

Acne vulgaris: management

[J] Addition of oral corticosteroids to oral isotretinoin for the treatment of severe inflammatory acne vulgaris

NG198

Evidence review underpinning recommendations 1.5.24 and 1.5.25 in the NICE guideline

June 2021

Final

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

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|---|----|
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1 Addition of oral corticosteroids to oral 2 isotretinoin for the treatment of severe 3 inflammatory acne vulgaris

4 Review question

5 Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe
6 acne (including acne conglobata and acne fulminans)?

7 Introduction

8 In the small number of patients with a severe inflammatory component to their acne vulgaris
9 there is a risk of increased inflammation and flare of their acne on starting oral retinoid
10 therapy under specialist supervision. The aim of the review is to consider the dosage
11 duration and effectiveness of corticosteroids in preventing this flare.

12 Summary of the protocol

13 Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome
14 (PICO) characteristics of this review.

15 Table 1: Summary of the protocol

| | |
|---------------------|---|
| Population | People ≥12 years-old with severe acne, including those with acne conglobata or fulminans |
| Intervention | Oral isotretinoin plus any of the following listed oral corticosteroids: <ul style="list-style-type: none">• Betamethasone• Deflazacort• Dexamethasone• Hydrocortisone• Methylprednisolone• Prednisone• Prednisolone |
| Comparison | The following comparisons will be considered: <ul style="list-style-type: none">• Oral isotretinoin plus any listed oral corticosteroid vs oral isotretinoin• Oral isotretinoin plus any listed oral corticosteroid vs oral isotretinoin plus any other listed oral corticosteroid |
| Outcomes | Critical <ul style="list-style-type: none">• Clinician-rated improvement:<ul style="list-style-type: none">○ percentage change in acne lesion count○ change or final score on a validated acne severity scale• Improvement of isotretinoin-induced flare:<ul style="list-style-type: none">○ clinician-rated change○ participant-reported change• Long-term side effects of corticosteroids Important <ul style="list-style-type: none">• Adverse effects of oral isotretinoin• Participant-reported improvement:<ul style="list-style-type: none">○ change in acne severity or symptoms (for example assessed |

using global self-assessment score)

- Short-term side effects of corticosteroids
- Skin-specific quality of life

1 For further details see the review protocol in appendix A.

2 **Methods and process**

3 This evidence review was developed using the methods and process described in [Developing](#)
4 [NICE guidelines: the manual](#). Methods specific to this review question are described in the
5 review protocol in appendix A and the methods document (supplementary document 1).

6 Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

7 **Clinical evidence**

8 **Included studies**

9 A systematic review of the clinical literature was conducted but no studies were identified
10 which were applicable to this review question.

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

12 **Excluded studies**

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

15 **Summary of clinical studies included in the evidence review**

16 No studies were identified which were applicable to this review question (and so there are no
17 evidence tables in Appendix D). No meta-analysis was undertaken for this review (and so
18 there are no forest plots in Appendix E).

19 **Quality assessment of clinical studies included in the evidence review**

20 No studies were identified which were applicable to this review question.

21 **Economic evidence**

22 **Included studies**

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

27 **Excluded studies**

28 No economic studies were reviewed at full text and excluded from this review.

29 **Economic model**

30 A simple cost calculation was undertaken in order to estimate the average cost of providing a
31 course of oral prednisolone (assuming a dose of 30 mg daily over 4 weeks) in people with
32 severe inflammatory acne treated with oral isotretinoin. The unit cost was taken from national

1 sources. The total cost of a course of oral prednisolone was estimated to be £14.46,
 2 comprising the drug acquisition cost, as it can be seen in Table 2. No additional health
 3 professional contacts were assumed for the treatment with oral corticosteroids, as monitoring
 4 can be undertaken by specialists at the same time with monitoring of treatment with
 5 isotretinoin.

6 **Table 2. Drug acquisition cost of a course of treatment with oral prednisolone**

| Resource | Unit cost | Total cost |
|---|--|--------------------|
| 30 mg of oral prednisolone per day, over 4 weeks [that is 6 tablets of 5mg per day and 6 boxes of 28 x 5 mg tablets required] | 28 x 5 mg tablets = £2.41 ¹ | 6 x £2.41 = £14.46 |

7 ¹ NHS Business Services Authority, NHS Prescription Services 2020. NHS England and Wales. Electronic Drug
 8 Tariff. Issue: February 2020. Compiled on the behalf of the Department of Health and Social Care.
 9 <https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff>

10 The committee's discussion of the evidence

11 Interpreting the evidence

12 *The outcomes that matter most*

13 Clinician-rated improvement in acne (percentage change in acne lesion count and change or
 14 final score on a validated acne severity scale) and improvement of isotretinoin-induced flare
 15 (clinician-rated and participant-reported change) were prioritised by the committee as critical
 16 outcomes because they indicate whether the treatment is efficacious. The side effect profile
 17 of corticosteroids includes particular conditions, such as hypertension, weight gain and
 18 osteoporosis which would commonly occur if they are used for 3 months or longer.
 19 Therefore, long-term side effects of corticosteroids were a critical outcome, whereas short-
 20 term side effects of corticosteroids were important outcomes because they are less likely to
 21 occur. Adverse effects of oral isotretinoin were also listed as an important outcome since a
 22 flare could be reported as a non-specific adverse event and corticosteroids are meant to
 23 suppress those. Participant-reported improvement in acne (change in acne severity or
 24 symptoms) and skin-specific quality of life were important outcomes because they indicate
 25 whether the person with acne vulgaris perceives an improvement in acne symptoms.

26 *The quality of the evidence*

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

28 *Benefits and harms*

29 No evidence was identified which was applicable to this review question. The committee
 30 discussed that corticosteroids would only be given to a very small group of people: those with
 31 acne fulminans who are going to start isotretinoin. The committee agreed that it is known that
 32 isotretinoin causes acne flares (severe acute worsening of acne), so it is common practice to
 33 also give oral corticosteroids which are known to suppress this due to their anti-inflammatory
 34 properties. Such flares can also happen to people with severe acne during treatment with
 35 oral isotretinoin and they would therefore also need a corticosteroid to help alleviate these
 36 symptoms. They noted that the most commonly used oral corticosteroids with the best
 37 balance of benefits and risks for this purpose is prednisolone and the consensus was that
 38 this is the most appropriate corticosteroid for this use. The use of prednisolone helps to
 39 manage inflammation, however it may be associated with adverse events (such as
 40 hypertension, weight gain and osteoporosis) particularly if taken long-term.

41 The committee also discussed that there was no evidence to support the duration and
 42 dosage of this treatment which should be personalised to individual people. They agreed that
 43 this would be tailored to each person by the dermatology consultant-led team when

1 prescribing oral isotretinoin (see evidence report D related to referral). They therefore did not
2 make a specific recommendation related to dosage and duration.

3 Even though there was no evidence, the committee did not prioritise a research
4 recommendation in this area because this problem affects a very small proportion of people
5 affected with acne vulgaris and therefore research studies would not be feasible.

6 **Cost effectiveness and resource use**

7 No economic evidence on the cost-effectiveness of oral corticosteroids added to oral
8 isotretinoin for the treatment of severe inflammatory acne vulgaris was identified. The
9 committee noted both the anticipated benefits following treatment with oral prednisolone in
10 people with severe inflammatory acne vulgaris treated with isotretinoin, and the low
11 intervention cost (£14.46 for a course of treatment with oral prednisolone on average) and
12 agreed that recommendations comprise efficient use of resources. Moreover, the committee
13 advised that recommendations are relevant to a small number of people with acne vulgaris
14 and concluded that the resource impact of recommendations is minimal.

15 **Recommendations supported by this evidence review**

16 This evidence review supports recommendations 1.5.24 and 1.5.25 in the guideline.

17 **References**

18 There were no studies identified that were applicable to this review question.

1 Appendices

2 Appendix A – Review protocol

3 Review protocol for review question: Is the addition of oral 4 corticosteroids to oral isotretinoin of benefit for the treatment of severe 5 acne (including acne conglobata and acne fulminans)?

6 **Table 3: Review protocol for corticosteroids for treatment of severe acne**
7 **vulgaris**

| Field | Content |
|-----------------------------------|---|
| PROSPERO registration number | CRD42019150497 |
| Review title | Addition of oral corticosteroids to oral isotretinoin for the treatment of severe inflammatory acne vulgaris |
| Review question | Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)? |
| Objective | The objective of this review is to determine what the most effective oral corticosteroid agent is when combined with oral isotretinoin in the treatment of severe acne (including acne conglobata and acne fulminans). |
| Searches | <p>The following databases will be searched:</p> <ul style="list-style-type: none"> • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE <p>Searches will be restricted by:</p> <ul style="list-style-type: none"> • Date: No restriction • Language of publication: English language only • Publication status: Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias • Standard exclusions filter (animal studies/low level publication types) will be applied • For each search (including economic searches), the principal database search strategy is quality assured by a second information specialist using an adaption of the PRESS 2015 Guideline Evidence-Based Checklist |
| Condition or domain being studied | <ul style="list-style-type: none"> • Severe nodulo-cystic acne, including <ul style="list-style-type: none"> ○ Acne conglobata ○ Acne fulminans ○ Severe acne vulgaris |
| Population | <ul style="list-style-type: none"> • Inclusion: People ≥12 years-old with severe acne, including those with acne conglobata or fulminans • Exclusion: Neonatal acne vulgaris |
| Intervention | <p>Oral isotretinoin plus any of the following listed oral corticosteroids:</p> <ul style="list-style-type: none"> • Betamethasone • Deflazacort • Dexamethasone |

| | |
|--------------------------------------|---|
| | <ul style="list-style-type: none"> • Hydrocortisone • Methylprednisolone • Prednisone • Prednisolone <p>Note: Oral corticosteroids can be given at the same time as, or before or after the start of, oral isotretinoin. All results will be pooled regardless of when the oral corticosteroid was administered.</p> |
| Comparator | <p>The following comparison will be considered:</p> <ul style="list-style-type: none"> • Oral isotretinoin plus any listed oral corticosteroid vs oral isotretinoin • Oral isotretinoin plus any listed oral corticosteroid vs oral isotretinoin plus any other listed oral corticosteroid |
| Types of study to be included | <ul style="list-style-type: none"> • Systematic reviews/meta-analyses of randomised controlled trials (RCTs) • Randomised or quasi-randomised controlled trials (individual or cluster) <p>If no RCT evidence is identified, the committee will make research recommendations if appropriate.</p> <p>Excluded study designs:</p> <ul style="list-style-type: none"> • Quasi- or non-randomised controlled studies • Case-control studies • Cohort studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Non-comparative studies <p>Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.</p> |
| Other exclusion criteria | <ul style="list-style-type: none"> • Studies with <50% completion data (that is drop-out of $\geq 50\%$) • Studies that do not report the level of acne severity in the study sample, or they include all ranges of severity, from mild to severe • Studies with indirect population: Where studies with a mixed population (i.e. include people with acne vulgaris and another condition, for example hirsutism) are identified, those with <66% of the relevant population will be excluded, unless subgroup analysis for acne vulgaris is reported |
| Context | <p>Recommendations will apply to those receiving care in any healthcare setting (for example community, primary care, secondary care, tertiary care).</p> |
| Primary outcomes (critical outcomes) | <p>Critical outcomes</p> <p>Efficacy</p> <ul style="list-style-type: none"> • Clinician-rated improvement <ul style="list-style-type: none"> ○ Percentage change in acne lesion count ○ Change or final score on a validated acne severity scale <p>Note: Percentage change data will be prioritised over change or final score on a validated acne severity scale and combined into this outcome.</p> <ul style="list-style-type: none"> • Improvement of isotretinoin-induced acne flare: <ul style="list-style-type: none"> ○ Clinician-rated change ○ Participant-reported change • Long-term side effects of corticosteroids |

| | |
|---|--|
| | Note: 'Long-term' defined as any side effect that occurs between 6 months and 2 years after stopping corticosteroids. |
| Secondary outcomes (important outcomes) | <p>Important outcomes</p> <ul style="list-style-type: none"> • Adverse effects of oral isotretinoin • Participant-reported improvement <ul style="list-style-type: none"> ○ Change in acne severity or symptoms (for example assessed using global self-assessment score) • Short-term side effects of corticosteroids • Skin-specific quality of life <p>Note: 'Short-term' defined as any side effect that occurs between 1 week and 6 months after stopping corticosteroids. Participants may still be on course of oral isotretinoin.</p> |
| Data extraction (selection and coding) | <ul style="list-style-type: none"> • All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. • Dual sifting will be performed on at least 10% of records; 90% agreement is required. • Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. • Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies including study reference, study characteristics (for example design, type of statistical analysis), participant characteristics (for example age, ethnicity, sex, acne severity, concurrent acne treatment), intervention(s) characteristics (intervention details for example dosage, length, duration, frequency, mode), outcomes, and risk of bias. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer. |
| Risk of bias (quality) assessment | Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual . |
| Strategy for data synthesis | <ul style="list-style-type: none"> • Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane's Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. For dichotomous outcomes, intention-to-treat (ITT) data will be used if available; if not then available data will be used. Final and change scores will be pooled and if any study reports both, change scores will be used in preference over final scores. • Sensitivity analysis will be conducted according to risk of bias of individual studies. Missing data will be accounted for in the risk of bias assessment. • Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 80% will be considered as serious and very serious heterogeneity, respectively. Heterogeneity will be explored as appropriate using |

| | | | |
|--|--|-------------------------------------|-------------------------------------|
| | <p>sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled.</p> <ul style="list-style-type: none"> • Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes <ul style="list-style-type: none"> ○ For risk ratios: 0.8 and 1.25. ○ For continuous outcomes: +/-0.5 times the baseline SD of the control arm. If there are 2 studies, the MID is calculated as +/- 0.5 times the mean of the SDs of the control arms at baseline. If there are 3 or more studies, the MID is calculated as +/- 0.5 times the median of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used. • The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ • Studies that do not use a validated scale to assess severity of acne are at high risk of bias. If appropriate, the contribution of such studies to an outcome will be accounted for using the GRADE domain of indirectness. | | |
| Analysis of sub-groups | No sub-group analysis will be performed. | | |
| Type and method of review | <input checked="" type="checkbox"/> | Intervention | |
| | <input type="checkbox"/> | Diagnostic | |
| | <input type="checkbox"/> | Prognostic | |
| | <input type="checkbox"/> | Qualitative | |
| | <input type="checkbox"/> | Epidemiologic | |
| | <input type="checkbox"/> | Service Delivery | |
| | <input type="checkbox"/> | Other (please specify) | |
| Language | English | | |
| Country | England | | |
| Anticipated or actual start date | 11 September 2019 | | |
| Anticipated completion date | 13 January 2021 | | |
| Stage of review at time of this submission | Review stage | Started | Completed |
| | Preliminary searches | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |
| | Piloting of the study selection process | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |
| | Formal screening of search results against eligibility criteria | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |

| | | | |
|--------------------------------------|--|-------------------------------------|-------------------------------------|
| | Data extraction | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |
| | Risk of bias (quality) assessment | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |
| | Data analysis | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |
| Named contact | <p>5a. Named contact National Guideline Alliance</p> <p>5b Named contact e-mail AcneManagement@nice.org.uk</p> <p>5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance</p> | | |
| Review team members | National Guideline Alliance | | |
| Funding sources/sponsor | This systematic review is being completed by the National Guideline Alliance, which receives funding from NICE. | | |
| Conflicts of interest | <p>All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.</p> | | |
| Collaborators | <p>Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/NG198/history</p> | | |
| Other registration details | Not applicable | | |
| Reference/URL for published protocol | https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=150497 | | |
| Dissemination plans | <p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none"> notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. | | |
| Keywords | Acne; acne conglobata; acne fulminans; adverse events; corticosteroid; flare; glucocorticoid; inflammation; oral isotretinoin; severe acne. | | |
| Details of existing review | Not applicable | | |

| | |
|-------------------------------|---|
| of same topic by same authors | |
| Current review status | <input checked="" type="checkbox"/> Ongoing |
| | <input checked="" type="checkbox"/> Completed but not published |
| | <input type="checkbox"/> Completed and published |
| | <input type="checkbox"/> Completed, published and being updated |
| | <input type="checkbox"/> Discontinued |
| Additional information | Not applicable |
| Details of final publication | https://www.nice.org.uk |

1 *GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally*
 2 *important difference; NHS: National health service; NICE: National Institute for Health and Care*
 3 *Excellence; RCT: randomised controlled trial; SD: standard deviation*
 4

5

6

Appendix B – Literature search strategies

Literature search strategies for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

Clinical search

Date of search: 13/03/2019

Database(s): Embase 1980 to 2019 Week 10, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 11, 2019

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

| # | Searches |
|----|---|
| 1 | exp Acne Vulgaris/ use ppez |
| 2 | exp acne/ use emez |
| 3 | acne.tw. |
| 4 | or/1-3 |
| 5 | exp Isotretinoin/ |
| 6 | (isotretinoi* or iso tretinoin or isotren or isotrex* or accutane or roaccut?an* or roacutan or roacnetan or isotane or decutan or clarus 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 4759-48-2 or accure or aknenormin or ciscutan or isotexal or isosupra or isotroin or atretin or nimegen or acnotin or ruatine or sotret or acnal or acnetrex or akinol or curacne or curatane or newtinon or pinple or procuta or retinoin or 13 cis tretinoin).tw. |
| 7 | 5 or 6 |
| 8 | 4 and 7 |
| 9 | limit 8 to english language |
| 10 | Letter/ use ppez |
| 11 | letter.pt. or letter/ use emez |
| 12 | note.pt. |
| 13 | editorial.pt. |
| 14 | Editorial/ use ppez |
| 15 | News/ use ppez |
| 16 | exp Historical Article/ use ppez |
| 17 | Anecdotes as Topic/ use ppez |
| 18 | Comment/ use ppez |
| 19 | Case Report/ use ppez |
| 20 | case report/ or case study/ use emez |
| 21 | (letter or comment*).ti. |
| 22 | or/10-21 |
| 23 | randomized controlled trial/ use ppez |
| 24 | randomized controlled trial/ use emez |
| 25 | random*.ti,ab. |
| 26 | or/23-25 |
| 27 | 22 not 26 |
| 28 | animals/ not humans/ use ppez |
| 29 | animal/ not human/ use emez |
| 30 | nonhuman/ use emez |
| 31 | exp Animals, Laboratory/ use ppez |
| 32 | exp Animal Experimentation/ use ppez |
| 33 | exp Animal Experiment/ use emez |
| 34 | exp Experimental Animal/ use emez |
| 35 | exp Models, Animal/ use ppez |
| 36 | animal model/ use emez |
| 37 | exp Rodentia/ use ppez |
| 38 | exp Rodent/ use emez |
| 39 | (rat or rats or mouse or mice).ti. |
| 40 | or/27-39 |
| 41 | 9 not 40 |
| 42 | Meta-Analysis/ |
| 43 | Meta-Analysis as Topic/ |
| 44 | systematic review/ |
| 45 | meta-analysis/ |
| 46 | (meta analy* or metanaly* or metaanaly*).ti,ab. |
| 47 | ((systematic or evidence) adj2 (review* or overview*)).ti,ab. |

| # | Searches |
|----|---|
| 48 | ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. |
| 49 | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 50 | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 51 | (search* adj4 literature).ab. |
| 52 | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 53 | cochrane.jw. |
| 54 | ((pool* or combined) adj2 (data or trials or studies or results)).ab. |
| 55 | (or/42-44,46,48-53) use ppez |
| 56 | (or/44-47,49-54) use emez |
| 57 | or/55-56 |
| 58 | clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti. |
| 59 | 58 use ppez |
| 60 | (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab. |
| 61 | 60 use ppez |
| 62 | crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab. |
| 63 | 62 use emez |
| 64 | 59 or 61 |
| 65 | 63 or 64 |
| 66 | 57 or 65 |
| 67 | 41 and 66 |
| 68 | limit 67 to yr="2018 -Current" |
| 69 | remove duplicates from 68 |

Adverse effects and cohort studies

Date of search: 13/03/2019

Database(s): Embase 1980 to 2019 Week 10, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 12, 2019

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

| # | Searches |
|----|--|
| 1 | exp Acne Vulgaris/ use ppez |
| 2 | exp acne/ use emez |
| 3 | acne.tw. |
| 4 | or/1-3 |
| 5 | exp Isotretinoin/ |
| 6 | (isotretinoin* or iso tretinoin or isotren or isotrex* or accutane or roacut?an* or roacutan or roacnetan or isotane or decutan or clarus 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 4759-48-2 or accure or aknenormin or ciscutan or isotexal or isosupra or isotroin or atretin or nimegen or acnotin or ruatine or sotret or acnal or acnetrex or akinol or curacne or curatane or newtinion or pinple or procuta or retinoin or 13 cis tretinoin).tw. |
| 7 | 5 or 6 |
| 8 | 4 and 7 |
| 9 | limit 8 to english language |
| 10 | Letter/ use ppez |
| 11 | letter.pt. or letter/ use emez |
| 12 | note.pt. |
| 13 | editorial.pt. |
| 14 | Editorial/ use ppez |
| 15 | News/ use ppez |
| 16 | exp Historical Article/ use ppez |
| 17 | Anecdotes as Topic/ use ppez |
| 18 | Comment/ use ppez |
| 19 | Case Report/ use ppez |
| 20 | case report/ or case study/ use emez |
| 21 | (letter or comment*).ti. |
| 22 | or/10-21 |
| 23 | randomized controlled trial/ use ppez |
| 24 | randomized controlled trial/ use emez |
| 25 | random*.ti,ab. |
| 26 | or/23-25 |
| 27 | 22 not 26 |

| # | Searches |
|----|---|
| 28 | animals/ not humans/ use ppez |
| 29 | animal/ not human/ use emez |
| 30 | nonhuman/ use emez |
| 31 | exp Animals, Laboratory/ use ppez |
| 32 | exp Animal Experimentation/ use ppez |
| 33 | exp Animal Experiment/ use emez |
| 34 | exp Experimental Animal/ use emez |
| 35 | exp Models, Animal/ use ppez |
| 36 | animal model/ use emez |
| 37 | exp Rodentia/ use ppez |
| 38 | exp Rodent/ use emez |
| 39 | (rat or rats or mouse or mice).ti. |
| 40 | or/27-39 |
| 41 | 9 not 40 |
| 42 | exp "Drug-Related Side Effects and Adverse Reactions"/ |
| 43 | exp Drug Overdose/ or exp Drug Misuse/ or exp Substance-Related Disorders/ |
| 44 | exp Medication Errors/ or exp Death/ |
| 45 | exp Carcinogens/ or exp Mutagens/ or exp Teratogens/ |
| 46 | exp Contraindications, Drug/ or exp Drug Interactions/ or exp Drug Resistance/ or exp Drug Tolerance/ or exp Poisoning/ or exp Treatment Failure/ |
| 47 | exp Hypersensitivity/ |
| 48 | Drug Monitoring/ |
| 49 | exp Product Surveillance, Postmarketing/ |
| 50 | exp Hepatitis, Chronic/ or "Chemical and Drug Induced Liver Injury, Chronic"/ |
| 51 | Dermatitis, Contact/ or exp Dermatitis, Allergic Contact/ or Dermatitis, Irritant/ or Dermatitis, Phototoxic/ |
| 52 | Burning Mouth Syndrome/ |
| 53 | Sleep Apnea, Obstructive/ |
| 54 | exp Arrhythmias, Cardiac/ |
| 55 | Heart Block/ |
| 56 | Hypercalcemia/ |
| 57 | Urinary Calculi/ |
| 58 | Tachyphylaxis/ |
| 59 | Substance Withdrawal Syndrome/ |
| 60 | Atrophy/ |
| 61 | Telangiectasis/ |
| 62 | Liver Diseases/ or Kidney Diseases/ |
| 63 | Disseminated Intravascular Coagulation/ |
| 64 | Multiple Organ Failure/ |
| 65 | Stevens-Johnson Syndrome/ |
| 66 | Epidermal Necrolysis, Toxic/ |
| 67 | Coma/ or Paralysis/ |
| 68 | Nausea/ or Vomiting/ |
| 69 | exp Inflammatory Bowel Diseases/ |
| 70 | Pseudotumor Cerebri/ |
| 71 | exp Pigmentation Disorders/ or exp Pigmentation/ |
| 72 | exp Suicide/ |
| 73 | Anxiety/ or Depression/ or Mood Disorders/ |
| 74 | (or/42-73) use ppez |
| 75 | exp adverse event/ |
| 76 | drug overdose/ or exp drug misuse/ or drug dependence/ |
| 77 | medication error/ or death/ |
| 78 | exp carcinogen/ or exp mutagenic agent/ or exp teratogenic agent/ |
| 79 | drug contraindication/ or drug interaction/ or drug resistance/ or drug tolerance/ or drug intoxication/ or treatment failure/ |
| 80 | exp hypersensitivity/ |
| 81 | exp drug monitoring/ |
| 82 | exp postmarketing surveillance/ |
| 83 | exp chronic hepatitis/ or toxic hepatitis/ |
| 84 | irritant dermatitis/ |
| 85 | burning mouth syndrome/ |
| 86 | sleep disordered breathing/ |
| 87 | exp heart arrhythmia/ |
| 88 | heart block/ |
| 89 | hypercalcemia/ |
| 90 | urolithiasis/ |
| 91 | tachyphylaxis/ |
| 92 | withdrawal syndrome/ |
| 93 | atrophy/ |
| 94 | telangiectasia/ |
| 95 | liver disease/ or kidney disease/ |

| # | Searches |
|-----|--|
| 96 | disseminated intravascular clotting/ |
| 97 | multiple organ failure/ |
| 98 | Stevens Johnson syndrome/ |
| 99 | toxic epidermal necrolysis/ |
| 100 | coma/ or paralysis/ |
| 101 | nausea/ or vomiting/ |
| 102 | exp inflammatory bowel disease/ |
| 103 | brain pseudotumor/ |
| 104 | exp pigment disorder/ or skin pigmentation/ |
| 105 | suicide/ |
| 106 | anxiety/ or exp depression/ or mood disorder/ |
| 107 | (or/75-106) use emez |
| 108 | ((adverse or undesirable or harm* or serious) adj3 (effect* or reaction* or event* or outcome*)).tw. |
| 109 | side effect*.tw. |
| 110 | ((drug or therapy or therapeutic or treatment) adj2 (effect* or efficacy)).tw. |
| 111 | withdrawal.tw. |
| 112 | (contraindicat* or contra-indicat*).tw. |
| 113 | (overdos* or misus* or abus*).tw. |
| 114 | (safe or safety).tw. |
| 115 | complication*.tw. |
| 116 | (treatment emergent or treatment fail*).tw. |
| 117 | metabolite*.tw. |
| 118 | (carcinogen* or mutagen* or teratogen*).tw. |
| 119 | (photoallergic reaction* or phototoxic*).tw. |
| 120 | (toxic* or pharmacotox* or neurotox* or cardiotox* or hepatotox* or immunotox* or immunocytotox* or nephrotox* or noxious).tw. |
| 121 | sensiti?ati*.tw. |
| 122 | (tolera* or rebound).tw. |
| 123 | (sting* or burn*).tw. |
| 124 | f?etal abnormal*.tw. |
| 125 | skin thinning.tw. |
| 126 | pigmentation.tw. |
| 127 | benign intracranial hypertension.tw. |
| 128 | (hepatitis or liver disease*).tw. |
| 129 | (nephritis or kidney disease*).tw. |
| 130 | (death or disab* or fatal* or suicid* or life threatening or hospitali?ation).tw. |
| 131 | (crohns or colitis).tw. |
| 132 | (anxiety or anxious or depress* or mood* or psychiatr* or psychotic).tw. |
| 133 | or/108-132 |
| 134 | 74 or 107 or 133 |
| 135 | 41 and 134 |
| 136 | exp Cohort Studies/ use ppez |
| 137 | cohort analysis/ |
| 138 | exp longitudinal study/ |
| 139 | prospective study/ |
| 140 | follow up/ |
| 141 | exp case control study/ |
| 142 | (or/137-141) use emez |
| 143 | exp Case-Control Studies/ use ppez |
| 144 | 136 or 143 |
| 145 | cohort*.tw. |
| 146 | (case and control*).tw. |
| 147 | (longitudinal or prospective or retrospective).tw. |
| 148 | or/145-147 |
| 149 | 142 or 144 or 148 |
| 150 | 135 and 149 |
| 151 | remove duplicates from 150 |
| 152 | limit 151 to yr="2013 -Current" |

Date of search: 12/03/2019

Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 3 of 12, March 2019; Cochrane Central Register of Controlled Trials, Issue 3 of 12, March 2019

| ID | Searches |
|----|--|
| #1 | MeSH descriptor: [Acne Vulgaris] explode all trees |
| #2 | acne:ti,ab |
| #3 | #1 or #2 |

| ID | Searches |
|----|--|
| #4 | MeSH descriptor: [Isotretinoin] this term only |
| #5 | (isotretinoi* or iso tretinoin or isotren or isotrex* or accutane or roaccutan or roaccuttan or roacuttan or roacutan or roacnetan or isotane or decutan or clarus 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 "4759-48-2" or accure or aknenormin or ciscutan or isotexal or isosupra or isotroin or atretin or nimegen or acnotin or ruatine or sotret or acnal or acnetrex or akinol or curacne or curatane or newtinon or pimple or procuta or retinoin or "13 cis tretinoin"):ti,ab |
| #6 | #4 or #5 |
| #7 | #3 and #6 with Cochrane Library publication date Between Mar 2018 and Mar 2019 |

Health Economics search

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

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

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

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

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

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

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

Search for health utility values

Date of initial search: 29/01/2019

Date of updated search: 06/05/2020

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

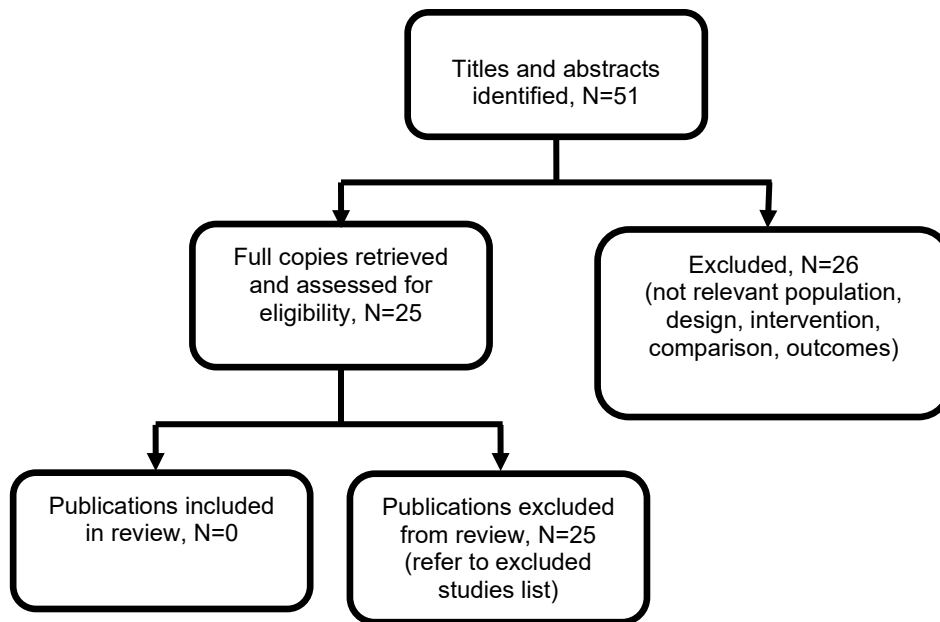
Multifile database codes: emez = Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

| # | Searches |
|----|--|
| 1 | exp Acne Vulgaris/ use ppez |
| 2 | exp acne/ use emez |
| 3 | acne.tw. |
| 4 | or/1-3 |
| 5 | Quality-Adjusted Life Years/ use ppez |
| 6 | Sickness Impact Profile/ |
| 7 | quality adjusted life year/ use emez |
| 8 | "quality of life index"/ use emez |
| 9 | (quality adjusted or quality adjusted life year*).tw. |
| 10 | (qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw. |
| 11 | (illness state* or health state*).tw. |
| 12 | (hui or hui2 or hui3).tw. |
| 13 | (multiattribute* or multi attribute*).tw. |
| 14 | (utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw. |
| 15 | utilities.tw. |
| 16 | (eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol* or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw. |
| 17 | (euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw. |
| 18 | (sf36 or sf 36 or sf thirty six or sf thirtysix).tw. |
| 19 | (time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw. |
| 20 | Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw. |
| 21 | Quality of Life/ and ec.fs. |
| 22 | Quality of Life/ and (health adj3 status).tw. |
| 23 | (quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez |
| 24 | (quality of life or qol).tw. and cost benefit analysis/ use emez |
| 25 | ((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab. |
| 26 | Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw. |
| 27 | cost benefit analysis/ use emez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw. |
| 28 | *quality of life/ and (quality of life or qol).ti. |
| 29 | quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw. |
| 30 | quality of life/ and health-related quality of life.tw. |
| 31 | Models, Economic/ use ppez |
| 32 | economic model/ use emez |
| 33 | or/5-32 |
| 34 | 4 and 33 |
| 35 | limit 34 to english language |
| 36 | limit 35 to yr="2004 -Current" |
| 37 | remove duplicates from 36 |

Appendix C – Clinical evidence study selection

Clinical study selection for: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

Figure 1: Study selection flow chart



Appendix D – Evidence tables

Evidence tables for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

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

Appendix E – Forest plots

Forest plots for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

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

Appendix F – GRADE tables

GRADE tables for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

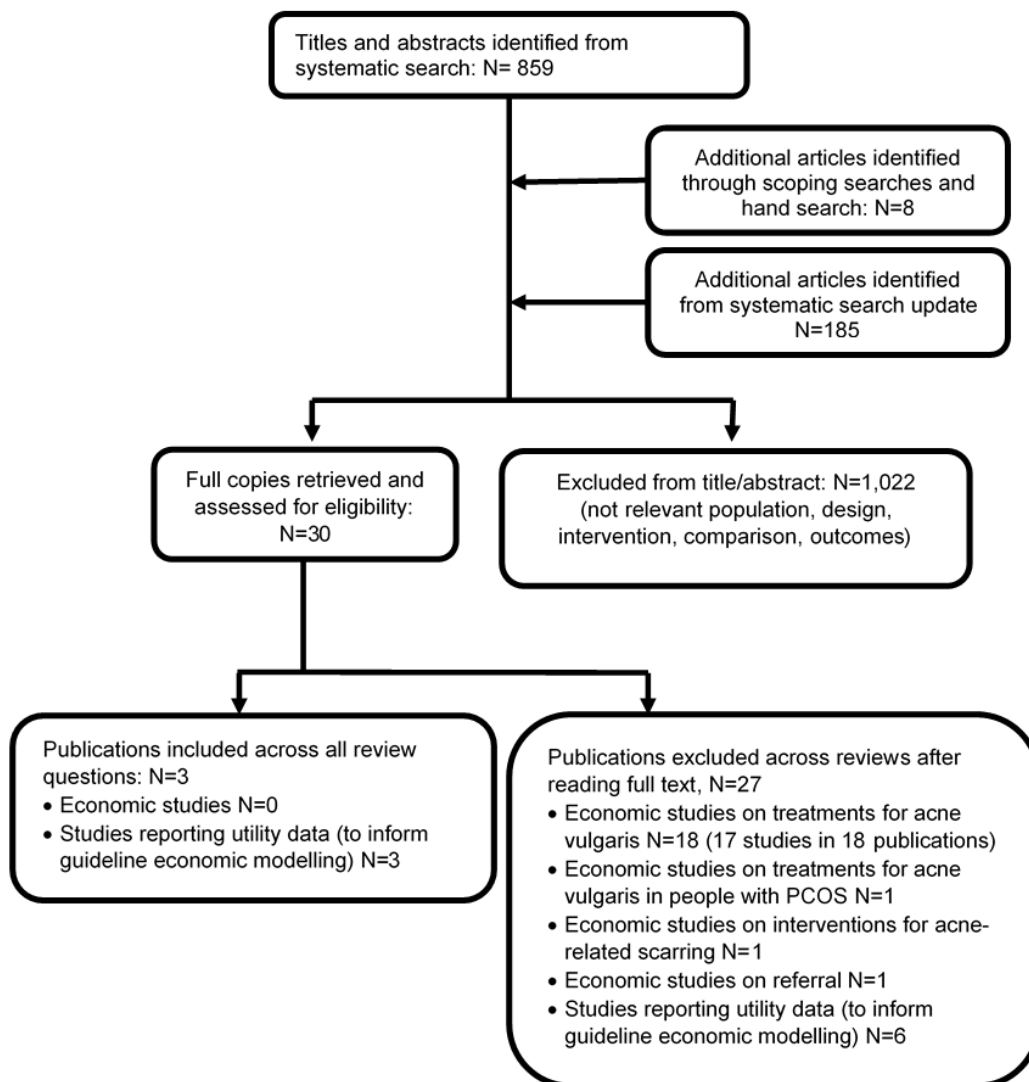
No evidence was identified which was applicable to this review question.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

A global health economics search was undertaken for all areas covered in the guideline. Figure 2 shows the flow diagram of the selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data.

Figure 2. Flow diagram of selection process for economic evaluations of interventions and strategies associated with the care of people with acne vulgaris and studies reporting acne vulgaris-related health state utility data



Appendix H – Economic evidence tables

Economic evidence tables for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

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

Appendix J – Economic analysis

Economic analysis for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

Clinical studies

| Study | Reason for Exclusion |
|---|---|
| Anonymous,, Correction: Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis (Journal of the American Academy of Dermatology (2017) 76(6) (1068-1076.e9)(S0190962216312890)(10.1016/j.jaad.2016.12.028)), Journal of the American Academy of Dermatology, 78, 431, 2018 | Erratum |
| Bernstein, J. E., Phillips, S. B., Fezatte, H. B., Treatment of nodulocystic acne with once weekly finasteride: A pilot study, Journal of Investigative Dermatology, 138 (5 Supplement 1), S178, 2018 | Conference abstract |
| Bremner, J. D., Shearer, K. D., McCaffery, P. J., Retinoic acid and affective disorders: the evidence for an association, Journal of Clinical PsychiatryJ Clin Psychiatry, 73, 37-50, 2012 | Systematic review exploring the relationship between isotretinoin, depression and suicidality. The reference list was checked for potentially relevant studies |
| Cannizzaro, M. V., Dattola, A., Garofalo, V., Del Duca, E., Bianchi, L., Reducing the oral isotretinoin skin side effects: efficacy of 8% omega-ceramides, hydrophilic sugars, 5% niacinamide cream compound in acne patients, Giornale Italiano di Dermatologia e VenereologiaG Ital Dermatol Venereol, 153, 161-164, 2018 | Article in Italian |
| Costa, C.S., Bagatin, E., Martimbianco, A.L.C., da Silva, E.M., Lúcio, M.M., Magin, P., Riera. R. Oral isotretinoin for acne. Cochrane Database Syst Rev, 11:CD009435, 2018 | Systematic review assesses the efficacy and safety of oral isotretinoin for acne vulgaris; included studies were checked for a potential inclusion |
| Chernyshov, P. V., Tomas-Aragones, L., Manolache, L., Svensson, A., Marron, S. E., Evers, A. W. M., Bettoli, V., Jemec, G. B., Szepietowski, J. C., Which acne treatment has the best influence on health-related quality of life? Literature review by the European Academy of Dermatology and Venereology Task Force on Quality of Life and Patient Oriented Outcomes, Journal of the European Academy of Dermatology & VenereologyJ Eur Acad Dermatol Venereol, 05, 05, 2018 | Review describing acne treatments affecting health-related quality of life. The reference list was checked for potentially relevant studies |
| Enders, S. J., Enders, J. M., Isotretinoin and psychiatric illness in adolescents and young adults, The Annals of pharmacotherapy, 37, 1124-7, 2003 | Narrative article examining causality between isotretinoin and psychiatric illness in adolescents and young adults. The reference list was checked for potentially relevant studies |
| Faghihi, G., Mokhtari, F., Fard, N.M., Motamedi, N., Hosseini, S.M. Comparing the Efficacy of Low Dose and Conventional Dose of Oral Isotretinoin in Treatment of Moderate and Severe Acne Vulgaris. J Res Pharm Pract, 6(4):233-238, 2017 | Study assesses the effect of low-dose isotretinoin with its conventional dose in participants with moderate and severe acne |

| | |
|---|---|
| Gencoglan, G., Inanir, I., Miskioglu, M., Gunduz, K., Evaluation of sequential effect of isotretinoin on the haematological parameters in patients with acne vulgaris, <i>Cutaneous & Ocular Toxicology</i> Cutan, 37, 139-142, 2018 | Not a RCT |
| Ghiasi, M., Mortazavi, H., Jafari, M., Efficacy of Folic Acid and Vitamin B ₁₂ Replacement Therapies in the Reduction of Adverse Effects of Isotretinoin: A Randomized Controlled Trial, <i>SKINmed</i> Skinmed, 16, 239-245, 2018 | Article not available |
| Huang, Y. C., Cheng, Y. C., Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis, <i>Journal of the American Academy of Dermatology</i> J Am Acad Dermatol, 76, 1068-1076.e9, 2017 | Systematic review exploring the relationship between isotretinoin treatment for acne and depression. The reference list was checked for potentially relevant studies |
| Jacobs, D. G., Deutsch, N. L., Brewer, M., Suicide, depression, and isotretinoin: is there a causal link?, <i>Journal of the American Academy of Dermatology</i> J Am Acad Dermatol, 45, S168-75, 2001 | Narrative review exploring the link between isotretinoin and depression. The reference list was checked for potentially relevant studies |
| Jones D.H., , Cunliffe W.J., , Löffler A., Cunliffe W.J., , Miller A.J. , A Comparative Study of 13-cis-Retinoic Acid and Erythromycin Therapy in Severe Acne, 293-301, 1984 | Book chapter |
| Khiali, S., Gharekhani, A., Entezari-Maleki, T., Isotretinoin; A review on the utilization pattern in pregnancy, <i>Advanced Pharmaceutical Bulletin</i> , 8, 377-382, 2018 | Not relevant as study evaluates the utilisation pattern of isotretinoin in pregnant women |
| Kontaxakis, V. P., Skourides, D., Ferentinos, P., Havaki-Kontaxaki, B. J., Papadimitriou, G. N., Isotretinoin and psychopathology: a review, 8, 2, 2009 | Review examining a potential relationship between isotretinoin and psychopathology. The reference list was checked for potentially relevant studies |
| Ludot, M., Mouchabac, S., Ferreri, F., Inter-relationships between isotretinoin treatment and psychiatric disorders: Depression, bipolar disorder, anxiety, psychosis and suicide risks, 5, 222-7, 2015 | Narrative review exploring the link between isotretinoin and depression and proposes guidelines for healthcare professionals. The reference list was checked for potentially relevant studies |
| Marqueling, A. L., Zane, L. T., Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review, <i>Seminars in Cutaneous Medicine & Surgery</i> Semin Cutan Med Surg, 26, 210-20, 2007 | Systematic review exploring the relationship between isotretinoin and the risk of depression and suicide. The reference list was checked for potentially relevant studies |
| Mirnezami, M., Rahimi, H., Is Oral Omega-3 Effective in Reducing Mucocutaneous Side Effects of Isotretinoin in Patients with Acne Vulgaris?, <i>Dermatology research and practice</i> , 2018 (no pagination), 2018 | Non relevant comparison, that is isotretinoin vs isotretinoin plus omega-3 |
| Oliveira, J. M., Sobreira, G., Velosa, J., Telles Correia, D., Filipe, P., Association of Isotretinoin With Depression and Suicide: A Review of Current Literature, <i>Journal of Cutaneous Medicine & Surgery</i> J Cutan Med Surg, 22, 58-64, 2018 | Review exploring the link between isotretinoin and depression/suicide. The reference list was checked for potentially relevant studies |
| Rea, S., Tucker, S., Frittelli, V., Gunnarsson, R., A feasibility study for a triple-blind randomized controlled trial investigating the effects of oral isotretinoin on mood and quality of life in patients with acne vulgaris, <i>Clinical & Experimental Dermatology</i> Clin Exp Dermatol, 43, 54-56, 2018 | Non relevant comparison, that is isotretinoin vs doxycycline |

| | |
|---|--|
| Strahan, J. E., Raimer, S., Isotretinoin and the controversy of psychiatric adverse effects, <i>International Journal of Dermatology/Int J Dermatol</i> , 45, 789-99, 2006 | Review exploring the link between isotretinoin and psychiatric adverse events. The reference list was checked for potentially relevant studies |
| Suuberg, A., Psychiatric and Developmental Effects of Isotretinoin (Retinoid) Treatment for Acne Vulgaris, <i>Current Therapeutic Research - Clinical and Experimental</i> , 90, 27-31, 2019 | Narrative review about psychiatric and developmental effects of isotretinoin. The reference list was checked for potentially relevant studies |
| Tan, T. H., Hallett, R., Yesudian, P. D., Efficacy and relapse rates of different Isotretinoin dosages in treating acne vulgaris: systemic review, <i>Clinical Medicine/Clin Med</i> , 16 Suppl 3, s34, 2016 | Conference abstract |
| Vallerand, I. A., Lewinson, R. T., Farris, M. S., Sibley, C. D., Ramien, M. L., Bulloch, A. G. M., Patten, S. B., Efficacy and adverse events of oral isotretinoin for acne: a systematic review, <i>British Journal of Dermatology/Br J Dermatol</i> , 178, 76-85, 2018 | Systematic review about clinical efficacy of oral isotretinoin. The reference list was checked for potentially relevant studies |
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Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

No research recommendations were made for this review question.