/12	
40. Phototoxicity	Pigatto 1986	**Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks**	Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks	0.33 (0.01 to 7.45)
		0/12	1/12	
41. Alopecia	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks	**Oral tetracycline 0.5 to 1 g/day for 16 weeks**	7.00 (0.39 to 124.83)

Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

		3/15	0/15	
	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 3/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	7.00 (0.40 to 122.44)
	Goldstein 1982	**Oral isotretinoin 1 mg/kg/day for 8 weeks** 9/28	Oral etretinate 1 mg/kg/day for 8 weeks 15/28	0.60 (0.32 to 1.14)
42. Dry hair	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks** 1/15	Oral tetracycline 0.5 to 1 g/day for 16 weeks 2/15	0.50 (0.05 to 4.94)
43. Dry eyes or xerophthalmia	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/day for 16 weeks 2/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 0/15	5.00 (0.26 to 96.13)
	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 2/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	5.00 (0.27 to 94.34)
	Rademaker 2013b	Oral isotretinoin 5 mg once daily 5/29	**Placebo** 2/30	2.92 (0.52 to 16.42)
	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 90/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 80/300	1.13 (0.87 to 1.45)
44. Eye irritation	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 16/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 6/28	2.67 (1.22 to 5.81)[a]
	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 84/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 71/300	1.18 (0.90 to 1.55)
45. Eye pain	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 6/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 1/28	6.00 (0.77 to 46.66)
46. Mild conjunctival injection (assessed only at 8 weeks)	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 7/28	Oral etretinate 1 mg/kg/day for 8 weeks 7/28	1.00 (0.40 to 2.48)

Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

47. Conjunctivitis	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks	**Oral tetracycline 0.5 to 1 g/day for 16 weeks**	3.00 (0.13 to 68.26)
		1/15	0/15	
48. Photophobia	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks	**Oral tetracycline 0.5 to 1 g/day for 16 weeks**	3.00 (0.13 to 68.26)
		1/15	0/15	
49. Pterygium, right eye	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks	**Oral tetracycline 0.5 to 1 g/day for 16 weeks**	3.00 (0.13 to 68.26)
		1/15	0/15	
50. Small posterior subcapsular cataract opacities	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks	**Oral tetracycline 0.5 to 1 g/day for 16 weeks**	5.00 (0.26 to 96.13)
		2/15	0/15	
51. Headache	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks	**Oral etretinate 1 mg/kg/day for 8 weeks**	2.00 (0.68 to 5.89)
		8/28	4/28	
	Rademaker 2013b	**Oral isotretinoin 5 mg once daily**	Placebo	0.36 (0.12 to 1.11)
		7/29	14/30	
	Strauss 2001	**Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks**	Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks	0.83 (0.57 to 1.23)
		40/300	48/300	
52. Lethargy	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks	**Oral etretinate 1 mg/kg/day for 8 weeks**	3.25 (1.21 to 8.75)[a]
		13/28	4/28	
53. Fatigue	Rademaker 2013b	Oral isotretinoin 5 mg once daily	Placebo	1.04 (0.19 to 5.62)
		3/29	3/30	
54. Tiredness	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks**	Oral tetracycline 0.5 to 1 g/day for 16 weeks	0.20 (0.01 to 3.85)
		0/15	2/15	
55. Joint pain	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks	**Oral etretinate 1 mg/kg/day for 8 weeks**	2.00 (0.55 to 7.22)
		6/28	3/28	
56. Back pain	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks**	1.45 (0.69 to 3.08)
		16/300	11/300	

Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

57. Musculoskeletal symptoms	Rademaker 2013b	Oral isotretinoin 5 mg once daily 6/29	**Placebo** 2/30	3.65 (0.67 to 19.85)
58. Increased thirst	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 9/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 7/28	1.29 (0.56 to 2.97)
	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks** 0/15	Oral tetracycline 0.5 to 1 g/day for 16 weeks 2/15	0.20 (0.01 to 3.85)
59. Increased appetite	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 6/28	**Oral etretinate 1 mg/kg/day for 8 weeks** 1/28	6.00 (0.77 to 46.66)
60. Anorexia	Pigatto 1986	**Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks** 2/12	Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks 3/12	0.67 (0.13 to 3.30)
61. Abdominal pain	Goldstein 1982	**Oral isotretinoin 1 mg/kg/day for 8 weeks** 3/28	Oral etretinate 1 mg/kg/day for 8 weeks 4/28	0.75 (0.18 to 3.05)
62. Nausea	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 1/28	Oral etretinate 1 mg/kg/day for 8 weeks 1/28	1.00 (0.07 to 15.21)
	Pigatto 1986	**Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks** 0/12	Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks 7/12	0.07 (0.00 to 1.05)
	Tan 2014	**Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel** 3/133	Oral doxycycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel (both once daily) 9/133	0.33 (0.09 to 1.20)
63. Vomiting	Pigatto 1986	**Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks** 0/12	Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks 3/12	0.14 (0.01 to 2.50)
	Tan 2014	**Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel** 10/133	Oral doxycycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel (both once daily)	0.10 (0.01 to 0.77)[a]

Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

		1/133		
64. Diarrhea	Pigatto 1986	**Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks** 0/12	Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks 2/12	0.14 (0.01 to 2.50)
65. Infections	Rademaker 2013b	**Oral isotretinoin 5 mg once daily** 11/29	Placebo 15/30	0.61 (0.22 to 1.72)
66. Indigestion	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks** 0/15	Oral tetracycline 0.5 to 1 g/day for 16 weeks 1/15	0.33 (0.01 to 7.58)
67. Decreased sweating	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks 1/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 0/15	3.00 (0.13 to 68.26)
68. Insomnia	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 8/28	Oral etretinate 1 mg/kg/day for 8 weeks 8/28	1.00 (0.44 to 2.29)
69. Mild psychiatric disorders	Strauss 2001	**Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks** 1/300	Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks 11/300	0.09 (0.01 to 0.70)[a]
70. Depressive episode (moving from BDI-II[b] scores ≤ 13 at baseline to > 13 during treatment)	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 7/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 6/300	1.17 (0.40 to 3.43)
71. Bone loss	Webster 2014	**Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20** 0/231	Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks 1/245	0.35 (0.01 to 8.63)
72. Bone age change	Webster 2014	**Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20** 4/192	Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks 5/204	0.85 (0.23 to 3.12)
73. Elevated serum triglycerides (> 140 mg/dL)	Goldstein 1982	**Oral isotretinoin 1 mg/kg/day for 8 weeks** 2/28	Oral etretinate 1 mg/kg/day for 8 weeks 3/28	0.67 (0.12 to 3.69)

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Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

74. Raised triglyceride levels	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks 4/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 0/15	9.00 (0.53 to 153.79)
75. Elevated serum triglycerides (during first 10 weeks of therapy)	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 4/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	9.00 (0.54 to 150.81)
76. Marked abnormality in serum triglycerides level (> 250 mg/dL and increase from baseline ≥ 100%)	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 75/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 48/300	1.56 (1.13, 2.16)[a]
77. Marked abnormality in serum cholesterol level (> 320 mg/dL and increase from baseline ≥ 50%)	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 1/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 0/300	3.00 (0.12 to 73.35)
78. Persistent elevated serum alkaline phosphatase (during therapy and follow-up phase)	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks 3/15	Oral tetracycline 0.5 to 1 g/day for 16 weeks 3/15	1.00 (0.24 to 4.18)
79. Raised alkaline phosphatase	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 4/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	9.00 (0.54 to 150.81)
80. Marked abnormality in alkaline phosphatase level (> 190 U/L and increase from baseline ≥ 50%)	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 0/300	Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks 0/300	Not estimable
81. Persistent raised SGOT[c] (AST)[d] and SGPT[e] (ALT)[f] levels (during therapy)	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks** 0/15	Oral tetracycline 0.5 to 1 g/day for 16 weeks 1/15	0.33 (0.01 to 7.58)
82. Raised AST[d] or ALT[f]	Pigatto 1986	**Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks**	Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks	0.09 (0.01 to 1.48)

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Table 3. Less serious adverse effects from RCTs. Oral isotretinoin versus itself (different formulations or combined with topical) or other active therapies *(Continued)*

		0/12	5/12	
83. Marked abnormality in ALT^f (SGPT)^e level (> 60 U/L and increase from baseline ≥ 50%)	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 8/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 7/300	1.14 (0.42 to 3.11)
84. Marked abnormality in AST^d (SGOT)^c level (> 50 U/L and increase from baseline ≥ 50%)	Strauss 2001	**Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks** 5/300	Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks 9/300	0.56 (0.19 to 1.64)
85. Persistent elevated serum protein (during therapy and follow-up phase)	Lester 1985	Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks 3/15	**Oral tetracycline 0.5 to 1 g/day for 16 weeks** 0/15	7.00 (0.39 to 124.83)
86. Raised serum protein	Pigatto 1986	Oral isotretinoin 1 mg/kg/day for 10 weeks followed by 0.5 mg/kg/day for 10 weeks 1/12	**Minocycline 100 mg/day for 10 weeks and then reduced to 50 mg/day for 10 weeks** 0/12	3.00 (0.13 to 67.06)
87. Marked abnormality in GGT^g level (> 120 U/L and increase from baseline ≥ 50%)	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 7/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 4/300	1.75 (0.52 to 5.92)
88. Marked abnormality in LDH^h level (> 500 U/L and increase from baseline ≥ 50%)	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 1/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** **0/300**	3.00 (0.12 to 73.35)
89. Transient abnormalities in semen evaluations	Goldstein 1982	Oral isotretinoin 1 mg/kg/day for 8 weeks 0/28	Oral etretinate 1 mg/kg/day for 8 weeks 0/28	Not estimable
	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks** 0/15	Oral tetracycline 0.5 to 1 g/day for 16 weeks 3/15	0.14 (0.01 to 2.55)

^{a}Results that showed a statistically significant difference between interventions
^{b}BDI-II (Beck Depression Inventory-II)
^{c}SGOT (serum glutamic oxaloacetic transaminase)

[d]AST (aspartate aminotransferase)
[e]SGPT (serum glutamic pyruvic transaminase)
[f]ALT (alanine aminotransferase)
[g]GGT (gamma-glutamyl transpeptidase)
[h]LDH (lactate dehydrogenase)
[*]The intervention groups which had lower less serious adverse event rates in each comparison are in bold.

Table 4. Dropout rates from RCTs. Oral isotretinoin alone or in combination versus other active topical or systemic active therapy

Dropout rates	Study	Comparison		Estimate of effect: risk ratio, 95% CI
		Intervention	**Control**	
		Number of participants who dropped out/Number of analysed participants	**Number of participants who dropped out/Number of analysed participants**	
1. Overall dropout rates	Gollnick 2001	**Oral isotretinoin 0.5 to 0.8 mg/kg/day for 6 months[*]** 2/35	Oral minocycline (50 mg twice daily) plus topical azelaic acid cream (twice daily) for 6 months 6/50	0.48 (0.10 to 2.22)
	Oprica 2007	Oral isotretinoin 1 mg/kg/day for 24 weeks 7/26	**Tetracycline 500 mg twice daily plus topical adapalene 0.1% once a day for 24 weeks** 6/26	1.17 (0.45 to 3.00)
	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 59/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 51/302	1.16 (0.83 to 1.63)
	Webster 2014	**Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20** 60/461	Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks 70/464	0.86 (0.63 to 1.19)
	Dhir 2008	Oral isotretinoin 20 mg twice a day for 24 weeks 5/30	Oral isotretinoin 20 mg twice a day along with topical clindamycin (1%) during the daytime and adapalene (0.1%) at bedtime for 24 weeks 5/30	1.00 (0.26 to 3.89)
	Faghihi 2014	Oral isotretinoin, 20 mg once a day plus vehicle neutral gel applied on the face twice daily, both for 8 weeks 0/29	Oral isotretinoin, 20 mg once a day plus 5% dapsone gel applied on the face twice daily, both for 8 weeks 0/29	Not estimable
	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks**	Oral tetracycline 0.5 to 1 g/day for 16 weeks	0.20 (0.01 to 3.85)

Table 4. Dropout rates from RCTs. Oral isotretinoin alone or in combination versus other active topical or systemic active therapy *(Continued)*

			0/15	2/15	
	Prendiville 1988	Oral isotretinoin 40 mg daily for 16 weeks 3/20	Dapsone 100 mg daily for 16 weeks 3/20	1.00 (0.23 to 4.37)
	Tan 2014	**Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel** **17/133**	Oral doxycycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel (both once daily) 28/133	0.61 (0.35 to 1.06)
2. Dropout rates due to improvement at 6 months	Oprica 2007	Oral isotretinoin 1 mg/kg/day for 24 weeks 1/26	**Tetracycline 500 mg twice daily plus topical adapalene 0.1% once a day for 24 weeks** 0/26	3.00 (0.13 to 70.42)
3. Dropout rates due to lack of efficacy	Gollnick 2001	**Oral isotretinoin 0.5 to 0.8 mg/kg/day for 6 months** **0/35**	Oral minocycline (50 mg twice daily) plus topical azelaic acid cream (twice daily) for 6 months 1/50	0.47 (0.02 to 11.27)
4. Dropout rates due to treatment failure	Lester 1985	**Oral isotretinoin 1.0 to 2.0 mg/kg/day for 16 weeks** **0/15**	Oral tetracycline 0.5 to 1 g/day for 16 weeks 2/15	0.20 (0.01 to 3.85)
5. Dropout rates, no improvement or worsening at 4 months	Oprica 2007	**Oral isotretinoin 1 mg/kg/day for 24 weeks** **0/26**	Tetracycline 500 mg twice daily plus topical adapalene 0.1% once a day for 24 weeks 2/26	0.20 (0.01 to 3.97)
6. Dropout rates due to adverse effects	Tan 2014	**Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel** **4/133**	Oral doxycycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel (both once daily) 6/133	0.67 (0.19 to 2.31)
7. Dropout rates due to adverse events	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 16/300	Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks 16/302	1.01 (0.51 to 1.98)
	Webster 2014	**Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20** **15/461**	Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks 19/464	0.79 (0.41 to 1.54)

Table 4.   Dropout rates from RCTs. Oral isotretinoin alone or in combination versus other active topical or systemic active therapy *(Continued)*

8. Dropout rates due to adverse effects (local skin irritation)	Gollnick 2001	**Oral isotretinoin 0.5 to 0.8 mg/kg/day for 6 months** 0/35	Oral minocycline (50 mg twice daily) plus topical azelaic acid cream (twice daily) for 6 months 1/50	0.47 (0.02 to 11.27)
9. Dropout rates due to adverse effects (gastric pain)	Gollnick 2001	**Oral isotretinoin 0.5 to 0.8 mg/kg/day for 6 months** 0/35	Oral minocycline (50 mg twice daily) plus topical azelaic acid cream (twice daily) for 6 months 1/50	0.47 (0.02 to 11.27)
10. Dropout rates due to adverse effect (hypersensitivity reaction)	Prendiville 1988	**Oral isotretinoin 40 mg daily for 16 weeks** 0/20	Dapsone 100 mg daily for 16 weeks 1/20	0.33 (0.01 to 7.72)
11. Dropout rates due to adverse effects (flare-up) at 2 months	Oprica 2007	Oral isotretinoin 1 mg/kg/day for 24 weeks 1/26	**Tetracycline 500 mg twice daily plus topical adapalene 0.1% once a day for 24 weeks** 0/26	3.00 (0.13 to 70.42)
12. Dropout rates due to adverse effect (severe xerosis) at 4 months	Oprica 2007	Oral isotretinoin 1 mg/kg/day for 24 weeks 2/26	**Tetracycline 500 mg twice daily plus topical adapalene 0.1% once a day for 24 weeks** 0/26	5.00 (0.25 to 99.34)
13. Dropout rates due to adverse effect (gastrointestinal disturbances) at 4 months	Oprica 2007	**Oral isotretinoin 1 mg/kg/day for 24 weeks** 0/26	Tetracycline 500 mg twice daily plus topical adapalene 0.1% once a day for 24 weeks 1/26	0.33 (0.01 to 7.82)
14. Dropout rates due to loss to follow-up	Tan 2014	**Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel** 4/133	Oral doxycycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel (both once daily) 6/133	0.67 (0.19 to 2.31)
	Webster 2014	**Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20** 60/461	Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks 70/464	0.81 (0.42 to 1.53)
15. Dropout rates due to poor compliance	Gollnick 2001	**Oral isotretinoin 0.5 to 0.8 mg/kg/day for 6 months** 1/35	Oral minocycline (50 mg twice daily) plus topical azelaic acid cream (twice daily) for 6 months 3/50	0.48 (0.05 to 4.39)
	Webster 2014	Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, fol-	**Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks** 5/464	1.61 (0.53 to 4.89)

Table 4. Dropout rates from RCTs. Oral isotretinoin alone or in combination versus other active topical or systemic active therapy *(Continued)*

		lowed by 1 mg/kg/day until week 20 8/461		
16. Dropout rates due to non-attendance or poor compliance	Prendiville 1988	Oral isotretinoin 40 mg daily for 16 weeks 3/20	**Dapsone 100 mg daily for 16 week**s 1/20	3.00 (0.34 to 26.45)
17. Dropout rates due to loss to follow-up, refusal of treatment or violation of the protocol	Strauss 2001	Standard oral isotretinoin 0.85 to 1.18 mg/kg/day for 20 weeks 43/300	**Micronised oral isotretinoin 0.32 to 0.4 mg/kg/day for 20 weeks** 35/302	1.24 (0.82 to 1.88)
18. Dropout rates due to dissatisfaction with treatment	Prendiville 1988	**Oral isotretinoin 40 mg daily for 16 weeks** 0/20	Dapsone 100 mg daily for 16 weeks 1/20	0.33 (0.01 to 7.72)
19. Dropout rates due to participant's request, withdrawal of consent	Tan 2014	**Oral isotretinoin (0.5 mg/kg/day for the first 4 weeks with escalation to 1 mg/kg/day for subsequent 16 weeks) plus vehicle gel** 3/133	Oral doxycycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel (both once daily) 8/133	0.38 (0.10 to 1.38)
	Webster 2014	Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20 15/461	Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks 15/464	1.01 (0.50 to 2.03)
20. Dropout rates due to other reasons (not specified)	Gollnick 2001	Oral isotretinoin 0.5 to 0.8 mg/kg/day for 6 months 1/35	**Oral minocycline (50 mg twice daily) plus topical azelaic acid cream (twice daily) for 6 months** 0/50	4.25 (0.18 to 101.39)
	Webster 2014	**Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20** 4/461	Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks 10/464	0.40 (0.13 to 1.27
21. Dropout rates due to other reasons (not specified) at 2 months	Oprica 2007	Oral isotretinoin 1 mg/kg/day for 24 weeks 1/26	Tetracycline 500 mg twice daily plus topical adapalene 0.1% once a day for 24 weeks 1/26	1.00 (0.07 to 15.15)
22. Dropout rates due to other reasons (not specified) at 4 months	Oprica 2007	Oral isotretinoin 1 mg/kg/day for 24 weeks 1/26	**Tetracycline 500 mg twice daily plus topical adapalene 0.1% once a day for 24 weeks**	3.00 (0.13 to 70.42)

Table 4. Dropout rates from RCTs. Oral isotretinoin alone or in combination versus other active topical or systemic active therapy *(Continued)*

			0/26	
23. Dropout rates due to other reasons (not specified) at 6 months	Oprica 2007	**Oral isotretinoin 1 mg/kg/day for 24 weeks** 1/26	Tetracycline 500 mg twice daily plus topical adapalene 0.1% once a day for 24 weeks 2/26	0.50 (0.05 to 5.18)
24. Dropout rates due to investigator's decision	Webster 2014	Standard oral isotretinoin, 0.5 mg/kg/day first 8 weeks, followed by 1 mg/kg/day until week 20 2/461	**Isotretinoin-Lidose, 1 mg/kg/day for 20 weeks** 1/464	2.01 (0.18 to 22.12)

* The intervention groups which had lower dropout rates in each comparison are in bold.

Table 5. Dropout rates from RCTs. Oral isotretinoin at different doses/schemes

Dropout rates	Study	Comparison		Estimate of effect: risk ratio, 95% CI
		Intervention	**Control**	
		Number of participants who dropped out/Number of analysed participants	**Number of participants who dropped out/Number of analysed participants**	
1. Overall dropout rates	Agarwal 2011	**1 mg/kg/day (alternate day), for 16 weeks*** 2/30	1 mg/kg/day, for 16 weeks 3/30	0.67 (0.12 to 3.71)
		20 mg (alternate day), for 16 weeks 1/30	1 mg/kg/day (alternate day), for 16 weeks 2/30	0.50 (0.05 to 5.22)
		20 mg (alternate day), for 16 weeks 1/30	1 mg/kg/day, for 16 weeks 3/30	0.33 (0.04 to 3.03)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 2/30	1 mg/kg/day, for 16 weeks 3/30	0.67 (0.12 to 3.71)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 2/30	1 mg/kg/day, (alternate day), for 16 weeks 2/30	1.00 (0.15 to 6.64)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 2/30	**20 mg (alternate day), for 16 weeks** **1/30**	2.00 (0.19 to 20.90)

Table 5. Dropout rates from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

Akman 2007	**0.5 mg/kg/day first 10 days, for 6 months (intermittent)** 0/22	0.5 mg/kg/day for 1 month, afterwards 0.5 mg/kg/daily first 10 days, for 5 months (continuous first month, then intermittent) 3/22	0.14 (0.01 to 2.61)
	0.5 mg/kg/day first 10 days, for 6 months (intermittent) 0/22	0.5 mg/kg/day, for 6 months 3/22	0.14 (0.01 to 2.61)
	0.5 mg/kg/day for 1 month, afterwards 0.5 mg/kg/day first 10 days, for 5 months (continuous first month, then intermittent) 3/22	0.5 mg/kg/day, for 6 months 3/22	1.00 (0.23 to 4.42)
Corlin 1984	0.05 mg/kg/day for 20 weeks 23/64	**0.1 mg/kg/day for 20 weeks** **8/62**	2.79 (1.35 to 5.75)[a]
	0.05 mg/kg/day for 20 weeks 23/64	**0.2 mg/kg/day for 20 weeks** **6/65**	3.89 (1.70 to 8.92)[a]
	0.1 mg/kg/day for 20 weeks 8/62	**0.2 mg/kg/day for 20 weeks** **6/65**	1.40 (0.51 to 3.80)
Cumurcu 2009	< 0.5 mg/kg/day for 90 days 1/25	> 0.5 mg/kg/day for 90 days 1/26	1.04 (0.07 to 15.74)
Lee 2011	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)** **3/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 4/20	0.75 (0.19 to 2.93)
	0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 4/20	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)** **3/20**	1.33 (0.34 to 5.21)
	0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 4/20	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 4/20	1.00 (0.29 to 3.45)
Strauss 1984 (primary reference)	0.1 mg/kg/day for 20 weeks 4/50	0.5 mg/kg/day for 20 weeks 4/50	1.00 (0.26 to 3.78)
	0.1 mg/kg/day for 20 weeks 4/50	**1.0 mg/kg/day for 20 weeks** **1/50**	4.00 (0.46 to 34.54)

Table 5. Dropout rates from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		0.5 mg/kg/day for 20 weeks 4/50	**1.0 mg/kg/day for 20 weeks** **1/50**	4.00 (0.46 to 34.54)
	Strauss 1984 (secondary reference)	**0.1 mg/kg/day for 20 weeks** **3/50**	0.5 mg/kg/day for 20 weeks 5/50	0.60 (0.15 to 2.38)
		0.1 mg/kg/day for 20 weeks **3/50**	1.0 mg/kg/day for 20 weeks 5/50	0.60 (0.15 to 2.38)
		0.5 mg/kg/day for 20 weeks 5/50	1.0 mg/kg/day for 20 weeks 5/50	1.00 (0.31 to 3.24)
	Van der Meeren 1983	0.5 mg/kg/day for 12 weeks 4/31	**1.0 mg/kg/day for 12 weeks** **3/27**	1.16 (0.28 to 4.73)
2. Dropout rates due to full acne remission	Corlin 1984	**0.05 mg/kg/day for 20 weeks** **0/64**	0.1 mg/kg/day for 20 weeks 1/62	0.32 (0.01 to 7.78)
		0.05 mg/kg/day for 20 weeks 0/64	0.2 mg/kg/day for 20 weeks 0/65	Not estimable
		0.1 mg/kg/day for 20 weeks 1/62	**0.2 mg/kg/day for 20 weeks** **0/65**	3.14 (0.13 to 75.72)
3. Dropout rates due to treatment failure after 12 weeks	Corlin 1984	0.05 mg/kg/day for 20 weeks 6/64	**0.1 mg/kg/day for 20 weeks** **2/62**	2.91 (0.61 to 13.85)
		0.05 mg/kg/day for 20 weeks 6/64	**0.2 mg/kg/day for 20 weeks** **1/65**	6.09 (0.75 to 49.20)
		0.1 mg/kg/day for 20 weeks 2/62	**0.2 mg/kg/day for 20 weeks** **1/65**	2.10 (0.20 to 22.54)
4. Dropout rates due to treatment failure after 12 weeks despite an increase in dose	Corlin 1984	0.05 mg/kg/day for 20 weeks 8/64	**0.1 mg/kg/day for 20 weeks** **2/62**	3.88 (0.86 to 17.53)
		0.05 mg/kg/day for 20 weeks 8/64	**0.2 mg/kg/day for 20 weeks** **0/65**	17.26 (1.02 to 292.95)[a]
		0.1 mg/kg/day for 20 weeks 2/62	**0.2 mg/kg/day for 20 weeks** **0/65**	5.24 (0.26 to 106.98)
5. Dropout rates due to adverse effects (blurred vision)	Cumurcu 2009	**< 0.5 mg/kg/day for 90 days** **0/25**	> 0.5 mg/kg/day for 90 days 1/26	0.35 (0.01 to 8.12)

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Table 5.   Dropout rates from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

6. Dropout rate due to adverse effects (raised serum triglycerides)	Lee 2011	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)** **0/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 1/20	0.33 (0.01 to 7.72)
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 0/20	0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose) 0/20	Not estimable
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) **0/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 1/20	0.33 (0.01 to 7.72)
7. Dropout rate due to adverse effects (raised liver function test)	Lee 2011	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)** **0/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 1/20	0.33 (0.01 to 7.72)
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 0/20	0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose) 0/20	Not estimable
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) **0/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 1/20	0.33 (0.01 to 7.72)
8. Dropout rates due to adverse effects (dry lips and dry skin)	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** **1/31**	1.0 mg/kg/day for 12 weeks 3/27	0.29 (0.03 to 2.63)
9. Dropout rates due to reasons not related to the intervention	Corlin 1984	0.05 mg/kg/day for 20 weeks 9/64	**0.1 mg/kg/day for 20 weeks** **3/62**	2.91 (0.83 to 10.24)
		0.05 mg/kg/day for 20 weeks 9/64	**0.2 mg/kg/day for 20 weeks** **5/65**	1.83 (0.65 to 5.16)
		0.1 mg/kg/day for 20 weeks **3/62**	0.2 mg/kg/day for 20 weeks 5/65	0.63 (0.16 to 2.52)
	Cumurcu 2009	< 0.5 mg/kg/day for 90 days 1/25	**> 0.5 mg/kg/day for 90 days** **0/26**	3.12 (0.13 to 73.06)
10. Dropout rates due to personal reasons	Lee 2011	0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose) 3/20	**0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose)**	1.50 (0.28 to 8.04)

Table 5. Dropout rates from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

				2/20	
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 4/20	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)** **3/20**	1.33 (0.34 to 5.21)	
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 4/20	**0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose)** **2/20**	2.00 (0.41 to 9.71)	
11. Dropout rates due to other reasons (not specified)	Van der Meeren 1983	0.5 mg/kg/day for 12 weeks 3/31	**1.0 mg/kg/day for 12 weeks** **0/27**	6.13 (0.33 to 113.50)	

a Results that showed a statistically significant difference between interventions

* The interventions groups which had lower dropout rates in each comparison are in bold.

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes

Adverse effect (AE) outcomes	Study	– Oral isotretinoin in different doses/therapeutic regimens		Estimate of effect: risk ratio, 95% CI
		Intervention **Number of participants who experienced the AE/Number of analysed participants**	**Control** **Number of participants who experienced the AE/Number of analysed participants**	
1. Clinical adverse effects - mucocutaneous				
1.1 Cheilitis (also chapped lips)	Agarwal 2011	**1 mg/kg/day (alternate day), for 16 weeks*** 26/28	1 mg/kg/day, for 16 weeks 27/27	0.93 (0.82 to 1.05)
		20 mg (alternate day), for 16 weeks 26/29	1 mg/kg/day (alternate day), for 16 weeks 26/28	0.97 (0.82 to 1.13)
		20 mg (alternate day), for 16 weeks 26/29	1 mg/kg/day, for 16 weeks 27/27	0.90 (0.78 to 1.03)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 22/28	1 mg/kg/day, for 16 weeks 27/27	0.79 (0.65 to 0.97)*a*
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks	1 mg/kg/day, (alternate day), for 16 weeks	0.85 (0.68 to 1.05)

			22/28	26/28	
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 22/28	20 mg (alternate day), for 16 weeks 26/29	0.88 (0.70 to 1.10)
	Corlin 1984	**0.05 mg/kg/day for 20 weeks** 34/64	0.1 mg/kg/day for 20 weeks 40/62	0.82 (0.61 to 1.11)
		0.05 mg/kg/day for 20 weeks 34/64	0.2 mg/kg/day for 20 weeks 44/65	0.78 (0.59 to 1.04)
		0.1 mg/kg/day for 20 weeks 40/62	0.2 mg/kg/day for 20 weeks 44/65	0.95 (0.74 to 1.22)
	Dhaked 2016	**20 mg alternate days for 24 weeks** **111/116**	20 mg daily for 24 weeks 115/118	0.98 (0.93 to1.03)
	Jones 1983a	**0.1 mg/kg/day for 16 weeks** 20/22	0.5 mg/kg/day for 16 weeks 29/30	0.94 (0.81 to 1.09)
		0.1 mg/kg/day for 16 weeks 20/22	1.0 mg/kg/day for 16 weeks 22/24	0.99 (0.83 to 1.19)
		0.5 mg/kg/day for 16 weeks 29/30	1.0 mg/kg/day for 16 weeks 22/24	1.05 (0.92 to 1.21)
	Strauss 1984	**0.1 mg/kg/day for 20 weeks** 35/46	0.5 mg/kg/day for 20 weeks 41/46	0.85 (0.71 to 1.03)
		0.1 mg/kg/day for 20 weeks 35/46	1.0 mg/kg/day for 20 weeks 46/49	0.95 (0.84 to 1.07)
		0.5 mg/kg/day for 20 weeks 41/46	1.0 mg/kg/day for 20 weeks 46/49	0.95 (0.84 to 1.07)
	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** 22/31	1.0 mg/kg/day for 12 weeks 20/27	0.96 (0.70 to 1.32)
1.2 Dry lips	Corlin 1984	**0.05 mg/kg/day for 20 weeks** 60/64	0.1 mg/kg/day for 20 weeks 62/62	0.94 (0.87 to 1.01)
		0.05 mg/kg/day for 20 weeks 60/64	0.2 mg/kg/day for 20 weeks 65/65	0.94 (0.87 to 1.01)
		0.1 mg/kg/day for 20 weeks	0.2 mg/kg/day for 20 weeks	1.00 (0.97 to 1.03)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		62/62	65/65	
	Van der Meeren 1983	0.5 mg/kg/day for 12 weeks 31/31	1.0 mg/kg/day for 12 weeks 27/27	1.00 (0.94 to 1.07)
1.3 Dry, chapped lips	Akman 2007	**0.5 mg/kg/day first 10 days of each month for 6 months (intermittent)** 16/22	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 18/19	0.77 (0.58 to 1.01)
		0.5 mg/kg/day first 10 days of each month for 6 months (intermittent) 16/22	0.5 mg/kg/day, for 6 months 19/19	0.74 (0.56 to 0.96)[a]
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 18/19	0.5 mg/kg/day, for 6 months 19/19	0.95 (0.82 to 1.09)
	Lee 2011	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)** 11/20	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 15/20	0.73 (0.46 to 1.17)
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 7/20	0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose) 11/20	0.64 (0.31 to 1.30)
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 7/20	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 15/20	0.47 (0.24 to 0.89)[a]
1.4 Dry skin	Agarwal 2011	**1 mg/kg/day (alternate day), for 16 weeks** 22/28	1 mg/kg/day, for 16 weeks 25/27	0.85 (0.68 to 1.06)
		20 mg (alternate day), for 16 weeks 23/29	1 mg/kg/day (alternate day), for 16 weeks 22/28	1.01 (0.77 to 1.32)
		20 mg (alternate day), for 16 weeks 23/29	1 mg/kg/day, for 16 weeks 25/27	0.86 (0.69 to 1.06)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks	1 mg/kg/day, for 16 weeks 25/27	0.77 (0.60 to 1.00)

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		20/28		
	1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 20/28	1 mg/kg/day, (alternate day), for 16 weeks 22/28	0.91 (0.67 to 1.23)
	1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 20/28	20 mg (alternate day), for 16 weeks 23/29	0.90 (0.67 to 1.21)
Akman 2007	**0.5 mg/kg/day first 10 days of each month, for 6 months** 13/22	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 13/19	0.86 (0.54 to 1.37)
	0.5 mg/kg/day first 10 days of each month, for 6 months 13/22	0.5 mg/kg/day, for 6 months 14/19	0.80 (0.52 to 1.24)
	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 13/19	0.5 mg/kg/day, for 6 months 14/19	0.93 (0.62 to 1.39)
Dhaked 2016	**20 mg alternate days for 24 weeks** **12/116**	20 mg daily for 24 weeks 20/118	0.61 (0.31 to 1.19)
Lee 2011	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)** 1/20	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 5/20	0.20 (0.03 to 1.56)
	0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 0/20	0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose) 1/20	0.33 (0.01 to 7.72)
	0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 0/20	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 5/20	0.09 (0.01 to 1.54)
Strauss 1984	**0.1 mg/kg/day for 20 weeks** 26/46	0.5 mg/kg/day for 20 weeks 40/46	0.65 (0.49 to 0.86)[a]
	0.1 mg/kg/day for 20 weeks 26/46	1.0 mg/kg/day for 20 weeks 40/49	0.69 (0.52 to 0.92)[a]
	0.5 mg/kg/day for 20 weeks	1.0 mg/kg/day for 20 weeks	1.07 (0.90 to 1.27)

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Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		40/46	40/49	
1.5 Peeling of fingertip skin	Akman 2007	**0.5 mg/kg/day first 10 days of each month, for 6 months** **0/22**	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 2/19	0.17 (0.01 to 3.41)
		0.5 mg/kg/day first 10 days of each month, for 6 months **0/22**	0.5 mg/kg/day, for 6 months 4/19	0.10 (0.01 to 1.69)
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months **2/19**	0.5 mg/kg/day, for 6 months 4/19	0.50 (0.10 to 2.41)
	Strauss 1984	**0.1 mg/kg/day for 20 weeks** **8/46**	0.5 mg/kg/day for 20 weeks 14/46	0.57 (0.27 to 1.23)
		0.1 mg/kg/day for 20 weeks **8/46**	1.0 mg/kg/day for 20 weeks 24/49	0.36 (0.18 to 0.71)[a]
		0.5 mg/kg/day for 20 weeks **14/46**	1.0 mg/kg/day for 20 weeks 24/49	0.62 (0.37 to 1.05)
1.6 Rashes or facial redness (also facial dermatitis)	Agarwal 2011	**1 mg/kg/day (alternate day), for 16 weeks** **7/28**	1 mg/kg/day, for 16 weeks 8/27	0.84 (0.36 to 2.01)
		20 mg (alternate day), for 16 weeks **5/29**	1 mg/kg/day (alternate day), for 16 weeks 7/28	0.69 (0.25 to 1.92)
		20 mg (alternate day), for 16 weeks **5/29**	1 mg/kg/day, for 16 weeks 8/27	0.58 (0.22 to 1.56)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks **7/28**	1 mg/kg/day, for 16 weeks 8/27	0.84 (0.36 to 2.01)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 7/28	1 mg/kg/day, (alternate day), for 16 weeks 7/28	1.00 (0.40 to 2.48)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 7/28	**20 mg (alternate day), for 16 weeks** **5/29**	1.45 (0.52 to 4.03)

Akman 2007	**0.5 mg/kg/day first 10 days of each month for 6 months** **1/22**	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 6/19	0.14 (0.02 to 1.09)
	0.5 mg/kg/day first 10 days of each month, for 6 months **1/22**	0.5 mg/kg/day, for 6 months 9/19	0.10 (0.01 to 0.69)*a*
	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months **6/19**	0.5 mg/kg/day, for 6 months 9/19	0.67 (0.30 to 1.50)
Corlin 1984	0.05 mg/kg/day for 20 weeks 18/64	0.1 mg/kg/day for 20 weeks 17/62	1.03 (0.58 to 1.80)
	0.05 mg/kg/day for 20 weeks **18/64**	0.2 mg/kg/day for 20 weeks 23/65	0.79 (0.48 to 1.33)
	0.1 mg/kg/day for 20 weeks **17/62**	0.2 mg/kg/day for 20 weeks 23/65	0.77 (0.46 to 1.31)
Dhaked 2016	20 mg alternate days for 24 weeks 3/116	20 mg daily for 24 weeks 3/118	1.02 (0.21 to 4.94)
Jones 1983a	**0.1 mg/kg/day for 16 weeks** **11/22**	0.5 mg/kg/day for 16 weeks 18/30	0.83 (0.50 to 1.39)
	0.1 mg/kg/day for 16 weeks **11/22**	1.0 mg/kg/day for 16 weeks 18/24	0.67 (0.41 to 1.07)
	0.5 mg/kg/day for 16 weeks **18/30**	1.0 mg/kg/day for 16 weeks 18/24	0.80 (0.55 to 1.16)
Strauss 1984	**0.1 mg/kg/day for 20 weeks** **11/46**	0.5 mg/kg/day for 20 weeks 20/46	0.55 (0.30 to 1.01)
	0.1 mg/kg/day for 20 weeks **11/46**	1.0 mg/kg/day for 20 weeks 33/49	0.36 (0.20 to 0.62)*a*
	0.5 mg/kg/day for 20 weeks **20/46**	1.0 mg/kg/day for 20 weeks 33/49	0.65 (0.44 to 0.95)*a*
Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** **5/31**	1.0 mg/kg/day for 12 weeks 8/27	0.54 (0.20 to 1.47)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

1.7 Skin fragility (also increased risk of damage to skin)	Corlin 1984	**0.05 mg/kg/day for 20 weeks** **5/64**	0.1 mg/kg/day for 20 weeks 6/62	0.81 (0.26 to 2.51)
		0.05 mg/kg/day for 20 weeks **5/64**	0.2 mg/kg/day for 20 weeks 9/65	0.56 (0.20 to 1.59)
		0.1 mg/kg/day for 20 weeks **6/62**	0.2 mg/kg/day for 20 weeks 9/65	0.70 (0.26 to 1.85)
	Strauss 1984	**0.1 mg/kg/day for 20 weeks** **7/46**	0.5 mg/kg/day for 20 weeks 14/46	0.50 (0.22 to 1.12)
		0.1 mg/kg/day for 20 weeks **7/46**	1.0 mg/kg/day for 20 weeks 19/49	0.39 (0.18 to 0.85)*a*
		0.5 mg/kg/day for 20 weeks **14/46**	1.0 mg/kg/day for 20 weeks 19/49	0.78 (0.45 to 1.38)
	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** **3/31**	1.0 mg/kg/day for 12 weeks 8/27	0.33 (0.10 to 1.11)
1.8 Scaling of skin (also rash, desquamation)	Jones 1983a	0.1 mg/kg/day for 16 weeks 6/22	0.5 mg/kg/day for 16 weeks 8/30	1.02 (0.41 to 2.53)
		0.1 mg/kg/day for 16 weeks **6/22**	1.0 mg/kg/day for 16 weeks 10/24	0.65 (0.29 to 1.50)
		0.5 mg/kg/day for 16 weeks **8/30**	1.0 mg/kg/day for 16 weeks 10/24	0.64 (0.30 to 1.37)
	Strauss 1984	**0.1 mg/kg/day for 20 weeks** **10/46**	0.5 mg/kg/day for 20 weeks 12/46	0.83 (0.40 to 1.73)
		0.1 mg/kg/day for 20 weeks **10/46**	1.0 mg/kg/day for 20 weeks 22/49	0.48 (0.26 to 0.91)*a*
		0.5 mg/kg/day for 20 weeks **12/46**	1.0 mg/kg/day for 20 weeks 22/49	0.58 (0.33 to 1.03)
	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** **19/31**	1.0 mg/kg/day for 12 weeks 20/27	0.83 (0.58 to 1.18)
1.9 Repeated scaling of skin	Corlin 1984	**0.05 mg/kg/day for 20 weeks** **13/64**	0.1 mg/kg/day for 20 weeks 18/62	0.70 (0.38, 1.30)
		0.05 mg/kg/day for 20 weeks	0.2 mg/kg/day for 20 weeks	0.46 (0.26 to 0.79)*a*

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		13/64	29/65	
		0.1 mg/kg/day for 20 weeks **18/62**	0.2 mg/kg/day for 20 weeks 29/65	0.65 (0.41 to 1.05)
1.10 Skin atrophy	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** **0/31**	1.0 mg/kg/day for 12 weeks 1/27	0.29 (0.01 to 6.88)
1.11 Dry mouth	Agarwal 2011	**1 mg/kg/day (alternate day), for 16 weeks** **8/28**	1 mg/kg/day, for 16 weeks 18/27	0.43 (0.23 to 0.82)[a]
		20 mg (alternate day), for 16 weeks **6/29**	1 mg/kg/day (alternate day), for 16 weeks 8/28	0.72 (0.29 to 1.82)
		20 mg (alternate day), for 16 weeks **6/29**	1 mg/kg/day, for 16 weeks 18/27	0.31 (0.15 to 0.66)[a]
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks **5/28**	1 mg/kg/day, for 16 weeks 18/27	0.27 (0.12 to 0.62)[a]
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks **5/28**	1 mg/kg/day, (alternate day), for 16 weeks 8/28	0.63 (0.23 to 1.68)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks **5/28**	20 mg (alternate day), for 16 weeks 6/29	0.86 (0.30 to 2.51)
	Akman 2007	0.5 mg/kg/day first 10 days of each month for 6 months 2/22	**0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months** **1/19**	1.73 (0.17 to 17.59)
		0.5 mg/kg/day first 10 days of each month for 6 months **2/22**	0.5 mg/kg/day, for 6 months 9/19	0.19 (0.05 to 0.78)[a]
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months **1/19**	0.5 mg/kg/day, for 6 months 9/19	0.11 (0.02 to 0.79)[a]
	Corlin 1984	0.05 mg/kg/day for 20 weeks 14/64	**0.1 mg/kg/day for 20 weeks** **12/62**	1.13 (0.57 to 2.25)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		0.05 mg/kg/day for 20 weeks **14/64**	0.2 mg/kg/day for 20 weeks 18/65	0.79 (0.43 to 1.45)
		0.1 mg/kg/day for 20 weeks **12/62**	0.2 mg/kg/day for 20 weeks 18/65	0.70 (0.37 to 1.33)
	Dhaked 2016	**20 mg alternate days for 24 weeks** **2/116**	20 mg daily for 24 weeks 3/118	0.68 (0.11 to 3.98)
	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** **5/31**	1.0 mg/kg/day for 12 weeks 12/27	0.36 (0.15, 0.90)[a]
1.12 Sore mouth	Strauss 1984	0.1 mg/kg/day for 20 weeks 6/46	0.5 mg/kg/day for 20 weeks 6/46	1.00 (0.35 to 2.87)
		0.1 mg/kg/day for 20 weeks **6/46**	1.0 mg/kg/day for 20 weeks 15/49	0.43 (0.18 to 1.00)
		0.5 mg/kg/day for 20 weeks **6/46**	1.0 mg/kg/day for 20 weeks 15/49	0.43 (0.18 to 1.00)
1.13 Dry nose	Agarwal 2011	**1 mg/kg/day (alternate day), for 16 weeks** **0/28**	1 mg/kg/day, for 16 weeks 7/27	0.06 (0.00 to 1.07)
		20 mg (alternate day), for 16 weeks 0/29	1 mg/kg/day (alternate day), for 16 weeks 0/28	Not estimable
		20 mg (alternate day), for 16 weeks **0/29**	1 mg/kg/day, for 16 weeks 7/27	0.06 (0.00 to 1.04)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 3/28	1 mg/kg/day, for 16 weeks 7/27	0.41 (0.12 to 1.44)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 3/28	**1 mg/kg/day, (alternate day), for 16 weeks** 0/28	7.00 (0.38 to 129.55)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 3/28	**20 mg (alternate day), for 16 weeks** **0/29**	7.24 (0.39 to 134.12)
	Corlin 1984	**0.05 mg/kg/day for 20 weeks** **17/64**	0.1 mg/kg/day for 20 weeks 18/62	0.91 (0.52 to 1.61)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		0.05 mg/kg/day for 20 weeks 17/64	0.2 mg/kg/day for 20 weeks 25/65	0.69 (0.41 to 1.15)
		0.1 mg/kg/day for 20 weeks 18/62	0.2 mg/kg/day for 20 weeks 25/65	0.75 (0.46 to 1.24)
	Dhaked 2016	**20 mg alternate days for 24 weeks** 1/116	20 mg daily for 24 weeks 4/118	0.25 (0.03 to 2.24)
	Strauss 1984	**0.1 mg/kg/day for 20 weeks** 23/46	0.5 mg/kg/day for 20 weeks 37/46	0.62 (0.45 to 0.86)[a]
		0.1 mg/kg/day for 20 weeks 23/46	1.0 mg/kg/day for 20 weeks 38/49	0.64 (0.47 to 0.89)[a]
		0.5 mg/kg/day for 20 weeks 37/46	1.0 mg/kg/day for 20 weeks 38/49	1.04 (0.84 to 1.28)
	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** 10/31	1.0 mg/kg/day for 12 weeks 17/27	0.51 (0.29 to 0.92)[a]
1.14 Epistaxis (also nasal bleeding)	Akman 2007	0.5 mg/kg/day first 10 days of each month for 6 months 0/22	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 0/19	Not estimable
		0.5 mg/kg/day first 10 days of each month for 6 months 0/22	0.5 mg/kg/day, for 6 months 2/19	0.17 (0.01 to 3.41)
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 0/19	0.5 mg/kg/day, for 6 months 2/19	0.20 (0.01 to 3.91)
	Jones 1983a	**0.1 mg/kg/day for 16 weeks** 6/22	0.5 mg/kg/day for 16 weeks 9/30	0.91 (0.38 to 2.18)
		0.1 mg/kg/day for 16 weeks 6/22	1.0 mg/kg/day for 16 weeks 11/24	0.60 (0.26 to 1.34)
		0.5 mg/kg/day for 16 weeks 9/30	1.0 mg/kg/day for 16 weeks 11/24	0.65 (0.33 to 1.32)
	Lee 2011	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose)	0.14 (0.01 to 2.60)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		0/20	3/20	
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 0/20	0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose) 0/20	Not estimable
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) **0/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 3/20	0.14 (0.01 to 2.60)
	Strauss 1984	**0.1 mg/kg/day for 20 weeks** **8/46**	0.5 mg/kg/day for 20 weeks 13/46	0.62 (0.28 to 1.34)
		0.1 mg/kg/day for 20 weeks **8/46**	1.0 mg/kg/day for 20 weeks 26/49	0.33 (0.17 to 0.65)[a]
		0.5 mg/kg/day for 20 weeks **13/46**	1.0 mg/kg/day for 20 weeks 26/49	0.53 (0.31 to 0.91)[a]
1.15 Dryness of other mucosal tissues	Akman 2007	**0.5 mg/kg/day first 10 days of each month, for 6 months** **0/22**	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 1/19	0.29 (0.01 to 6.72)
		0.5 mg/kg/day first 10 days of each month, for 6 months **0/22**	0.5 mg/kg/day, for 6 months 4/19	0.10 (0.01 to 1.69)
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months **1/19**	0.5 mg/kg/day, for 6 months 4/19	0.25 (0.03 to 2.04)
1.16 Dry eyes	Agarwal 2011	**1 mg/kg/day (alternate day), for 16 weeks** **0/28**	1 mg/kg/day, for 16 weeks 10/27	0.05 (0.00 to 0.75)[a]
		20 mg (alternate day), for 16 weeks 0/29	1 mg/kg/day (alternate day), for 16 weeks 0/28	Not estimable
		20 mg (alternate day), for 16 weeks **0/29**	1 mg/kg/day, for 16 weeks 10/27	0.04 (0.00 to 0.72)[a]
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks	1 mg/kg/day, for 16 weeks 10/27	0.29 (0.09 to 0.94)[a]

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		3/28		
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 3/28	**1 mg/kg/day, (alternate day), for 16 weeks** **0/28**	7.00 (0.38 to 129.55)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 3/28	**20 mg (alternate day), for 16 weeks** **0/29**	7.24 (0.39 to 134.12)
	Dhaked 2016	**20 mg alternate days for 24 weeks** **2/116**	20 mg daily for 24 weeks 9/118	0.23 (0.05 to 1.02)
1.17 Dry or irritated eyes	Akman 2007	0.5 mg/kg/day first 10 days of each month, for 6 months 2/22	**0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months** **1/19**	1.73 (0.17 to 17.59)
		0.5 mg/kg/day first 10 days of each month, for 6 months **2/22**	0.5 mg/kg/day, for 6 months 3/19	0.58 (0.11 to 3.09)
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months **1/19**	0.5 mg/kg/day, for 6 months 3/19	0.33 (0.04 to 2.93)
1.18 Irritation of eyes	Strauss 1984	**0.1 mg/kg/day for 20 weeks** **20/46**	0.5 mg/kg/day for 20 weeks 23/46	0.87 (0.56 to 1.35)
		0.1 mg/kg/day for 20 weeks **8/46**	1.0 mg/kg/day for 20 weeks 26/49	0.33 (0.17 to 0.65)[a]
		0.5 mg/kg/day for 20 weeks **23/46**	1.0 mg/kg/day for 20 weeks 28/49	0.88 (0.60 to 1.28)
1.19 Conjunctivitis	Corlin 1984	0.05 mg/kg/day for 20 weeks 6/64	**0.1 mg/kg/day for 20 weeks** **5/62**	1.16 (0.37 to 3.61)
		0.05 mg/kg/day for 20 weeks 6/64	**0.2 mg/kg/day for 20 weeks** **5/65**	1.22 (0.39 to 3.79)
		0.1 mg/kg/day for 20 weeks 5/62	0.2 mg/kg/day for 20 weeks 5/65	1.05 (0.32 to 3.45)
	Jones 1983a	**0.1 mg/kg/day for 16 weeks** **0/22**	0.5 mg/kg/day for 16 weeks 4/30	0.15 (0.01 to 2.65)

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		0.1 mg/kg/day for 16 weeks 0/22	1.0 mg/kg/day for 16 weeks 5/24	0.10 (0.01 to 1.69)
		0.5 mg/kg/day for 16 weeks 4/30	1.0 mg/kg/day for 16 weeks 5/24	0.64 (0.19 to 2.13)
1.20 Blepharo-conjunctivitis	Cumurcu 2009	< 0.5 mg/kg/day for 90 days 2/25	> 0.5 mg/kg/day for 90 days 5/26	0.42 (0.09 to 1.95)
1.21 Severe ble-pharoconjunc-tivitis	Cumurcu 2009	< 0.5 mg/kg/day for 90 days 0/25	> 0.5 mg/kg/day for 90 days 1/26	0.35 (0.01 to 8.12)
1.22 Blurred vi-sion	Cumurcu 2009	< 0.5 mg/kg/day for 90 days 0/25	> 0.5 mg/kg/day for 90 days 1/26	0.35 (0.01 to 8.12)
1.23 Contact lens intolerance	Cumurcu 2009	< 0.5 mg/kg/day for 90 days 0/25	> 0.5 mg/kg/day for 90 days 1/26	0.35 (0.01 to 8.12)
1.24 Pruritus (al-so itching)	Akman 2007	0.5 mg/kg/day first 10 days of each month, for 6 months 3/22	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 3/19	0.86 (0.20 to 3.79)
		0.5 mg/kg/day first 10 days of each month, for 6 months 3/22	0.5 mg/kg/day, for 6 months 6/19	0.43 (0.12 to 1.50)
		0.5 mg/kg/day for 1 month, fol-lowed by 0.5 mg/kg/day first 10 days of each month for 5 months 3/19	0.5 mg/kg/day, for 6 months 6/19	0.50 (0.15 to 1.71)
	Corlin 1984	0.05 mg/kg/day for 20 weeks 10/64	0.1 mg/kg/day for 20 weeks 8/62	1.21 (0.51 to 2.87)
		0.05 mg/kg/day for 20 weeks 10/64	0.2 mg/kg/day for 20 weeks 8/65	1.27 (0.54 to 3.01)
		0.1 mg/kg/day for 20 weeks 8/62	0.2 mg/kg/day for 20 weeks 8/65	1.05 (0.42 to 2.62)
	Dhaked 2016	20 mg alternate days for 24 weeks 5/116	20 mg daily for 24 weeks 11/118	0.46 (0.16 to 1.29)
	Strauss 1984	0.1 mg/kg/day for 20 weeks 22/46	0.5 mg/kg/day for 20 weeks 17/46	1.29 (0.80 to 2.10)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		0.1 mg/kg/day for 20 weeks **22/46**	1.0 mg/kg/day for 20 weeks 33/49	0.71 (0.50 to 1.02)
		0.5 mg/kg/day for 20 weeks **17/46**	1.0 mg/kg/day for 20 weeks 33/49	0.55 (0.36 to 0.84)*a*
	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** **10/31**	1.0 mg/kg/day for 12 weeks 15/27	0.58 (0.31, 1.07)
1.25 Hair loss	Akman 2007	0.5 mg/kg/day first 10 days of each month, for 6 months 0/22	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 0/19	Not estimable
		0.5 mg/kg/day first 10 days of each month, for 6 months 0/22	0.5 mg/kg/day, for 6 months 0/19	Not estimable
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 0/19	0.5 mg/kg/day, for 6 months 0/19	Not estimable
	Corlin 1984	0.05 mg/kg/day for 20 weeks 7/64	**0.1 mg/kg/day for 20 weeks** **6/62**	1.13 (0.40 to 3.18)
		0.05 mg/kg/day for 20 weeks 7/64	0.2 mg/kg/day for 20 weeks 7/65	1.02 (0.38, 2.73)
		0.1 mg/kg/day for 20 weeks **6/62**	0.2 mg/kg/day for 20 weeks 7/65	0.90 (0.32 to 2.53)
	Dhaked 2016	**20 mg alternate days for 24 weeks** **3/116**	20 mg daily for 24 weeks 7/118	0.44 (0.11 to 1.64)
	Strauss 1984	0.1 mg/kg/day for 20 weeks 12/46	0.5 mg/kg/day for 20 weeks 12/46	1.00 (0.50 to 1.99)
		0.1 mg/kg/day for 20 weeks **12/46**	1.0 mg/kg/day for 20 weeks 17/49	0.75 (0.40 to 1.40)
		0.5 mg/kg/day for 20 weeks **12/46**	1.0 mg/kg/day for 20 weeks 17/49	0.75 (0.40 to 1.40)
	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** **0/31**	1.0 mg/kg/day for 12 weeks 3/27	0.13 (0.01 to 2.32)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

1.26 Sunburn	Strauss 1984	0.1 mg/kg/day for 20 weeks 7/46	**0.5 mg/kg/day for 20 weeks** **4/46**	1.75 (0.55 to 5.57)
		0.1 mg/kg/day for 20 weeks 7/46	**1.0 mg/kg/day for 20 weeks** **5/49**	1.49 (0.51 to 4.37)
		0.5 mg/kg/day for 20 weeks **4/46**	1.0 mg/kg/day for 20 weeks 5/49	0.85 (0.24 to 2.98)
1.27 Oral apht-hous	Dhaked 2016	**20 mg alternate days for 24 weeks** **0/116**	20 mg daily for 24 weeks 1/118	0.34 (0.01 to 8.24)
1.28 Urticaria	Dhaked 2016	**20 mg alternate days for 24 weeks** **3/116**	20 mg daily for 24 weeks 4/118	0.76 (0.17 to 3.33)
1.29 Pigmenta-tion of face	Dhaked 2016	**20 mg alternate days for 24 weeks** **1/116**	20 mg daily for 24 weeks 0/118	3.05 (0.12 to 74.14)
1.30 Dermo-graphism	Dhaked 2016	**20 mg alternate days for 24 weeks** **1/116**	20 mg daily for 24 weeks 0/118	3.05 (0.12 to 74.14)
2. Clinical ad-verse effects (other than mu-cocutaneous)				
2.1 Headache	Strauss 1984	0.1 mg/kg/day for 20 weeks 10/46	**0.5 mg/kg/day for 20 weeks** **5/46**	2.00 (0.74 to 5.40)
		0.1 mg/kg/day for 20 weeks **10/46**	1.0 mg/kg/day for 20 weeks 12/49	0.89 (0.43 to 1.85)
		0.5 mg/kg/day for 20 weeks **5/46**	1.0 mg/kg/day for 20 weeks 12/49	0.44 (0.17 to 1.16)
	Dhaked 2016	**20 mg alternate days for 24 weeks** **1/116**	20 mg daily for 24 weeks 2/118	0.51 (0.05 to 5.53)
2.2 Bone/joint aches and pains	Akman 2007	0.5 mg/kg/day first 10 days of each month, for 6 months 0/22	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 0/19	Not estimable
		0.5 mg/kg/day first 10 days of each month, for 6 months 0/22	0.5 mg/kg/day, for 6 months 0/19	Not estimable

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 0/19	0.5 mg/kg/day, for 6 months 0/19	Not estimable
	Strauss 1984	**0.1 mg/kg/day for 20 weeks** **8/46**	0.5 mg/kg/day for 20 weeks 11/46	0.73 (0.32 to 1.64)
		0.1 mg/kg/day for 20 weeks **8/46**	1.0 mg/kg/day for 20 weeks 15/49	0.57 (0.27 to 1.21)
		0.5 mg/kg/day for 20 weeks **11/46**	1.0 mg/kg/day for 20 weeks 15/49	0.78 (0.40 to 1.52)
2.3 Arthralgia	Jones 1983a	0.1 mg/kg/day for 16 weeks 4/22	0.5 mg/kg/day for 16 weeks 5/30	1.09 (0.33 to 3.60)
		0.1 mg/kg/day for 16 weeks **4/22**	1.0 mg/kg/day for 16 weeks 7/24	0.62 (0.21 to 1.84)
		0.5 mg/kg/day for 16 weeks **5/30**	1.0 mg/kg/day for 16 weeks 7/24	0.57 (0.21 to 1.58)
	Dhaked 2016	**20 mg alternate days for 24 weeks** **0/116**	20 mg daily for 24 weeks 1/118	0.34 (0.01 to 8.24)
2.4 Muscular cramps or pains	Akman 2007	0.5 mg/kg/day first 10 days of each month for 6 months 0/22	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 0/19	Not estimable
		0.5 mg/kg/day first 10 days of each month for 6 months 0/22	0.5 mg/kg/day, for 6 months 0/19	Not estimable
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 0/19	0.5 mg/kg/day, for 6 months 0/19	Not estimable
2.5 Muscle cramps	Strauss 1984	0.1 mg/kg/day for 20 weeks 8/46	**0.5 mg/kg/day for 20 weeks** **4/46**	2.00 (0.65 to 6.18)
		0.1 mg/kg/day for 20 weeks **8/46**	1.0 mg/kg/day for 20 weeks 11/49	0.77 (0.34 to 1.75)
		0.5 mg/kg/day for 20 weeks	1.0 mg/kg/day for 20 weeks	0.39 (0.13 to 1.13)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		11/46	15/49	
2.6 Muscle pain	Corlin 1984	**0.05 mg/kg/day for 20 weeks** **6/64**	0.1 mg/kg/day for 20 weeks 6/62	0.97 (0.33 to 2.84)
		0.05 mg/kg/day for 20 weeks 6/64	**0.2 mg/kg/day for 20 weeks** **5/65**	1.22 (0.39 to 3.79)
		0.1 mg/kg/day for 20 weeks 6/62	**0.2 mg/kg/day for 20 weeks** **5/65**	1.26 (0.40 to 3.91)
	Dhaked 2016	20 mg alternate days for 24 weeks 2/116	20 mg daily for 24 weeks 2/118	1.02 (0.14 to 7.10)
	Van der Meeren 1983	**0.5 mg/kg/day for 12 weeks** **1/31**	1.0 mg/kg/day for 12 weeks 1/27	0.87 (0.06 to 13.27)
2.7 Fatigue	Akman 2007	0.5 mg/kg/day first 10 days of each month, for 6 months 0/22	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 0/19	Not estimable
		0.5 mg/kg/day first 10 days of each month, for 6 months **0/22**	0.5 mg/kg/day, for 6 months 1/19	0.29 (0.01 to 6.72)
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months **0/19**	0.5 mg/kg/day, for 6 months 1/19	0.33 (0.01 to 7.70)
	Strauss 1984	0.1 mg/kg/day for 20 weeks 12/46	**0.5 mg/kg/day for 20 weeks** **8/46**	1.50 (0.68 to 3.32)
		0.1 mg/kg/day for 20 weeks **12/46**	1.0 mg/kg/day for 20 weeks 19/49	0.67 (0.37 to 1.23)
		0.5 mg/kg/day for 20 weeks **8/46**	1.0 mg/kg/day for 20 weeks 19/49	0.45 (0.22 to 0.92)[a]
2.8 Excessive thirst	Akman 2007	**0.5 mg/kg/day first 10 days of each month for 6 months** **2/22**	0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 4/19	0.43 (0.09 to 2.10)
		0.5 mg/kg/day first 10 days of each month, for 6 months	0.5 mg/kg/day, for 6 months 3/19	0.58 (0.11 to 3.09)

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		2/22		
		0.5 mg/kg/day for 1 month, followed by 0.5 mg/kg/day first 10 days of each month for 5 months 4/19	**0.5 mg/kg/day, for 6 months** **3/19**	1.33 (0.34, 5.17)
	Strauss 1984	0.1 mg/kg/day for 20 weeks 14/46	**0.5 mg/kg/day for 20 weeks** **11/46**	1.27 (0.65 to 2.50)
		0.1 mg/kg/day for 20 weeks 14/46	**1.0 mg/kg/day for 20 weeks** **11/49**	1.36 (0.69 to 2.67)
		0.5 mg/kg/day for 20 weeks 11/46	1.0 mg/kg/day for 20 weeks 11/49	1.07 (0.51, 2.22)
2.9 Malaise	Jones 1983a	**0.1 mg/kg/day for 16 weeks** **1/22**	0.5 mg/kg/day for 16 weeks 2/30	0.68 (0.07 to 7.05)
		0.1 mg/kg/day for 16 weeks **1/22**	1.0 mg/kg/day for 16 weeks 4/24	0.27 (0.03 to 2.26)
		0.5 mg/kg/day for 16 weeks **2/30**	1.0 mg/kg/day for 16 weeks 4/24	0.40 (0.08 to 2.00)
2.10 Frequent mood changes	Kapadia 2005	**20 mg/daily for 24 weeks** **0/30**	40 mg/daily 3/30	0.14 (0.01 to 2.65)
2.11 Insomnia	Strauss 1984	0.1 mg/kg/day for 20 weeks 12/46	**0.5 mg/kg/day for 20 weeks** **6/46**	2.00 (0.82, 4.87)
		0.1 mg/kg/day for 20 weeks **12/46**	1.0 mg/kg/day for 20 weeks 14/49	0.91 (0.47, 1.76)
		0.5 mg/kg/day for 20 weeks **6/46**	1.0 mg/kg/day for 20 weeks 14/49	0.46 (0.19 to 1.09)
2.12 Nausea	Strauss 1984	0.1 mg/kg/day for 20 weeks 14/46	**0.5 mg/kg/day for 20 weeks** **4/46**	3.50 (1.25 to 9.84)
		0.1 mg/kg/day for 20 weeks 14/46	**1.0 mg/kg/day for 20 weeks** **6/49**	2.49 (1.04 to 5.92)
		0.5 mg/kg/day for 20 weeks **4/46**	1.0 mg/kg/day for 20 weeks 6/49	0.71 (0.21 to 2.36)
2.13 Decreased appetite	Strauss 1984	0.1 mg/kg/day for 20 weeks	**0.5 mg/kg/day for 20 weeks**	1.50 (0.58 to 3.87)

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		9/46	**6/46**	
		0.1 mg/kg/day for 20 weeks 9/46	**1.0 mg/kg/day for 20 weeks** **7/49**	1.37 (0.56 to 3.38)
		0.5 mg/kg/day for 20 weeks **6/46**	1.0 mg/kg/day for 20 weeks 7/49	0.91 (0.33 to 2.52)
2.14 Increased appetite	Strauss 1984	**0.1 mg/kg/day for 20 weeks** **1/46**	0.5 mg/kg/day for 20 weeks 3/46	0.33 (0.04 to 3.09)
		0.1 mg/kg/day for 20 weeks **1/46**	1.0 mg/kg/day for 20 weeks 2/49	0.53 (0.05 to 5.68)
		0.5 mg/kg/day for 20 weeks 3/46	**1.0 mg/kg/day for 20 weeks** **2/49**	1.60 (0.28 to 9.13)
2.15 Abdominal pain	Strauss 1984	0.1 mg/kg/day for 20 weeks 8/46	**0.5 mg/kg/day for 20 weeks** **2/46**	4.00 (0.90 to 17.83)
		0.1 mg/kg/day for 20 weeks **8/46**	1.0 mg/kg/day for 20 weeks 9/49	0.95 (0.40 to 2.24)
		0.5 mg/kg/day for 20 weeks **2/46**	1.0 mg/kg/day for 20 weeks 9/49	0.24 (0.05 to 1.04)
2.16 Eye pain	Strauss 1984	0.1 mg/kg/day for 20 weeks 8/46	**0.5 mg/kg/day for 20 weeks** **5/46**	1.60 (0.57 to 4.53)
		0.1 mg/kg/day for 20 weeks **8/46**	1.0 mg/kg/day for 20 weeks 9/49	0.95 (0.40 to 2.24)
		0.5 mg/kg/day for 20 weeks **5/46**	1.0 mg/kg/day for 20 weeks 9/49	0.59 (0.21 to 1.64)
2.17 Double vision	Strauss 1984	0.1 mg/kg/day for 20 weeks 3/46	**0.5 mg/kg/day for 20 weeks** **2/46**	1.50 (0.26 to 8.56)
		0.1 mg/kg/day for 20 weeks **3/46**	1.0 mg/kg/day for 20 weeks 4/49	0.80 (0.19 to 3.38)
		0.5 mg/kg/day for 20 weeks **2/46**	1.0 mg/kg/day for 20 weeks 4/49	0.53 (0.10 to 2.77)
2.18 Fever	Strauss 1984	0.1 mg/kg/day for 20 weeks 4/46	**0.5 mg/kg/day for 20 weeks** **2/46**	2.00 (0.39 to 10.39)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		0.1 mg/kg/day for 20 weeks 4/46	**1.0 mg/kg/day for 20 weeks** **1/49**	4.26 (0.49 to 36.73)
		0.5 mg/kg/day for 20 weeks 2/46	**1.0 mg/kg/day for 20 weeks** **1/49**	2.13 (0.20 to 22.71)
2.19 Bruising	Strauss 1984	0.1 mg/kg/day for 20 weeks 2/46	0.5 mg/kg/day for 20 weeks 2/46	1.00 (0.15 to 6.80)
		0.1 mg/kg/day for 20 weeks **2/46**	1.0 mg/kg/day for 20 weeks 4/49	0.53 (0.10 to 2.77)
		0.5 mg/kg/day for 20 weeks **2/46**	1.0 mg/kg/day for 20 weeks 4/49	0.53 (0.10 to 2.77)
2.20 Forgetful-ness	Dhaked 2016	**20 mg alternate days for 24 weeks** **0/116**	20 mg daily for 24 weeks 1/118	0.34 (0.01 to 8.24)
2.21 Menstrual ir-regularities	Dhaked 2016	20 mg alternate days for 24 weeks 2/25	**20 mg daily for 24 weeks** **1/20**	1.60 (0.16 to 16.4)
3. Serum labora-tory adverse ef-fects				
3.1 Raised lipid blood levels	Agarwal 2011	**1 mg/kg/day (alternate day), for 16 weeks** **1/28**	1 mg/kg/day, for 16 weeks 2/27	0.48 (0.05 to 5.01)
		20 mg (alternate day), for 16 weeks **0/29**	1 mg/kg/day (alternate day), for 16 weeks 1/28	0.32 (0.01 to 7.59)
		20 mg (alternate day), for 16 weeks **0/29**	1 mg/kg/day, for 16 weeks 2/27	0.19 (0.01 to 3.72)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks **0/28**	1 mg/kg/day, for 16 weeks 2/27	0.19 (0.01 to 3.85)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks **0/28**	1 mg/kg/day, (alternate day), for 16 weeks 1/28	0.33 (0.01 to 7.85)
		1 mg/kg/day for 1 week/4 weeks (in-termittent), for 16 weeks 0/28	20 mg (alternate day), for 16 weeks 0/29	Not estimable

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

3.2 Abnormal lipid profile	Dhaked 2016	**20 mg alternate days for 24 weeks** **1/116**	20 mg daily for 24 weeks 4/118	0.25 (0.03 to 2.24)
3.3 Increased triglycerides	Lee 2011	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)** **0/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 1/20	0.33 (0.01 to 7.72)
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 0/20	0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose) 0/20	Not estimable
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) **0/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 1/20	0.33 (0.01 to 7.72)
	Strauss 1984	**0.1 mg/kg/day for 20 weeks** **2/46**	0.5 mg/kg/day for 20 weeks 5/46	0.40 (0.08 to 1.96)
		0.1 mg/kg/day for 20 weeks **2/46**	1.0 mg/kg/day for 20 weeks 12/49	0.18 (0.04 to 0.75)[a]
		0.5 mg/kg/day for 20 weeks **5/46**	1.0 mg/kg/day for 20 weeks 12/49	0.44 (0.17 to 1.16)
3.4 Decreased HDL (high-density lipoprotein) levels	Strauss 1984	**0.1 mg/kg/day for 20 weeks** **6/46**	0.5 mg/kg/day for 20 weeks 9/46	0.67 (0.26 to 1.72)
		0.1 mg/kg/day for 20 weeks **6/46**	1.0 mg/kg/day for 20 weeks 8/49	0.80 (0.30 to 2.13)
		0.5 mg/kg/day for 20 weeks 9/46	**1.0 mg/kg/day for 20 weeks** **8/49**	1.20 (0.51 to 2.84)
3.5 Liver enzymes elevation	Agarwal 2011	**1 mg/kg/day (alternate day), for 16 weeks** **0/28**	1 mg/kg/day, for 16 weeks 1/27	0.32 (0.01 to 7.57)
		20 mg (alternate day), for 16 weeks 0/29	1 mg/kg/day (alternate day), for 16 weeks 0/28	Not estimable
		20 mg (alternate day), for 16 weeks **0/29**	1 mg/kg/day, for 16 weeks 1/27	0.31 (0.01 to 7.33)

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks **0/28**	1 mg/kg/day, for 16 weeks 1/27	0.32 (0.01 to 7.57)
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 0/28	1 mg/kg/day, (alternate day), for 16 weeks 0/28	Not estimable
		1 mg/kg/day for 1 week/4 weeks (intermittent), for 16 weeks 0/28	20 mg (alternate day), for 16 weeks 0/29	Not estimable
	Lee 2011	**0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose)** **0/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 1/20	0.33 (0.01 to 7.72)
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) 0/20	0.25 to 0.4 mg/kg/day for 24 weeks (continuous low dose) 0/20	Not estimable
		0.5 to 0.7 mg/kg/day, first 1 week in every 4 weeks for 24 weeks (intermittent conventional dose) **0/20**	0.5 to 0.7 mg/kg/day for 24 weeks (continuous conventional dose) 1/20	0.33 (0.01 to 7.72)
3.6 Abnormal liver function test	Dhaked 2016	**20 mg alternate days for 24 weeks** **1/116**	20 mg daily for 24 weeks 3/118	0.34 (0.03 to 3.21)
3.7 Increased aspartate aminotransferase levels	Jones 1983a	**0.1 mg/kg/day for 16 weeks** **4/22**	0.5 mg/kg/day for 16 weeks 13/30	0.42 (0.16 to 1.11)
		0.1 mg/kg/day for 16 weeks **4/22**	1.0 mg/kg/day for 16 weeks 19/24	0.23 (0.09 to 0.57)[a]
		0.5 mg/kg/day for 16 weeks **13/30**	1.0 mg/kg/day for 16 weeks 19/24	0.55 (0.35, 0.87)[a]
	Strauss 1984	0.1 mg/kg/day for 20 weeks 8/46	**0.5 mg/kg/day for 20 weeks** **7/46**	1.14 (0.45 to 2.89)
		0.1 mg/kg/day for 20 weeks **8/46**	1.0 mg/kg/day for 20 weeks 9/49	0.95 (0.40 to 2.24)
		0.5 mg/kg/day for 20 weeks **7/46**	1.0 mg/kg/day for 20 weeks 9/49	0.83 (0.34 to 2.04)

Table 6. Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

3.8 Increased LDH (lactate de-hydrogenase)	Strauss 1984	0.1 mg/kg/day for 20 weeks 11/46	0.5 mg/kg/day for 20 weeks 11/46	1.00 (0.48, 2.07)
		0.1 mg/kg/day for 20 weeks 11/46	**1.0 mg/kg/day for 20 weeks 10/49**	1.17 (0.55, 2.50)
		0.5 mg/kg/day for 20 weeks 11/46	**1.0 mg/kg/day for 20 weeks 10/49**	1.17 (0.55 to 2.50)
3.9 Increased to-tal protein levels	Strauss 1984	0.1 mg/kg/day for 20 weeks 8/46	**0.5 mg/kg/day for 20 weeks 2/46**	4.00 (0.90 to 17.83)
		0.1 mg/kg/day for 20 weeks 8/46	**1.0 mg/kg/day for 20 weeks 5/49**	1.70 (0.60 to 4.83)
		0.5 mg/kg/day for 20 weeks 2/46	1.0 mg/kg/day for 20 weeks 5/49	0.43 (0.09 to 2.09)
3.10 Increased platelets	Strauss 1984	**0.1 mg/kg/day for 20 weeks 2/46**	0.5 mg/kg/day for 20 weeks 5/46	0.40 (0.08 to 1.96)
		0.1 mg/kg/day for 20 weeks 2/46	1.0 mg/kg/day for 20 weeks 4/49	0.53 (0.10 to 2.77)
		0.5 mg/kg/day for 20 weeks 5/46	**1.0 mg/kg/day for 20 weeks 4/49**	1.33 (0.38 to 4.66)
4. Urinary labo-ratory adverse effects				
4.1 Increased specific gravity	Strauss 1984	**0.1 mg/kg/day for 20 weeks 3/46**	0.5 mg/kg/day for 20 weeks 5/46	0.60 (0.15 to 2.37)
		0.1 mg/kg/day for 20 weeks 3/46	1.0 mg/kg/day for 20 weeks 7/49	0.46 (0.13 to 1.66)
		0.5 mg/kg/day for 20 weeks 5/46	1.0 mg/kg/day for 20 weeks 7/49	0.76 (0.26 to 2.23)
4.2 Increased white blood count	Strauss 1984	0.1 mg/kg/day for 20 weeks 2/46	0.5 mg/kg/day for 20 weeks 2/46	1.00 (0.15, 6.80)
		0.1 mg/kg/day for 20 weeks 2/46	1.0 mg/kg/day for 20 weeks 7/49	0.30 (0.07 to 1.39)
		0.5 mg/kg/day for 20 weeks	1.0 mg/kg/day for 20 weeks	0.30 (0.07 to 1.39)

Table 6.   Less serious adverse effects from RCTs. Oral isotretinoin at different doses/schemes *(Continued)*

		2/46	7/49	
5. Bacteriological laboratory adverse effects				
5.1 Staphylococcus aureus colonization of the conjunctiva day 45	Cumurcu 2009	**< 0.5 mg/kg/day for 90 days** **4/25**	> 0.5 mg/kg/day for 90 days 10/26	0.42 (0.15 to 1.16)
5.2 Staphylococcus aureus colonization of the conjunctiva day 90	Cumurcu 2009	**< 0.5 mg/kg/day for 90 days** **5/25**	> 0.5 mg/kg/day for 90 days 10/26	0.52 (0.21 to 1.31)
5.3 Staphylococcus aureus colonization of the conjunctiva follow-up	Cumurcu 2009	**< 0.5 mg/kg/day for 90 days** **3/25**	> 0.5 mg/kg/day for 90 days 4/26	0.78 (0.19 to 3.14)

*a*Results that showed a statistically significant difference between interventions

*b*LDH: lactate dehydrogenase

*The intervention groups which had lower less serious adverse event rates in each comparison are in bold.

APPENDICES

Appendix 1. Skin Specialised Register (CRSW) search strategy

acne AND (isotretinoin or accutane or roaccutane or isotane or decutan or clarus or claravis or amnesteem or sotret or izotek or oratane or isotret or isoface or lurantal or isoacne or "13-cis-Retinoic Acid" or "Ro 4 3780" or "13 cis Retinoic Acid" or "Ro 4-3780" or "Ro 43780" or "4759-48-2" or accure or aknenormin or ciscutan or isohexal or isotretinoin-A or isosupra or isotroin or oratane or atretin or nimegen or acnotin or ruatine or sotret or tretin or roaccutan or roaccuttan or roacnetan or roacutan or roacuttan or "ro 04 3780" or acnal or acnetrex or akinol or curacne or curatane or "iso tretinoin" or "isoretinoic acid" or isoretinoin or isotren or isotrex or isotret-hexal or newtinon or pinple or procuta or retinoin or "13 cis tretinoin")

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor Acne Vulgaris explode all trees
#2 (acne)
#3 (#1 OR #2)
#4 MeSH descriptor Isotretinoin explode all trees
#5 isotretinoin or accutane or roaccutane or isotane or decutan or clarus or claravis or amnesteem or sotret or izotek or oratane or isotret or isoface or lurantal or isoacne or "13-cis-Retinoic Acid" or "Ro 4 3780" or "13 cis Retinoic Acid" or "Ro 4-3780" or "Ro 43780" or "4759-48-2" or accure or aknenormin or ciscutan or isohexal or isotretinoin-A or isosupra or isotroin or oratane or atretin or nimegen or acnotin or ruatine or sotret or tretin or roaccutan or roaccuttan or roacnetan or roacutan or roacuttan or "ro 04 3780" or acnal or acnetrex or akinol or curacne or curatane or "iso tretinoin" or "isoretinoic acid" or isoretinoin or isotren or isotrex or isotret-hexal or newtinon or pinple or procuta or retinoin or "13 cis tretinoin"
#6 (#4 OR #5)
#7 (#3 AND #6)

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Acne Vulgaris/
2. acne.mp.
3. 1 or 2

4. isotretinoin.mp. or exp ISOTRETINOIN/

5. accutane.mp.

6. roaccutane.mp.

7. isotane.mp.

8. decutan.mp.

9. clarus.mp.

10. claravis.mp.

11. amnesteem.mp.

12. sotret.mp.

13. izotek.mp.

14. oratane.mp.

15. isotret.mp.

16. isoface.mp.

17. lurantal.mp.

18. isoacne.mp.

19. 13-cis-Retinoic Acid.mp.

20. Ro 4 3780.mp.

21. 13 cis Retinoic Acid.mp.

22. Ro 4-3780.mp.

23. Ro 43780.mp.

24. 4759-48-2.rn.

25. accure.mp.

26. aknenormin.mp.

27. ciscutan.mp.

28. isohexal.mp.

29. isotretinoin-A.mp.

30. isosupra.mp.

31. isotroin.mp.

32. oratane.mp.

33. atretin.mp.

34. nimegen.mp.

35. acnotin.mp.

36. ruatine.mp.

37. sotret.mp.

38. tretin.mp.

39. (roaccutan or roaccuttan or roacnetan or roacutan or roacuttan).mp.

40. "ro 04 3780".mp.

41. (acnal or acnetrex or akinol).mp.

42. (curacne or curatane).mp.

43. iso tretinoin.mp.

44. isoretinoic acid.mp.

45. (isoretinoin or isotren or isotrex or isotret-hexal).mp.

46. newtinon.mp.

47. pinple.mp.

48. procuta.mp.

49. retinoin.mp.

50. 13 cis tretinoin.mp.

51. or/4-50

52. 3 and 51

53. randomized controlled trial.pt.

54. controlled clinical trial.pt.

55. randomized.ab.

56. placebo.ab.

57. clinical trials as topic.sh.

58. randomly.ab.

59. trial.ti.

60. 53 or 54 or 55 or 56 or 57 or 58 or 59

61. (animals not (humans and animals)).sh.

62. 60 not 61

63. 52 and 62

Lines 53-62: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision).

Appendix 4. Embase (Ovid) search strategy

1. exp Acne Vulgaris/
2. acne.ti,ab.
3. 1 or 2
4. isotretinoin.mp. or exp ISOTRETINOIN/
5. accutane.mp.
6. roaccutane.mp.
7. isotane.mp.
8. decutan.mp.
9. clarus.mp.
10. claravis.mp.
11. amnesteem.mp.
12. sotret.mp.
13. izotek.mp.
14. oratane.mp.
15. isotret.mp.
16. isoface.mp.
17. lurantal.mp.
18. isoacne.mp.
19. 13-cis-Retinoic Acid.mp.
20. Ro 4 3780.mp.
21. 13 cis Retinoic Acid.mp.
22. Ro 4-3780.mp.
23. Ro 43780.mp.
24. 4759-48-2.rn.
25. accure.mp.
26. aknenormin.mp.
27. ciscutan.mp.
28. isohexal.mp.
29. isotretinoin-A.mp.
30. isosupra.mp.
31. isotroin.mp.
32. oratane.mp.
33. atretin.mp.
34. nimegen.mp.
35. acnotin.mp.
36. ruatine.mp.
37. sotret.mp.
38. tretin.mp.
39. (roaccutan or roaccuttan or roacnetan or roacutan or roacuttan).mp.
40. "ro 04 3780".mp.
41. (acnal or acnetrex or akinol).mp.
42. (curacne or curatane).mp.
43. iso tretinoin.mp.
44. isoretinoic acid.mp.
45. (isoretinoin or isotren or isotrex or isotret-hexal).mp.
46. newtinon.mp.
47. pinple.mp.
48. procuta.mp.
49. retinoin.mp.
50. 13 cis tretinoin.mp.
51. or/4-50
52. crossover procedure.sh.
53. double-blind procedure.sh.
54. single-blind procedure.sh.
55. (crossover$ or cross over$).tw.
56. placebo$.tw.
57. (doubl$ adj blind$).tw.

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58. allocat$.tw.
59. trial.ti.
60. randomized controlled trial.sh.
61. random$.tw.
62. or/52-61
63. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
64. human/ or normal human/
65. 63 and 64
66. 63 not 65
67. 62 not 66
68. 3 and 51 and 67

Appendix 5. PsycINFO (Ovid) search strategy

1. isotretinoin.mp.
2. accutane.mp.
3. roaccutane.mp.
4. isotane.mp.
5. decutan.mp.
6. clarus.mp.
7. claravis.mp.
8. amnesteem.mp.
9. sotret.mp.
10. izotek.mp.
11. oratane.mp.
12. isotret.mp.
13. isoface.mp.
14. lurantal.mp.
15. isoacne.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
16. 13-cis-Retinoic Acid.mp.
17. Ro 4 3780.mp.
18. 13 cis Retinoic Acid.mp.
19. Ro 4-3780.mp.
20. Ro 43780.mp.
21. accure.mp.
22. aknenormin.mp.
23. ciscutan.mp.
24. isohexal.mp.
25. isotretinoin-A.mp.
26. isosupra.mp.
27. isotroin.mp.
28. oratane.mp.
29. atretin.mp.
30. nimegen.mp.
31. acnotin.mp.
32. ruatine.mp.
33. sotret.mp.
34. tretin.mp.
35. (roaccutan or roaccuttan or roacnetan or roacutan or roacuttan).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
36. "ro 04 3780".mp.
37. (acnal or acnetrex or akinol).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
38. (curacne or curatane).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
39. iso tretinoin.mp.
40. isoretinoic acid.mp.
41. (isoretinoin or isotren or isotrex or isotret-hexal).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
42. newtinon.mp.
43. pinple.mp.
44. procuta.mp.
45. retinoin.mp.
46. 13 cis tretinoin.mp.

47. acne.mp.
48. or/1-46
49. 47 and 48
50. double-blind.tw.
51. random$ assigned.tw.
52. control.tw.
53. 50 or 51 or 52
54. 49 and 53

Lines 50-53: a therapy filter for PsycINFO (Ovid) created by the Health Information Research Unit at McMaster University.

Appendix 6. LILACS search strategy

acne and (isotretinoin or isotretinoina or accutane or roaccutane or isotane or decutan or clarus or claravis or amnesteem or sotret or izotek or oratane or isotret or isoface or lurantal or isoacne or accure or aknenormin or ciscutan or isohexal or isosupra or isotroin or oratane or atretin or nimegen or acnotin or ruatine or sotret or tretin or roaccutan or roaccuttan or roacnetan or roacutan or roacuttan or acnal or acnetrex or akinol or curacne or curatane or isoretinoin or isotren or isotrex or newtinon or pinple or procuta or retinoin)

In LILACS we searched using the above terms and the Controlled clinical trials topic-specific query filter.

Appendix 7. MEDLINE (Ovid) adverse effects search strategy

1. exp *Isotretinoin/ae, ct, po, to [Adverse Effects, Contraindications, Poisoning, Toxicity]
2. accutane.ti,ab.
3. roaccutane.ti,ab.
4. isotane.ti,ab.
5. decutan.ti,ab.
6. clarus.ti,ab.
7. claravis.ti,ab.
8. amnesteem.ti,ab.
9. sotret.ti,ab.
10. izotek.ti,ab.
11. oratane.ti,ab.
12. isotret.ti,ab.
13. isoface.ti,ab.
14. lurantal.ti,ab.
15. isoacne.ti,ab.
16. 13-cis-Retinoic Acid.ti,ab.
17. Ro 4 3780.ti,ab.
18. 13 cis Retinoic Acid.ti,ab.
19. Ro 4-3780.ti,ab.
20. Ro 43780.ti,ab.
21. 4759-48-2.ti,ab.
22. accure.ti,ab.
23. aknenormin.ti,ab.
24. ciscutan.ti,ab.
25. isohexal.ti,ab.
26. isotretinoin-A.ti,ab.
27. isosupra.ti,ab.
28. isotroin.ti,ab.
29. oratane.ti,ab.
30. atretin.ti,ab.
31. nimegen.ti,ab.
32. acnotin.ti,ab.
33. ruatine.ti,ab.
34. sotret.ti,ab.
35. tretin.ti,ab.
36. (roaccutan or roaccuttan or roacnetan or roacutan or roacuttan).ti,ab.
37. "ro 04 3780".ti,ab.
38. (acnal or acnetrex or akinol).ti,ab.
39. (curacne or curatane).ti,ab.
40. iso tretinoin.ti,ab.
41. isoretinoic acid.ti,ab.

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42. (isoretinoin or isotren or isotrex or isotret-hexal).ti,ab.
43. newtinon.ti,ab.
44. pinple.ti,ab.
45. procuta.ti,ab.
46. retinoin.ti,ab.
47. 13 cis tretinoin.ti,ab.
48. exp *Isotretinoin/
49. isotretinoin.ti,ab.
50. or/2-49
51. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp clinical trials, phase iv/
52. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
53. exp hypersensitivity/ or exp drug hypersensitivity/ or exp drug eruptions/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
54. exp anaphylaxis/ or exp conjunctivitis, allergic/ or exp dermatitis, atopic/ or exp food hypersensitivity/ or exp respiratory hypersensitivity/ or exp urticaria/
55. side effect$.ti,ab.
56. exp Poisoning/
57. exp hepatitis, toxic/ or exp hepatitis, chronic, drug-induced/
58. exp Substance-Related Disorders/
59. exp Drug Toxicity/
60. exp Abnormalities, Drug-Induced/
61. exp Teratogens/
62. exp Mutagens/
63. exp Carcinogens/
64. metabolite$.ti,ab.
65. exp dermatitis, contact/ or exp dermatitis, allergic contact/ or exp dermatitis, irritant/ or exp dermatitis, phototoxic/
66. photoallergic reaction$.ti,ab.
67. exp dermatitis, allergic contact/ or exp dermatitis, photoallergic/
68. phototoxicit$.ti,ab.
69. (sensitization or sensitisation).ti,ab.
70. exp Burning Mouth Syndrome/
71. stinging.ti,ab.
72. burning.ti,ab.
73. fetal abnormalit$.ti,ab.
74. exp Drug Monitoring/
75. drug effect$.ti,ab.
76. Sleep Apnea, Obstructive/
77. ARRHYTHMIA/
78. (safe or safety).ti,ab.
79. toxicity.ti,ab.
80. noxious.ti,ab.
81. complication$.ti,ab.
82. treatment emergent.ti,ab.
83. tolerability.ti,ab.
84. rebound.ti,ab.
85. Hypercalcemia/ci [Chemically Induced]
86. Urinary Calculi/ci [Chemically Induced]
87. Tachyphylaxis/ci, de [Chemically Induced, Drug Effects]
88. Substance Withdrawal Syndrome/ci, de [Chemically Induced, Drug Effects]
89. ATROPHY/ci [Chemically Induced]
90. TELANGIECTASIS/ci [Chemically Induced]
91. skin thinning.ti,ab.
92. Liver Diseases/ci [Chemically Induced]
93. Kidney Diseases/ci [Chemically Induced]
94. Disseminated Intravascular Coagulation/ci [Chemically Induced]
95. Multiple Organ Failure/ci [Chemically Induced]
96. Stevens-Johnson Syndrome/ci [Chemically Induced]
97. Epidermal Necrolysis, Toxic/ci [Chemically Induced]
98. Heart Block/ci [Chemically Induced]
99. COMA/ci [Chemically Induced]
100. PARALYSIS/ci [Chemically Induced]
101. exp Nausea/

102. exp Vomiting/
103. benign intracranial hypertension.ti,ab. or exp Pseudotumor Cerebri/
104. exp Pigmentation Disorders/ or pigmentation.ti,ab. or exp Pigmentation/
105. lupus induced hepatitis.ti,ab.
106. suicide/ or suicidal ideation/ or suicide, attempted/
107. suicide.ti,ab.
108. inflammatory bowel diseases/ or crohn disease/
109. Colitis, Ulcerative/
110. Anxiety/
111. Depression/
112. Mood Disorders/
113. mood disturbance$.ti,ab.
114. (anxiety or depression or mood).ti,ab.
115. or/51-114
116. 50 and 115
117. 1 or 116

The above strategy was combined with the cohort/case-control filter from BMJ Clinical Evidence for MEDLINE, and limited to humans:
1. exp Cohort Studies/
2. cohort$.tw.
3. controlled clinical trial.pt.
4. Epidemiologic Methods/
5. limit 4 to yr=1966-1989
6. exp case-control studies/
7. (case$ and control$).tw.
8. or/1-3,5-7

Appendix 8. Embase (Ovid) adverse effects search strategy

11. accutane.ti,ab.
2. roaccutane.ti,ab.
3. isotane.ti,ab.
4. decutan.ti,ab.
5. clarus.ti,ab.
6. claravis.ti,ab.
7. amnesteem.ti,ab.
8. sotret.ti,ab.
9. izotek.ti,ab.
10. oratane.ti,ab.
11. isotret.ti,ab.
12. isoface.ti,ab.
13. lurantal.ti,ab.
14. isoacne.ti,ab.
15. 13-cis-Retinoic Acid.ti,ab.
16. Ro 4 3780.ti,ab.
17. 13 cis Retinoic Acid.ti,ab.
18. Ro 4-3780.ti,ab.
19. Ro 43780.ti,ab.
20. 4759-48-2.ti,ab.
21. accure.ti,ab.
22. aknenormin.ti,ab.
23. ciscutan.ti,ab.
24. isohexal.ti,ab.
25. isotretinoin-A.ti,ab.
26. isosupra.ti,ab.
27. isotroin.ti,ab.
28. oratane.ti,ab.
29. atretin.ti,ab.
30. nimegen.ti,ab.
31. acnotin.ti,ab.
32. ruatine.ti,ab.
33. sotret.ti,ab.

34. tretin.ti,ab.
35. (roaccutan or roaccuttan or roacnetan or roacutan or roacuttan).ti,ab.
36. "ro 04 3780".ti,ab.
37. (acnal or acnetrex or akinol).ti,ab.
38. (curacne or curatane).ti,ab.
39. iso tretinoin.ti,ab.
40. isoretinoic acid.ti,ab.
41. (isoretinoin or isotren or isotrex or isotret-hexal).ti,ab.
42. newtinon.ti,ab.
43. pinple.ti,ab.
44. procuta.ti,ab.
45. retinoin.ti,ab.
46. 13 cis tretinoin.ti,ab.
47. exp *Isotretinoin/
48. isotretinoin.ti,ab.
49. or/1-48
50. side effect$.ti,ab.
51. metabolite$.ti,ab.
52. photoallergic reaction$.ti,ab.
53. phototoxicit$.ti,ab.
54. (sensitization or sensitisation).ti,ab.
55. stinging.ti,ab.
56. burning.ti,ab.
57. fetal abnormalit$.ti,ab.
58. (toxic effect$ or drug effect$).ti,ab.
59. (safe or safety).ti,ab.
60. toxicity.ti,ab.
61. noxious.ti,ab.
62. complication$.ti,ab.
63. tolerability.ti,ab.
64. treatment emergent.ti,ab.
65. tolerability.ti,ab.
66. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
67. rebound.ti,ab.
68. skin thinning.ti,ab.
69. lupus induced hepatitis.ti,ab.
70. exp postmarketing surveillance/
71. exp drug surveillance program/
72. exp drug hypersensitivity/ or exp hypersensitivity reaction/ or exp delayed hypersensitivity/ or exp hypersensitivity/ or exp immediate type hypersensitivity/
73. exp drug eruption/
74. exp anaphylaxis/
75. exp allergic conjunctivitis/
76. exp atopic dermatitis/
77. exp food allergy/
78. exp respiratory tract allergy/
79. exp urticaria/
80. exp intoxication/
81. exp toxic hepatitis/
82. exp addiction/
83. exp drug toxicity/
84. exp teratogenic agent/
85. exp mutagenic agent/
86. exp carcinogen/
87. exp contact dermatitis/
88. exp skin allergy/
89. exp irritant dermatitis/
90. exp phototoxicity/
91. exp photodermatosis/ or exp photoallergy/
92. exp burning mouth syndrome/
93. exp drug monitoring/
94. exp sleep apnea syndrome/

95. exp heart arrhythmia/
96. hypercalcemia/
97. urolithiasis/
98. tachyphylaxis/
99. withdrawal syndrome/
100. atrophy/
101. telangiectasia/
102. liver disease/
103. kidney disease/
104. disseminated intravascular clotting/
105. multiple organ failure/
106. Stevens Johnson syndrome/
107. toxic epidermal necrolysis/
108. heart block/
109. coma/
110. paralysis/
111. nausea/
112. vomiting/
113. benign intracranial hypertension.ti,ab. or exp brain pseudotumor/
114. exp pigment disorder/
115. exp pigmentation/
116. pigmentation.ti,ab.
117. exp adverse drug reaction/
118. exp drug safety/
119. mood disorder/
120. suicidal ideation/
121. suicide.ti,ab.
122. suicide/ or suicide attempt/
123. anxiety/
124. depression/
125. (anxiety or depression or mood).ti,ab.
126. enteritis/
127. inflammatory bowel disease.ti,ab.
128. Crohn disease/
129. ulcerative colitis/
130. exp *isotretinoin/ae, to [Adverse Drug Reaction, Drug Toxicity]
131. or/50-129
132. 49 and 131
133. 130 or 132

The above strategy was combined with the cohort/case-control filter from BMJ Clinical Evidence for EMBASE and limited to humans:
1. exp cohort analysis/
2. exp longitudinal study/
3. exp prospective study/
4. exp follow up/
5. cohort$.tw.
6. exp case control study/
7. (case$ and control$).tw.
8. or/1-7

WHAT'S NEW

Date	Event	Description
20 February 2019	Amended	Republished with edits for clarification

CONTRIBUTIONS OF AUTHORS

CSC, RR and EB are the contact persons within the editorial base.
CSC and RR coordinated contributions from the co-authors.
CSC, RR and ALCM wrote the final draft of the review.
CSC, EB, RR, ALCM screened papers against eligibility criteria.
CSC and EB obtained data on ongoing and unpublished studies.
CSC, EB, RR, ALCM appraised the quality of papers.
CSC, EB, RR, ALCM extracted data for the review and sought additional information about papers.
CSC entered data into RevMan.
CSC, EB, EKS and RR analysed and interpreted data.
CSC and RR worked on the methods sections.
CSC, EB and PM drafted the clinical sections of the background and responded to the clinical comments of the referees.
CSC, RR and ALCM responded to the methodology and statistics comments of the referees.
MML was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes were relevant to consumers.
CSC, RR, ALCM, EB, EMKS and PM are the guarantors of the update.

Disclaimer

DECLARATIONS OF INTEREST

Caroline S Costa: I received a grant from Coordenacao de Aperfeicoamento de Pessoal de Nivel Superior (Capes), fundacao do Ministerio da Educacao (MEC), a Brazilian government granting agency.
Ediléia Bagatin: I received money from Bayer for: board membership for studies and research on adult female acne; for expert testimony on work for guidelines of treatment for adult female acne; for lectures in the Continuing Medical Education Program on adult female acne; and support for participation in the International Congress of Dermatology to present work on adult female acne.
Ana Luiza C Martimbianco: none known
Edina MK da Silva: none known
Marília M Lúcio: none known
Parker Magin: none known
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Electronic searches:

We intended to search for nonrandomised controlled trials (nonRCTs) (case-control and cohort) on adverse effects of oral isotretinoin for acne only in MEDLINE, but we carried out an additional search in Embase. We had also planned to use the Skin Group's standard adverse effects search strategy and the disease and intervention terms, but actually used an amended version and did not search on disease. Both deviations from our original plans were due to our intention of undertaking a very comprehensive search on adverse effects of oral isotretinoin, a drug associated with alarming safety concerns.

Compared with the published protocol, there were some alterations in the tasks completed by review authors: CSC, EB and RR assessed the titles and abstracts of studies retrieved in the search rather than just CSC and EB.

Type of interventions:

We have included studies analysing oral isotretinoin versus oral isotretinoin plus systemic or topical treatments, as these combinations of anti-acne drugs may be seen in clinical daily practice (Zaenglein 2016). This comparison was not in our inclusion criteria during protocol phase.

Types of outcomes measures:

In the review, we clarified what the definition of a serious adverse event was: "We classified an adverse effect as serious if it: was fatal; life threatening; permanently disabling; or required hospitalisation."

Types of outcomes measures:

Some of the outcomes were measured at different time points. To make reporting easier, we classified outcome measurements into short- and long-term.

Measures of treatment effect:

In our protocol, we had planned to use both risk ratio and risk difference to measure dichotomous outcomes. Instead of this, we decided to report only risk ratios, as there is empirical evidence of increased consistency in relative effect measures than in absolute effect measures (Deeks 2002; Engels 2000).

Assessment of reporting biases:

We could not use funnel plots to assess reporting biases, as originally planned, once we established that none of our meta-analyses had included more than three studies (Higgins 2011).

Data synthesis:

Instead of not pooling data from studies when significant methodological or clinical heterogeneity were detected (I^2 value higher than 50%), we decided to pool data using the random-effects model and explore the possible reasons for heterogeneity. Further, we kept the narrative approach to report measures of effect from each study separately, as we had stated in our protocol. When there was no statistical heterogeneity from the chi-square test (I^2), we applied the random-effects model to pool data (instead of the fixed-effects model, as we had previously planned).

Subgroup analysis and investigation of heterogeneity:

We found a huge diversity of intervention characteristics among each one of our eligible trials, especially regarding comparisons of different doses and therapeutic regimens of oral isotretinoin. Subgroup analyses that considered severity of acne, treatment duration, degree of improvement in acne severity, age, and gender, as we planned to conduct at the protocol stage, were not feasible due to scarce data and small number of studies in each meta-analysis.

Sensitivity analysis:

We could not carry out a sensitivity analysis of results from our included RCTs as we intended by excluding trials of low and moderate risk of bias (we referred to this as methodological quality at the time the protocol was written), due to the scarcity of studies and data in each one of our analyses of effects.

'Summary of findings' table and GRADE:

We had not planned to include a 'Summary of findings' ('SoF') table and the GRADE system (Guyatt 2011) to evaluate the quality of evidence in our review at the time the protocol was published. However, following the Cochrane Skin Group's recommendations, we added this table to summarise the outcomes for the main comparison, oral isotretinoin versus oral antibiotics plus topical agents. The GRADE system was applied to assess the quality of the whole body of evidence for each outcome presented in this review.

I N D E X   T E R M S

Medical Subject Headings (MeSH)

Administration, Oral; Anti-Bacterial Agents [administration & dosage]; Dermatologic Agents [*administration & dosage] [adverse effects]; Isotretinoin [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Child; Female; Humans; Male; Middle Aged; Young Adult