National Institute for Health and Care Excellence

Draft for consultation

Acne vulgaris: management

[K] Intralesional corticosteroids for the treatment of individual acne vulgaris lesions

NICE guideline number tbc

Evidence review underpinning recommendation 1.5.25 in the NICE guideline

December 2020

Draft for Consultation

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

Disclaimer

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

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

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ISBN:

Contents

Intralesional corticosteroids for the treatment of individual acne vulgaris lesions

Review question

What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

Introduction

Some people with acne develop large painful cysts and nodules. Treatments given by mouth do not always help these lesions as the active ingredient in the medication might not be able to get into the cyst or nodule. Another approach is to inject treatments into the inflamed lesion, and the most common injection used is a steroid. Steroids are known to reduce inflammation. This review looks at whether this approach to treatment is effective and considers whether any type of steroid works particularly well.

Summary of the protocol

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

Table 1: Summary of the protocol

Population	People with extremely inflamed nodular and cystic lesions of acne vulgaris
Intervention	Any type of intralesional corticosteroid injection (any dosage) or combination thereof, including: • Betamethasone • Dexamethasone • Hydrocortisone • Methylprednisolone • Prednisolone • Triamcinolone acetonide • Triamcinolone diacetate
Comparison	Any other intralesional steroid injection (any dosage) or combination thereof: • Placebo • No treatment • Waiting list

Outcomes	**Critical**
	• Change in studied acne lesion(s) during and after treatment course (for example size, redness, pain/discomfort):
	  ○ Investigator-assessed status
	  ○ Participant-reported status
	• Scarring of studied lesions
	• Satisfaction with treatment
	Important
	• Relapse of studied acne lesion after treatment at follow-up
	• Local side effects (for example tissue atrophy, pigment change)

For further details see the review protocol in appendix A.

Methods and process

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

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

Clinical evidence

Included studies

One randomised controlled trial (Levine 1983) reporting results from 2 studies was included in this review (Table 2). The study reported on 2 interventions, triamcinolone acetonide and betamethasone phosphate. Seventeen participants with severe nodulocystic acne were randomised to receive:

- triamcinolone acetonide or saline injection (n=9, 64 cystic lesions were randomised to receive the intervention and 9 lesions to receive saline injection)
- betamethasone phosphate or saline injection (n=8, 48 cystic lesions received the intervention and 9 lesions received saline injection; not reported if lesions were chosen randomly).

One relevant outcome of improvement of acne was reported.

The results of this study are presented narratively as no sufficient data was reported to undertake a meaningful analysis.

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

Excluded studies

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

Summary of clinical studies included in the evidence review

Summary of the study that was included in this review is presented in Table 2.

Table 2: Summary of included study

Study	Population	Intervention	Comparison	Outcomes
Levine 1983 RCT USA	Participants with severe nodulocystic acne N=17 randomised to: • Triamcinolone study (n=9) ○ age range between 16 and 35 years, n=8 men, n=1 woman • Betamethasone study (n=8)	• Triamcinolone acetonide injection (0.63, 1.25, 2.5 mg/mL) • Betamethasone phosphate injection (0.75, 1.5, 3.0 mg/mL) 1/10 of a millilitre of drug or saline control was given	• Saline injection	• Improvement in nodulocystic acne - the response of an individual cyst was evaluated using an investigator rated scale ranging from 0 to 3: 0 = cyst did not respond to treatment or became worse, 1 = mild (33%) but poor response, 2 =

	○ n=7 men, n=1 woman, ○ age not reported	for every 1 cm of the cyst's diameter		significant flattening (66%), 3 = complete flattening (100%)

RCT: randomised controlled trial

See the full evidence table in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of included study in the evidence review

Since data from the study included in this review was reported as means only (no standard deviations were reported), no grading of outcomes based on GRADE was undertaken. See the evidence statements in the section below and, for risk of bias, the evidence table in appendix D.

Economic evidence

Included studies

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

Excluded studies

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

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation. However, unit costs of injectable steroids were collected, as shown in Table 3, to inform potential recommendations.

Table 3. Unit costs of injectable steroids

Resource	Unit costs	Source
Triamcinolone acetonide 10mg/1ml suspension for injection ampoules	5 for £4.47	NHS Business Services Authority. Electronic Drug Tariff, September 2019. Available from: http://www.drugtariff.nhsbsa.nhs.uk
Triamcinolone acetonide 40mg/1ml suspension for injection vials	5 for £7.45	
Betamethasone sodium phosphate 4mg/1ml solution for injection ampoules	5 for £23.92	

Evidence statements

Since data from the included study was reported as mean only, no GRADE assessment was carried out and therefore evidence statements are included:

- Triamcinolone acetonide study

  One study (n=9, high risk of bias) reported that all 3 concentrations of triamcinolone acetonide injections (0.63, 1.25 and 2.5 mg/mL) were equally effective at 3 days and 7 days after the injection. Not reported if the difference between triamcinolone and saline was statistically significant.

- Betamethasone phosphate study

  One study (n=8, high risk of bias) reported no statistically significant difference between betamethasone phosphate and saline injections for the improvement of nodulocystic acne neither after 1 week nor 1 month after the injection (p=0.16). In terms of the concentrations used (0.75, 1.5 and 3.0 mg/mL), it was reported that these concentrations had little if any effect when used intralesionally in the treatment of nodulocystic acne (no p-values were reported).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Investigator-assessed and participant-reported change in acne lesions were prioritised by the committee as critical outcomes because these indicate effectiveness of a specific pharmacological intervention. Scarring of lesions was also chosen as a critical outcome because it can have a negative impact on quality of life. Satisfaction with treatment was another critical outcome as it indicates acceptability of the intervention and also whether the person receiving the intervention perceives an improvement in acne lesions. Relapse of acne lesions after treatment and local side effects were chosen as important outcomes because they indicate effectiveness and safety of a particular intervention.

The quality of the evidence

Risk of bias of the included study was high. Biases were mainly related to the study not reporting randomisation procedure and allocation concealment (both triamcinolone acetonide and betamethasone phosphate studies) and not reporting if outcome assessors were aware of the intervention received by study participants (triamcinolone acetonide study). In the betamethasone phosphate study neither participants nor investigators were blinded.

Benefits and harms

Overall, the evidence on the use of steroids for severe inflamed acne vulgaris lesions was very limited. However, the committee thought it was important to make a recommendation because even though the condition usually affects a small proportion of those with acne vulgaris, it results in severe inflamed acne vulgaris lesions which are very uncomfortable and unsightly. The committee reviewed 2 studies presented in one article from 1983 and considered that, although the study populations were small and the studies were quite old and of poor quality, there were sufficiently positive results to recommend that a dermatologist should consider the use of intralesional triamcinolone acetonide in the treatment of severe inflamed acne vulgaris lesions. In one of the studies they reported on three different concentrations of triamcinolone, the lowest concentration being 0.63mg/ml. All doses gave an improvement, and there was no difference between this dose and the higher two doses of 1.25 and 2.50mg/ml. In that study, they used one tenth of a millilitre (0.1ml) of drug for every cm of the cyst's diameter. The committee decided that asking people to specifically calculate 0.63 mg/ml from stock solutions might lead to errors in the calculations, and some patients might receive incorrect doses, so they agreed that 0.6mg/ml would be appropriate (0.3ml of the 10mg/ml ampule diluted to 5ml with 0.9% normal saline). In that way the committee put the emphasis on small volume, to ensure that people use an appropriately low amount of drug. It allows an ability to alter the volume and the concentration to account for the lesion they are injecting because the calculation takes into account the diameter. This means that doses are tailored to the individual lesion. The other study reported in the same paper looked at betamethasone phosphate injections suggesting hardly any benefit after one week and no benefit a month after treatment. Taking these factors into consideration the committee did not think that a recommendation about betamethasone phosphate was appropriate.

The committee also discussed possible side effects of triamcinolone acetonide injections, particularly since a small but poor response was observed even in the placebo arm. These could be hypopigmentation if too much drug is given superficially (especially in people with darker skin) or, skin atrophy which can lead to depressed scars and also the risk of an injection in the wrong place. However, they agreed that the recommended amount (0.6mg/mL) is very small and is unlikely to cause side effects. In the committee's opinion, usually severe inflamed acne lesions respond well to low concentrations of triamcinolone acetonide and flatten out quite quickly as triamcinolone acetonide shortens the life of the lesion and leads to better outcomes for people with acne vulgaris. They also discussed that it is a useful treatment for those with inflammatory acne vulgaris whilst they are waiting, for example, for isotretinoin treatment to start. They therefore decided that the benefits would outweigh possible harms.

The committee agreed that this should be carried out by a member of the dermatology consultant-led team because these treatments could cause skin damage if carried out by a person who may not have the relevant level of expertise.

Even though the study providing the evidence for this topic was conducted a long time ago and it was of limited quality the committee discussed the option of recommending further research. However, they decided not prioritise this for a research recommendation since severe inflamed acne lesions usually affect a small proportion of those with acne making such research difficult to conduct.

Cost effectiveness and resource use

No economic evidence was identified for this review question. The committee considered the resource implications associated with the recommendation and concluded that these were small and that offering injections of triamcinolone acetonide solution to people with severe inflamed acne lesions by a specialist in dermatology is an efficient use of healthcare resources. In drawing this conclusion, the committee considered the low cost of triamcinolone acetonide injection ampules (5 for £4.47) and the fact that the content of one ampule can be used in more than one lesion in the same person. The cost of the intervention also includes the specialist's time, as it may involve an additional visit. However, the committee agreed that optimally the injection can be offered during an existing appointment and in these cases no further contact with a specialist is needed, which reduces the cost of the intervention down to the drug acquisition cost. The committee acknowledged that acne vulgaris cysts and associated symptoms like flare, pain and discomfort are often self-improved within a month without an intervention, but agreed that the benefits of the injection in reducing symptoms for the person with acne vulgaris sooner rather than later outweigh the intervention costs. Moreover, providing the intervention and resolving symptoms sooner may reduce the cost of potential future visits that may be needed if symptoms are present for a longer time (that is if the intervention is not offered).

Recommendations supported by this evidence review

This evidence review supports recommendation 1.5.25 in the guideline.

References

Levine 1983

Levine RM, Rasmussen JE. Intralesional corticosteroids in the treatment of nodulocystic acne. Arch Dermatol 1983, 119(6):480-1

Appendices

Appendix A – Review protocol

Review protocol for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

Table 4: Review protocol for intralesional corticosteroids in the treatment of individual acne vulgaris lesions

Field	Content
PROSPERO registration number	CRD42020173277
Review title	Intralesional corticosteroids for treatment of inflamed acne lesions
Review question	What is the effectiveness of intralesional corticosteroids in the treatment of inflamed nodules and cysts in acne vulgaris?
Objective	The objective of this review is to establish the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date: No restriction • Language of publication: English language only • Publication status: Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias • 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	• Extremely inflamed acne vulgaris
Population	• Inclusion: People of any age with extremely inflamed nodular and cystic lesions of acne vulgaris • Exclusion: Neonatal acne
Intervention	Any type of intralesional corticosteroid injection (any dosage) or combination thereof, including: • Betamethasone • Dexamethasone • Hydrocortisone • Methylprednisolone • Prednisolone • Triamcinolone acetonide

Field	Content
	• Triamcinolone diacetate Note: results will be pooled by type of corticosteroid. Intralesional steroids are offered to people concurrently receiving active treatment for acne so data regarding this will be extracted. Participants in each arm should be eligible for the same acne treatments.
Comparator	Any other intralesional steroid injection (any dosage), or combination thereof • Placebo • No treatment • Waiting list
Types of study to be included	Included study designs: • Systematic reviews/meta-analyses of randomised controlled trials (RCTs) • Randomised parallel group controlled trials (individual or cluster) Excluded study designs: • Quasi or non-randomised controlled trials • Split-face/-body randomised controlled trials • Case-control studies • Cohort studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Non-comparative studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	• Studies with <50% completion data (that is drop-out of ≥ 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 (that is 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	Recommendations will apply to those receiving care in any healthcare settings (for example community, primary, secondary, and tertiary care).

Primary outcomes (critical outcomes)	**Critical outcomes**
	• Change in studied acne lesion(s) during and after treatment course (for example size, redness, pain/discomfort)
	  ○ Investigator-assessed status
	  ○ Participant-reported status
	Note: results on investigator-assessed and participant-reported status will be reported separately.
	• Scarring of studied lesions
	• Satisfaction with treatment

Secondary outcomes (important outcomes)	**Important outcomes** • Relapse of studied acne lesion after treatment at follow-up • Local side effects (for example tissue atrophy, pigment change)
Data extraction (selection and coding)	• All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the

Field	Content	
	retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. • Duplicate screening will not be undertaken for this question. • 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. 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 Cochrane Rob tool, v.2 as described in Developing NICE guidelines: the manual.	
Strategy for data synthesis	• 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 I2 statistic. I2 values of greater than 50% and 80% will be considered as serious and very serious heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. • Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes ○ 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/.	
Analysis of sub-groups	No sub-group analysis will be performed.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic

Field	Content		
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date			
Anticipated completion date	13 January 2021		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	5a. Named contact National Guideline Alliance 5b Named contact e-mail AcneManagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/gid-ng10109/documents/committee-member-list		

Field	Content	
Other registration details	Not applicable	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=173277	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Acne vulgaris; betamethasone; corticosteroid; cyst; dexamethasone; glucocorticoid; hydrocortisone; inflammation; intralesional; lesion; methylprednisolone; nodule; prednisolone; steroid; triamcinolone acetonide; triamcinolone diacetate.	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	Not applicable	
Details of final publication	www.nice.org.uk	

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

Appendix B – Literature search strategies

Literature search strategies for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

Clinical search

Date of initial search: 06/08/2019

Database(s): Embase Classic+Embase 1947 to 2019 August 05, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to August 05, 2019

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

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emczd
3	acne.tw.
4	or/1-3
5	intradermal drug administration/
6	intralesional drug administration/
7	soft tissue drug administration/
8	subcutaneous drug administration/
9	exp injection/
10	(or/5-9) use emczd
11	Injections, Intralesional/
12	exp Injections, Subcutaneous/
13	(or/11-12) use ppez
14	(intradermal drug administration or intralesional drug administration or subcutaneous drug administration).fs.
15	(inject* or intraderm* or intra derm* or intralesion* or intra lesion* or soft tissue* or subcutaneous or subderm*).tw.
16	or/10,13-15
17	4 and 16
18	steroid/ use emczd
19	exp corticosteroid/ use emczd
20	Steroids/ use ppez
21	exp Glucocorticoids/ use ppez
22	betamethasone/
23	dexamethasone/
24	hydrocortisone/
25	methylprednisolone/
26	prednisolone/
27	triamcinolone acetonide/
28	triamcinolone diacetate/ use emczd
29	(corticosteroid* or glucocorticoid* or steroid* or betamethasone or dexametha?one or hydrocortisone or methylfluorprednisolone or methyl fluorprednisolone or methylprednisolone or methyl prednisolone or prednisolone or triamcinolon*).tw.
30	or/18-29
31	17 and 30
32	Letter/ use ppez
33	letter.pt. or letter/ use emczd
34	note.pt.
35	editorial.pt.
36	Editorial/ use ppez
37	News/ use ppez
38	exp Historical Article/ use ppez
39	Anecdotes as Topic/ use ppez
40	Comment/ use ppez
41	Case Report/ use ppez
42	case report/ or case study/ use emczd
43	(letter or comment*).ti.
44	or/32-43
45	randomized controlled trial/ use ppez
46	randomized controlled trial/ use emczd

#	Searches
47	random*.ti,ab.
48	or/45-47
49	44 not 48
50	animals/ not humans/ use ppez
51	animal/ not human/ use emczd
52	nonhuman/ use emczd
53	exp Animals, Laboratory/ use ppez
54	exp Animal Experimentation/ use ppez
55	exp Animal Experiment/ use emczd
56	exp Experimental Animal/ use emczd
57	exp Models, Animal/ use ppez
58	animal model/ use emczd
59	exp Rodentia/ use ppez
60	exp Rodent/ use emczd
61	(rat or rats or mouse or mice).ti.
62	or/49-61
63	31 not 62
64	limit 63 to english language

Date of initial search: 06/08/2019

Database(s): The Cochrane Library: Cochrane Database of Systematic Reviews, Issue 8 of 12, August 2019; Cochrane Central Register of Controlled Trials, Issue 8 of 12, August 2019

ID	Searches
#1	MeSH descriptor: [Acne Vulgaris] explode all trees
#2	acne:ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Injections, Intralesional] this term only
#5	MeSH descriptor: [Injections, Subcutaneous] explode all trees
#6	(inject* or intraderm* or intra derm* or intralesion* or intra lesion* or soft tissue* or subcutaneous or subderm*):ti,ab
#7	{or #4-#6}
#8	#3 and #7
#9	MeSH descriptor: [Steroids] this term only
#10	MeSH descriptor: [Glucocorticoids] explode all trees
#11	MeSH descriptor: [Betamethasone] explode all trees
#12	MeSH descriptor: [Dexamethasone] explode all trees
#13	MeSH descriptor: [Hydrocortisone] explode all trees
#14	MeSH descriptor: [Methylprednisolone] explode all trees
#15	MeSH descriptor: [Prednisolone] explode all trees
#16	MeSH descriptor: [Triamcinolone] explode all trees
#17	(corticosteroid* or glucocorticoid* or steroid* or betamethasone or dexamethasone or dexamethazone or hydrocortisone or methylfluorprednisolone or methyl fluorprednisolone or methylprednisolone or methyl prednisolone or prednisolone or triamcinolon*):ti,ab
#18	{or #9-#17}
#19	#8 and #18

Health Economics search

Date of initial search: 12/12/2018

Date of updated search: 06/05/2020

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

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

#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez
3	acne.tw.
4	or/1-3
5	Economics/
6	Value of life/
7	exp "Costs and Cost Analysis"/

#	Searches
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

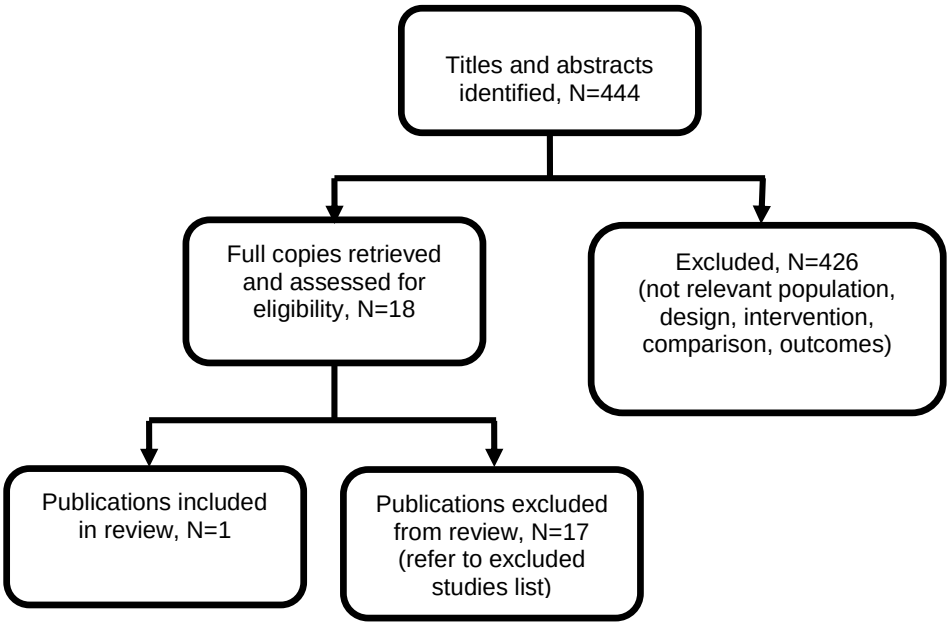
#	Searches
1	exp Acne Vulgaris/ use ppez
2	exp acne/ use emez
3	acne.tw.
4	or/1-3
5	Quality-Adjusted Life Years/ use ppez
6	Sickness Impact Profile/
7	quality adjusted life year/ use emez
8	"quality of life index"/ use emez
9	(quality adjusted or quality adjusted life year*).tw.
10	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
11	(illness state* or health state*).tw.
12	(hui or hui2 or hui3).tw.
13	(multiattibute* or multi attribute*).tw.
14	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
15	utilities.tw.

#	Searches
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 review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

Figure 1: Study selection flow chart



Appendix D – Evidence tables

Evidence tables for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

Table 5: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Levine, R. M., Rasmussen, J. E., Intralesional corticosteroids in the treatment of nodulocystic acne, Archives of DermatologyArch Dermatol, 119, 480-1, 1983 **Ref Id** 869160 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To evaluate the effectiveness of intralesional injections of	**Sample size** N=17 n=9 randomised to receive triamcinolone n=8 randomised to receive betamethasone **Characteristics** Participants had severe nodulocystic acne. <u>Triamcinolone study</u> age range - 16-35 years; n=8 men, n=1 woman <u>Betamethasone study</u> age not reported n=7 men, n=1 woman **Inclusion criteria** Participants with cystic acne.	**Interventions** <u>Triamcinolone study (n=9)</u> 64 randomly assigned cystic lesions were injected with 3 different concentrations of triamcinolone acetonide (2.5, 1.25, and 0.63 mg/mL). The mean number of cysts injected was 7 per participant; most cysts were approximately 1 cm in diameter. Each cyst received 1 injection. Saline injection was also given. <u>Betamethasone study (n=8)</u> All participants received betamethasone phosphate at concentrations of 3.0, 1.5, and 0.75 mg/mL as well as saline control injections.	**Details** The volume of injected material was tailored to individual lesions. One tenth of a millilitre of drug or saline control was given for every cm of the cyst's diameter. Injections were delivered using a tuberculin syringe and a 30-gauge needle. All participants had been treated for at least 8 weeks with oral antibiotics (tetracycline) and topical medications (benzoyl peroxide and tretinoin).	**Results** <u>Triamcinolone study</u> *Concentration 0.63 mg/mL* Average improvement of lesions at day: • 3 after injection: 2.5 • 7 after injection: 2.6 *Concentration 1.25 mg/mL* Average improvement of lesions at day: • 3 after injection: 2.4 • 7 after injection: 2.4 *Concentration 2.50 mg/mL* Average improvement of lesions at day: • 3 after injection: 2.5 • 7 after injection: 2.6 *Saline control:* Average improvement of lesions at day: • 3 after injection: 0.9 • 7 after injection:1.3 Not reported if the difference between triamcinolone and saline injections was statistically significant. <u>Betamethasone study</u> *Concentration 3.0 mg/mL* Average improvement of lesions at: • 1 week after injection: 1.04 (range 0 - 2) • 1 month after injection: 3.0 *Concentration 1.5 mg/mL*	**Limitations** **Cochrance RoB Tool v2.0** <u>Triamcinolone study</u> Selection bias: some concerns (no information provided about randomisation and allocation concealment) Performance bias: high risk of bias (it is reported that saline injection was not coded as it contains no particular matter and can be readily distinguished from triamcinolone) Attrition bias: low risk of bias Detection bias: high risk of bias (not reported if outcome assessors were aware of the intervention received by study participants) Reporting bias: low risk of bias Other bias Overall risk of bias: high risk of bias <u>Betamethasone study</u> Selection bias: some concerns (no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
corticosteroids in the therapy for nodulocystic acne. **Study dates** Not reported **Source of funding** Not reported	**Exclusion criteria** Not reported			Average improvement of lesions at: • 1 week after injection: 1.25 (range 0 - 2) • 1 month after injection: 3.0 *Concentration 0.75 mg/mL* Average improvement of lesions at: • 1 week after injection: 0.75 (range 0 - 1) • 1 month after injection: 3.0 *Saline control:* Average improvement of lesions at: • 1 week after injection: 0.89 (range 0 - 1) • 1 month after injection: 3.0 No statistically significant difference between betamethasone and saline injections (p=0.16) *The response of an individual cyst was evaluated using an investeigator rated scale ranging from 0 to 3: rating of 0 = cysts that did not respond or became worse, rating of 1 = a mild (33%) response, rating of 2 = significant flattering (66%), rating of 3 = complete flattening (100%) of the cyst.	information provided about randomisation and allocation concealment) Performance bias: high risk of bias (not blinded) Attrition bias: low risk of bias Detection bias: high risk of bias (not blinded) Reporting bias: low risk of bias Other bias Overall risk of bias: high risk of bias **Other information** A very poorly reported study

Appendix E – Forest plots

Forest plots for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

This section includes forest plots only for outcomes that are meta-analysed. No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F – GRADE tables

GRADE tables for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

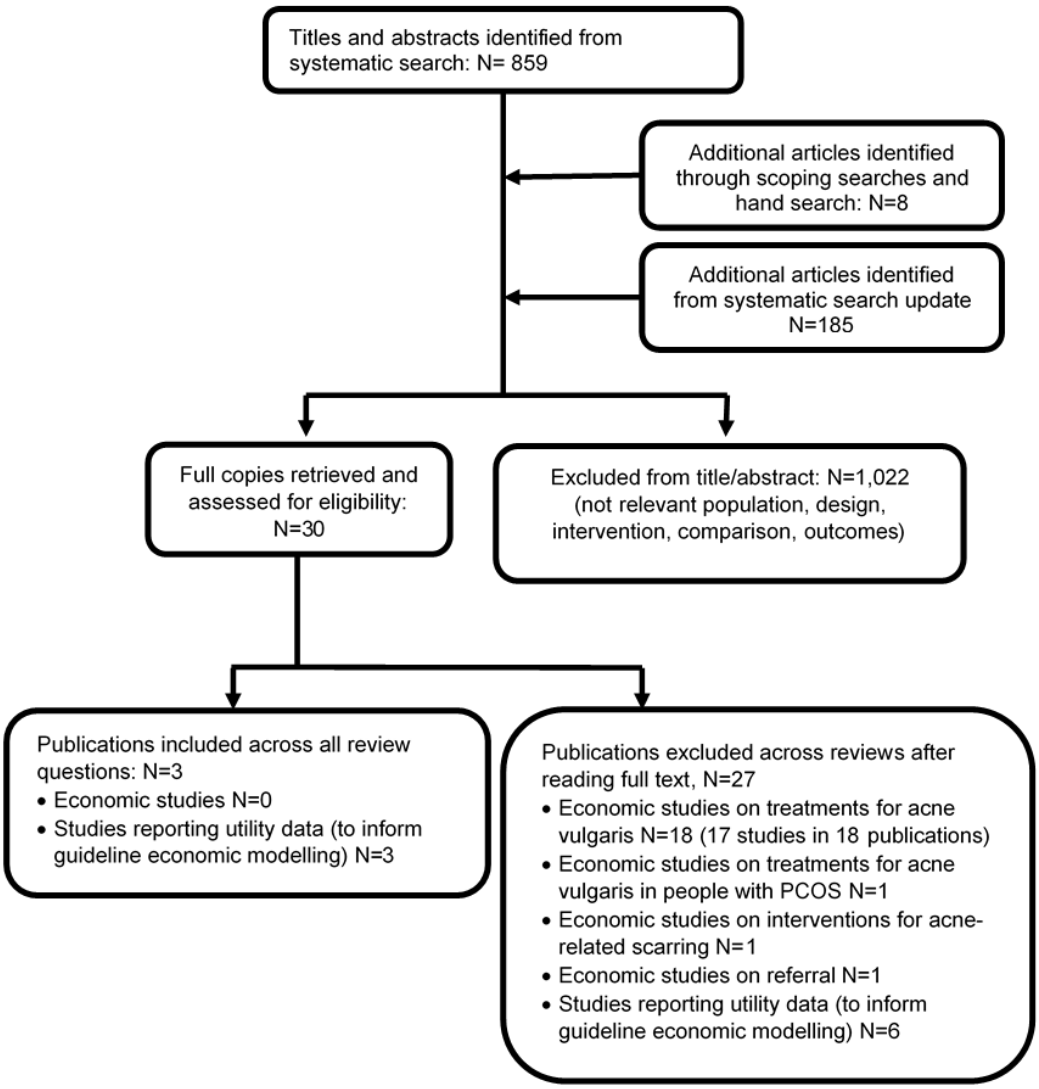
Since data from the included study was reported as mean only, no grading of outcomes based on GRADE was undertaken.

Appendix G - Economic evidence study selection

Economic evidence study selection for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

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: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

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

Appendix J – Economic analysis

Economic analysis for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

Clinical studies

Table 6: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Berman, B., Patel, J. K., Perez, O. A., Viera, M. H., Amini, S., Block, S., Zell, D., Tadicherla, S., Villa, A., Ramirez, C., De Araujo, T., Evaluating the tolerability and efficacy of etanercept compared to triamcinolone acetonide for the intralesional treatment of keloids, Journal of Drugs in Dermatology, 7, 757-61, 2008	Not relevant study population as it includes people with keloids and not with inflamed nodular or cystic lesions of acne vulgaris
Commens, C., Intralesional corticosteroids. Treating dermatological conditions, Current Therapeutics, 28, 129-136, 1987	Descriptive article about the use of intralesional corticosteroids for various inflammatory skin conditions
Dinh Huu, N., Nguyen Huu, S., Le Thi, X., Van, T. N., Thi Minh, P. P., Trinh Minh, T., Hoang Van, T., Tran Cam, V., Le Huyen, M., Tran Hau, K., Gandolfi, M., Satolli, F., Feliciani, C., Tirant, M., Vojvodic, A., Lotti, T., Successful treatment of intralesional triamcilonon acetonide injection in keloid patients, Open Access Macedonian Journal of Medical Sciences, 7, 275-278, 2019	Not relevant study population as it includes people with keloids and not with inflamed nodular or cystic lesions of acne vulgaris
Fitzpatrick, R. E., Treatment of inflamed hypertrophic scars using intralesional 5-FU, Dermatologic Surgery, 25, 224-32, 1999	Paper describes the author's experience in the use of 5-fluorouracil agent in treating hypertrophic scars and some case reports
Goodman, G. J., The management of acne scarring, Hong Kong Journal of Dermatology and Venereology, 17, 106-108, 2009	Conference abstract
Hayashi, T., Furukawa, H., Oyama, A., Funayama, E., Saito, A., Murao, N., Yamamoto, Y., A new uniform protocol of combined corticosteroid injections and ointment application reduces recurrence rates after surgical keloid/hypertrophic scar excision, Dermatologic Surgery, 38, 893-897, 2012	Not relevant intervention as corticosteroid was injected (plus topical steroid ointment application) after surgical keloid and hypertrophic scar excision
Joseph, J. H., The Case for Synthetic Injectables, Facial Plastic Surgery Clinics of North America, 23, 433-445, 2015	An overview of two products that are currently being used as permanent soft tissue fillers in the USA (polymethyl methacrylate (PMMA) (Bellafill) and LIS oil) used in an off-label capacity
Layton, A. M., Yip, J., Cunliffe, W. J., A comparison of intralesional triamcinolone and cryosurgery in the treatment of acne keloids, British Journal of DermatologyBr J Dermatol, 130, 498-501, 1994	Not relevant study population as it includes people with acne keloids and not with inflamed nodular or cystic lesions of acne vulgaris
Lee, S. J., Hyun, M. Y., Park, K. Y., Kim, B. J., A tip for performing intralesional triamcinolone acetonide injections in acne patients, Journal of the American Academy of Dermatology, 71, e127-8, 2014	A short report about performing intralesional triamcinolone acetonide injections

Leeming, J. A. L., INTRALESIONAL TRIAMCINOLONE in THE TREATMENT of CYSTIC AC, South African medical journal, 39, 567-570, 1965	Not a RCT; also the study population included people with generalised pustular and cystic acne, nodular acneiform lesions, localised cystic and suppurative cystic lesions, hidradenitis suppurativa and perifolliculitis abscedens et suffodiens
Mahajan, B. B., Garg, G., Therapeutic efficacy of intralesional triamcinolone acetonide versus intralesional triamcinolone acetonide plus lincomycin in the treatment of nodulocystic acne, Indian Journal of Dermatology, Venereology and Leprology, 69, 217-219, 2003	Not a RCT
Pace, B. F., Triamcinolone hexacetonide as adjunctive therapy in cystic acne, Southern medical journal, 61, 1204-1206, 1968	Not a RCT
Payapvipapong, K., Niumpradit, N., Piriyanand, C., Buranaphalin, S., Nakakes, A., The treatment of keloids and hypertrophic scars with intralesional bleomycin in skin of color, Journal of Cosmetic Dermatology, 14, 83-90, 2015	Not relevant study population as it includes people with keloids and hypertrophic scars and not with inflamed nodular or cystic lesions of acne vulgaris
Potter, R. A., Intralesional triamcinolone and adrenal uppression in acne vulgaris, Journal of Investigative Dermatology, 57, 364-370, 1971	Not a RCT
Rebello, D. J., Intralesional triamcinolone acetonide in skin diseases other than psoriasis, British Journal of Dermatology, 74, 358-60, 1962	Not a RCT and also a mixed population with various skin conditions
Savitt, L. E., Injections of hydrocortisone into dermatologic lesions, Archives of dermatology (1960), 76, 780-782, 1957	Not a RCT and also a mixed population with various skin conditions
Weidman, A. I., Treatment of psoriasis and other dermatoses with intralesional injections of triamcinolone acetonide, Current Therapeutic Research, Clinical & ExperimentalCurr Ther Res Clin Exp, 5, 7-11, 1963	Not a RCT and also a mixed population with various skin conditions mainly those with psoriasis

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What is the effectiveness of intralesional corticosteroids in the treatment of individual acne vulgaris lesions?

No research recommendations were made for this review question.