Cost-effectiveness of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris

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Abstract

Background. Acne vulgaris is a common skin condition that may cause psychosocial distress. There is evidence that topical treatment combinations, chemical peels and photochemical therapy (combined blue/red light) are effective for mild-to-moderate acne, while topical treatment combinations, oral antibiotics combined with topical treatments, oral isotretinoin and photodynamic therapy are most effective for moderate-to-severe acne. Effective treatments have varying costs. The National Institute for Health and Care Excellence (NICE) in England considers cost-effectiveness when producing national clinical, public health and social care guidance.

Aim. To assess the cost-effectiveness of treatments for mild-to-moderate and moderate-to-severe acne to inform relevant NICE guidance.

Methods. A decision-analytical model compared costs and quality-adjusted life-years (QALYs) of effective topical pharmacological, oral pharmacological, physical and combined treatments for mild-to-moderate and moderate-to-severe acne, from the perspective of the National Health Service in England. Effectiveness data were derived from a network meta-analysis. Other model input parameters were based on published sources, supplemented by expert opinion.

Results. All of the assessed treatments were more cost-effective than treatment with placebo (general practitioner visits without active treatment). For mild-to-moderate acne, topical treatment combinations and photochemical therapy (combined blue/red light) were most cost-effective. For moderate-to-severe acne, topical treatment combinations, oral antibiotics combined with topical treatments, and oral isotretinoin were the most cost-effective. Results showed uncertainty, as reflected in the wide confidence intervals around mean treatment rankings.

Conclusion. A range of treatments are cost-effective for the management of acne. Well-conducted studies are needed to examine the long-term clinical efficacy and cost-effectiveness of the full range of acne treatments.

Introduction

Acne vulgaris is the eighth most common disease globally1 and a common presentation to dermatologists.2 Acne may have a detrimental physical,
psychological and social impact. A network meta-analysis (NMA), assessing topical pharmacological, oral pharmacological, physical and combined treatments, found that topical treatment combinations, chemical peels and photochemical therapy (combined blue/red light) are effective treatments for mild-to-moderate acne, while topical treatment combinations, oral antibiotics combined with topical treatments, oral isotretinoin and photodynamic therapy (PDT) are most effective for moderate-to-severe acne. Effective treatments have varying treatment costs, including drug acquisition, time of the healthcare professional [HCP; general practitioner (GP) or specialist dermatologist] and special equipment. Evidence on the cost-effectiveness of acne treatments is currently lacking. Thus, our study objective was to examine the cost-effectiveness of effective treatments for mild-to-moderate and moderate-to-severe acne from the perspective of the National Health Service (NHS) in England, using decision-analytical economic modelling.

This economic analysis informed the development of National Institute for Health and Care Excellence (NICE) guidance for the management of acne in England. NICE considers cost-effectiveness when producing national guidance for health and social care services. The guideline was developed by a committee of clinical academics, HCPs and service users with expertise and experience in acne. The committee contributed to the development of the economic model by providing advice on the natural history of acne and its treatment patterns in England, and on model assumptions where evidence was lacking.

Methods

Population
The study population comprised people with mild-to-moderate and moderate-to-severe acne presenting to primary care services. Separate analyses were conducted for males and females with moderate-to-severe acne because (i) the intervention cost of oral isotretinoin is higher for females due to pregnancy tests and increased monitoring visits, and (ii) sex-specific discontinuation data were available for moderate-to-severe acne.

Interventions
We included treatment classes showing evidence of efficacy vs. placebo [indicated by 95% credible intervals (CrI) around the effects not crossing the ‘no effect’ line] in the NMA that informed the NICE guideline (the source NMA). We considered only treatment classes with ≥ 50 observations across randomized controlled trials (RCTs) included in the efficacy NMA, as this was deemed the minimum adequate evidence base to enable robust conclusions on clinical and cost-effectiveness.

One intervention from each treatment class was selected as representative for costing purposes. All interventions were assumed to be delivered within the NHS. Selection of interventions assessed in the economic analysis (Table 1) was based on their availability and usage in the UK, practicalities of use (e.g. fixed topical treatment combinations were preferred to non-fixed formulations), the size of their evidence base and their risk of side effects relative to other interventions within the class.

Economic model structure
A decision tree was constructed to estimate total NHS costs and quality-adjusted life years (QALYs) for each treatment over 1 year (Fig. 1). This time horizon, determined by the available follow-up data, was deemed adequate to capture longer-term outcomes and costs of acne treatment without significant extrapolation. Patients were modelled as having excellent, good, moderate or no perceived improvement following treatment (Supplementary Data S1 provides full details of the model).

Clinical model inputs
Relative effects on efficacy [percentage change in total acne lesion count from baseline (%CFB)], discontinuation due to any reason and discontinuation due to side effects were obtained from the source NMA (Supplementary Data S2). For mild-to-moderate acne, the economic analysis considered only treatments with evidence of efficacy in a bias-adjusted NMA, owing to indication of small study bias.

To obtain absolute effects for each treatment and outcome, we combined NMA relative effects with absolute effects of a reference treatment. We selected adapalene (topical retinoid) as the reference treatment based on data availability. Absolute effects for adapalene were estimated from large RCTs included in the source NMA, and discontinuation data from a small non-UK observational study (Supplementary Data S3).

Patients’ perception of their acne improvement may differ from the clinical measurement of improvement.
Table 1 Types of treatment, classes and interventions assessed in the economic analysis for each level of acne severity.

| Class                        | Intervention                                                                 |
|------------------------------|------------------------------------------------------------------------------|
| Mild-to-moderate acne        |                                                                               |
| Topical monotherapies (including topical antibiotic monotherapy) |                                                                               |
| Topical retinoids            | Adapalene                                                                    |
| BPO (own class)              | BPO                                                                          |
| Topical macrolides           | Topical erythromycin                                                        |
| Topical treatment combinations (some include a topical antibiotic) |                                                                               |
| BPO + topical retinoids      | BPO + adapalene                                                             |
| BPO + topical lincosamides   | BPO + topical clindamycin                                                    |
| BPO + topical macrolides     | BPO + topical erythromycin                                                  |
| Topical retinoids + topical lincosamides | Topical tretinoin + topical clindamycin                                      |
| Topical macrolides + topical lincosamides | Topical erythromycin + topical clindamycin                                 |
| Physical treatments          |                                                                               |
| Chemical peels               | Salicylic acid peel                                                         |
| Photochemical therapy (blue light) (own class) | Photochemical therapy (blue light)                                           |
| Photochemical therapy (combined blue/red light) (own class) | (combined blue/red light)                                                   |
| Treatment with placebo       | Treatment with placebo                                                      |
| Treatment with placebo (own class) | Treatment with placebo                                                      |

| Moderate-to-severe acne      |                                                                               |
| Topical monotherapies (including topical antibiotic monotherapy) |                                                                               |
| Topical retinoids            | Adapalene                                                                    |
| BPO (own class)              | BPO                                                                          |
| Topical lincosamides         | Topical clindamycin                                                         |
| Topical treatment combinations (some include a topical antibiotic) |                                                                               |
| BPO + topical retinoids      | BPO + adapalene                                                             |
| BPO + topical lincosamides   | BPO + topical clindamycin                                                    |
| BPO + topical macrolides     | BPO + topical erythromycin                                                  |
| Topical retinoids + topical lincosamides | Topical tretinoin + topical clindamycin                                      |
| BPO + topical retinoids + topical lincosamides | BPO + topical tretinoin + topical clindamycin                               |
| Oral antibiotic monotherapies |                                                                               |
| Oral tetracyclines           | Oral lymecycline                                                            |
| Oral antibiotics combined with topical treatments |                                                                               |
| Oral tetracyclines + topical retinoids | Oral lymecycline + adapalene                                                 |
| Oral tetracyclines + azelaic acid | Oral lymecycline + azelaic acid                                              |
| Oral tetracyclines + BPO + topical retinoids | Oral lymecycline + BPO + adapalene                                           |
| Oral isotretinon             |                                                                               |
| Oral isotretinoin; total cumulative dose ≥ 120 mg/kg (single course) | Oral isotretinoin daily dose ≥ 0.5 mg/kg                                      |
| Oral isotretinoin; total cumulative dose < 120 mg/kg (single course) | Oral isotretinoin daily dose ≥ 0.5 mg/kg                                     |
| Physical treatments          |                                                                               |
| Photodynamic therapy (own class) | Photodynamic therapy                                                        |
| Photochemical therapy (red light) (own class) | Photochemical therapy (red light)                                             |

Table 1 continued

| Class                        | Intervention                                                                 |
|------------------------------|------------------------------------------------------------------------------|
| Treatment with placebo       | Treatment with placebo (own class)                                           |
| Treatment with placebo (own class) | Treatment with placebo                                                      |

BPO, benzoyl peroxide. aApplied and monitored by health professionals. bModelled as general practitioner visits without active treatment. cForm of phototherapy that involves a source of light (e.g. red light, blue light, broad-spectrum light, daylight) and a photosensitizing chemical (e.g. 5-aminolaevulinic acid or methyl aminolaevulinate).

as expressed by %CFB. The relationship between the two (Table 2) was determined using published trial evidence. The same evidence was used to determine the distribution around the mean %CFB at treatment endpoint, in order to estimate the proportion of people with excellent, good, moderate and no improvement for each treatment (Supplementary Data S4). Owing to limited and heterogeneous evidence, the risk of relapse following excellent, good and moderate improvement was based on expert opinion.

Utility data

Utility values express people’s preferences regarding health-related quality of life (HRQoL) on a scale from 0 (death) to 1 (perfect health) and are necessary for estimating QALYs. The utility values used in the economic model (Table 2) were determined using utility data from two studies identified from a systematic search, a published mapping algorithm, utility values of the UK general young adult population and further assumptions (Supplementary Data S5).

Resource use and cost data

The analysis included intervention costs for people who completed a course of treatment and those who discontinued early and the costs of average acne care (AAC), which comprises a mixture of care currently received by people with acne in the NHS, which may include GP consultations, specialist dermatologist care, drug treatment or no treatment. AAC represented NHS care provided to people with acne following early treatment discontinuation, completion of a course of physical treatment, inadequate improvement or relapse. Costs were estimated by combining resource use with respective unit costs.

Intervention resource use was based on relevant descriptions from RCTs included in the source NMA.
modified to reflect optimal routine practice in the UK. This incorporated (as relevant) the drug dosage and optimal duration, time of the HCP (GP and/or specialist care), laboratory testing for people receiving oral isotretinoin and any equipment used. Resource use related to AAC was obtained from UK primary care consultation and prescription data, supplemented with expert opinion and further assumptions, particularly regarding specialist care received by a proportion of people with acne. Unit costs were obtained from national sources and other published literature. Intervention costs are summarized in Table 3, with full details on methods used for their estimation reported in Supplementary Data S6. Details of the estimation of the AAC cost are shown in Supplementary Data S7.

Figure 1 Schematic diagram of the economic model structure for people with mild-to-moderate and people with moderate-to-severe acne vulgaris. Chemical peels were assessed only in people with mild-to-moderate acne. Oral isotretinoin was assessed only in people with moderate-to-severe acne.

Table 2 Relationship between percentage change in total acne lesion count from baseline, perceived acne improvement and utility value.

| Acne health state                      | Perceived improvement | Mild-to-moderate acne | Moderate-to-severe acne |
|----------------------------------------|-----------------------|-----------------------|-------------------------|
| Health states relating to %CFB         |                       |                       |                         |
| 71.26–100% reduction in acne lesions  | Excellent             | 0.94                  | 0.94                    |
| 53.14–71.26% reduction in acne lesions | Good                  | 0.90                  | 0.87                    |
| 28.20–53.14% reduction in acne lesions | Moderate              | 0.86                  | 0.79                    |
| < 28.20% reduction or any % increase in acne lesions | None                  | 0.82                  | 0.72                    |
| Other health states                    |                       |                       |                         |
| Baseline (start of model)              | NA                    | 0.82                  | 0.72                    |
| Reduction in utility due to intolerable side effects | NA                    | –0.04                | –0.07                   |

%CFB, percentage change in total lesion count from baseline; NA, not applicable. *Supplementary Data S5.
Table 3 Intervention costs of treatments for mild-to-moderate and moderate-to-severe acne following a full course (acute and maintenance treatment) and early discontinuation (2019 prices).

| Type of treatment | Treatment class and modelled intervention | Cost (£) (full course) | Cost (£) (early discontinuation) |
|-------------------|------------------------------------------|------------------------|----------------------------------|
|                   |                                          | Acute                  | Maint                            | Total                            |
| Mild-to-moderate   |                                          |                        |                                  |                                  |
| acne              | Topical monotherapies^b                   |                        |                                  |                                  |
|                   | Topical retinoid: adapalene               | £110.86                | £71.86                          | £182.72                         | £55.43                          |
|                   | BPO (topical)                            | £86.26                 | £47.26                          | £133.52                         | £43.13                          |
|                   | Topical macrolides: erythromycin         | £105.75                | £66.75                          | £172.50                         | £48.25                          |
|                   | Topical treatment combinations^c          |                        |                                  |                                  |
|                   | BPO + topical retinoid: BPO + adapalene   | £117.06                | £78.06                          | £195.12                         | £58.53                          |
|                   | BPO + topical lincosamide: BPO + clindamycin | £117.42              | £78.42                          | £195.84                         | £52.14                          |
|                   | BPO + topical macrolide: BPO + erythromycin | £114.01              | £75.01                          | £189.02                         | £52.38                          |
|                   | Topical retinoid + topical lincosamide: tretinoin + clindamycin | £113.82              | £74.82                          | £188.64                         | £50.94                          |
|                   | Topical macrolides + topical anti-fungals: erythromycin + bifonazole | £121.90              | £79.67                          | £201.57                         | £54.71                          |
|                   | Physical treatments                       |                        |                                  |                                  |
|                   | Chemical peels: salicylic acid peel       | £702.86                | NA                              | £702.86                         | £126.59                         |
|                   | Photochemical therapy (blue light or combined blue/red light) | £546.14           | NA                              | £546.14                         | £253.21                         |
|                   | Treatment with placebo^d                  |                        |                                  |                                  |
|                   | Treatment with placebo                    | £78.00                | £39.00                          | £117.00                         | £39.00                          |
| Moderate-to-severe |                                          |                        |                                  |                                  |
| acne              | Topical monotherapies^b                   |                        |                                  |                                  |
|                   | Topical retinoid: adapalene               | £127.29                | £88.29                          | £215.58                         | £55.43                          |
|                   | BPO (topical)                            | £90.39                 | £51.39                          | £141.78                         | £43.13                          |
|                   | Topical lincosamides: clindamycin         | £121.30                | £73.64                          | £194.94                         | £56.32                          |
|                   | Topical treatment combinations^c          |                        |                                  |                                  |
|                   | BPO + topical retinoid: BPO + adapalene   | £136.59                | £97.59                          | £234.18                         | £58.53                          |
|                   | BPO + topical lincosamide: BPO + clindamycin | £143.70              | £91.56                          | £235.26                         | £65.28                          |
|                   | BPO + topical macrolide: BPO + erythromycin | £136.64              | £88.39                          | £225.03                         | £61.63                          |
|                   | Topical retinoid + topical lincosamide: tretinoin + clindamycin | £137.70              | £86.76                          | £224.46                         | £62.88                          |
|                   | BPO + topical retinoid + topical lincosamide: clindamycin | £150.09              | £99.15                          | £249.24                         | £67.01                          |
|                   | Oral antibiotic monotherapies             |                        |                                  |                                  |
|                   | Oral tetracycline: lymecycline            | £108.64                | £61.98                          | £170.62                         | £46.66                          |
|                   | Oral antibiotics combined with topical treatments | £157.93          | £111.27                         | £269.20                         | £63.09                          |
|                   | Oral tetracycline + topical retinoid: lymecycline + adapalene | £131.09              | £79.94                          | £211.03                         | £55.64                          |
|                   | Oral tetracycline + azelaic acid (topical): lymecycline + azelaic acid | £167.23              | £120.57                         | £287.80                         | £66.19                          |
|                   | Oral isotretinoin                         |                        |                                  |                                  |
|                   | Oral isotretinoin: total cumulative dose ≥ 120 mg/kg (single course); daily dose ≥ 0.5 mg/kg | £902.20          | £902.20                         | £1192.40                        | £130.90                         |
|                   | Oral isotretinoin: total cumulative dose < 120 mg/kg (single course); daily dose ≥ 0.5 mg/kg | £869.32          | £869.32                         | £1738.64                        | £296.94                         |
|                   | Treatment with placebo^d                  |                        |                                  |                                  |
|                   | Treatment with placebo                    | £78.00                | £39.00                          | £117.00                         | £39.00                          |

BPO, benzoyl peroxide; F, costs for females; M, costs for males; Maint, maintenance; NA, not applicable. ^aCosts included drug acquisition, healthcare professional time, laboratory testing for oral isotretinoin, procedure costs for photochemical and photodynamic therapies; no costs of contraception included for oral or topical retinoids. ^bIncluding topical antibiotic monotherapy; ^cpotentially including topical antibiotic component; ^dmodelled as general practitioner visits without active treatment.

Costs were expressed in 2019 prices. Discounting of costs and benefits was not needed as the time horizon of the analysis was 1 year.

**Statistical analysis**

To account for the uncertainty around input parameter point estimates, a probabilistic analysis was undertaken.
with input parameters being assigned probability distributions.\textsuperscript{19} Subsequently, 10 000 model iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. The mean costs and QALYs for each treatment were calculated by averaging across the 10 000 iterations. The net monetary benefit (NMB) for each intervention was estimated for each iteration and averaged across the 10 000 iterations, determined by the formula:

\[
\text{NMB} = E \times \lambda - C,
\]

where \( E \) and \( C \) are the effects (QALYs) and costs of each intervention respectively, and \( \lambda \) represents the willingness to pay (WTP) per QALY, set at the NICE lower cost-effectiveness threshold of £20 000 per QALY.\textsuperscript{20} The intervention with the highest NMB is the most cost-effective.\textsuperscript{21} The mean ranking by cost-effectiveness (out of 10 000 iterations) is also reported for each intervention, with a rank of 1 indicating highest cost-effectiveness.

Supplementary Data S8 reports the model input values with probability distributions and additional sensitivity analyses conducted to test the robustness of the results.

Model validation
The economic model was constructed following the guideline committee’s expert advice. All inputs and model formulae were systematically checked. The model was tested for logical consistency. The results were discussed with the committee to confirm plausibility.

Results
Table 4 shows the results of the economic analysis for treatments for mild-to-moderate acne (same for both sexes) and for moderate-to-severe acne in females. Results for treatments for moderate-to-severe acne in males (Supplementary Table S1) differed from those for females only in the ranking of oral isotretinoin, which was higher for males and is attributable to its lower intervention cost due to less intensive monitoring compared with females. The results are characterized by uncertainty, reflected in the wide 95% CIs around mean rankings.

The cost-effectiveness plane (Fig. 2) depicts the mean incremental costs and QALYs of all treatments vs. treatment with placebo (placed at the origin) in each analysis, ordered by magnitude of clinical benefits (QALYs). The cost-effectiveness acceptability frontier\textsuperscript{21} (Fig. 3) shows the most cost-effective treatments for a range of values of WTP for a QALY (between £0 and £40 000 per QALY) and the probability of each treatment being cost-effective.

The results were overall robust to the scenarios explored through deterministic sensitivity analysis (Supplementary Data S9). The relative cost-effectiveness of physical therapies (chemical peels, photochemical therapies, PDT) and oral isotretinoin was reduced when the efficacy of the reference treatment (topical retinoid) was reduced or when the spread around the mean %CFB was increased. The latter was caused by ceiling effects, as people reached 100% improvement and could not improve further.

Discussion
Our analysis explored the relative cost-effectiveness of a wide range of topical pharmacological, oral pharmacological, physical and combined treatments for acne stratified by severity level. All treatments were more cost-effective than treatment with placebo (modelled as GP visits without active treatment). For mild-to-moderate acne, the most cost-effective treatments included topical treatment combinations and photochemical therapy (combined blue/red light). For moderate-to-severe acne, the most cost-effective treatments included topical treatment combinations, oral antibiotics combined with topical treatments, and oral isotretinoin.

To our knowledge, this is the first analysis exploring the relative cost-effectiveness of a wide range of treatment options for acne from a healthcare perspective, considering, in addition to drug acquisition costs, HCP resource use, including costs associated with inadequate response to treatment or relapse. Previous economic studies (identified through a systematic search conducted to inform the NICE guideline)\textsuperscript{19} made limited comparisons of acne treatments, and the majority considered exclusively drug acquisition costs. A number of studies were simple cost analyses and most of them were characterized by important methodological limitations (Supplementary Data S10). Therefore, no robust conclusions can be drawn from the existing economic literature.

In our analysis, we used efficacy and discontinuation data derived from a large systematic review and NMA.\textsuperscript{5} This approach combines direct (i.e. head-to-head comparisons) and indirect evidence (e.g. comparisons through a common comparator) and allows simultaneous comparisons across all options while preserving randomization.\textsuperscript{22,23} There was some
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Table 4  | Cost-effectiveness results for treatments for mild-to-moderate and moderate-to-severe acne.a,b  | Mean per person  |
|-----------------|---------------------------------------------------------------|-----------------|
| Type of treatment | Class/Int | n\(^c\) | NMB/ person | QALY | Int cost | Total cost | Mean rank (95% CI) |
| Mild-to-moderate acne (both sexes) | | | | | | | |
| Physical treatment | Photochemical therapy (blue/red light) | 69 | £17 163 | 0.885 | £370 | £545 | 4.42 (1–11) |
| Topical treatment combination | BPO + topical retinoid (adapalene) | 1057 | £17 123 | 0.868 | £121 | £242 | 3.39 (1–7) |
| Topical treatment combination | Topical retinoid (tretinoin) + topical lincosamide (clindamycin) | 276 | £17 105 | 0.867 | £120 | £234 | 3.94 (1–9) |
| Topical treatment combination | Topical macrolide (erythromycin) + topical antifungal (bifonazole) | 74 | £17 061 | 0.865 | £112 | £247 | 5.37 (1–12) |
| Physical treatment | Chemical peel (salicylic acid peel) | 101 | £17 029 | 0.888 | £621 | £736 | 6.63 (1–12) |
| Topical treatment combination | BPO + topical macrolide (erythromycin) | 351 | £17 017 | 0.863 | £112 | £239 | 5.83 (1–11) |
| Topical monotherapy | Topical retinoid: adapalene | 1623 | £16 957 | 0.860 | £107 | £242 | 6.59 (3–10) |
| Topical treatment combination | BPO + topical lincosamide (clindamycin) | 992 | £16 956 | 0.860 | £115 | £245 | 6.75 (3–10) |
| Topical monotherapy | BPO | 1109 | £16 937 | 0.858 | £79 | £216 | 7.14 (3–11) |
| Physical treatment | Photochemical therapy (blue light) | 138 | £16 928 | 0.876 | £410 | £588 | 7.75 (1–12) |
| Topical antibiotic monotherapy | Topical macrolide: erythromycin | 765 | £16 859 | 0.855 | £97 | £236 | 8.96 (5–11) |
| Treatment with placebo | Treatment with placebo | 2005 | £16 704 | 0.846 | £67 | £217 | 11.23 (9–12) |
| Moderate-to-severe acne (females) | | | | | | | |
| Topical treatment combination | Topical retinoid (tretinoin) + topical lincosamide (clindamycin) | 1548 | £16 460 | 0.838 | £160 | £299 | 2.92 (1–8) |
| Oral antibiotic + topical treatment | Oral tetracycline (lymecycline) + BPO + topical retinoid (adapalene) | 556 | £16 351 | 0.835 | £196 | £344 | 3.43 (1–9) |
| Oral antibiotic + topical treatment | Oral tetracycline (lymecycline) + topical azelaic acid | 50 | £16 231 | 0.827 | £132 | £306 | 5.54 (1–15) |
| Oral isotretinoin | Oral isotretinoin; total cumulative dose ≥ 120 mg/kg | 182 | £16 122 | 0.848 | £755 | £832 | 5.91 (1–16) |
| Topical antibiotic monotherapy | Topical lincosamide (clindamycin) | 1479 | £15 986 | 0.814 | £134 | £303 | 6.44 (2–12) |
| Topical treatment combination | BPO + topical retinoid (adapalene) | 217 | £15 975 | 0.815 | £146 | £329 | 6.96 (1–15) |
| Oral antibiotic + topical treatment | Oral tetracycline (lymecycline) + topical retinoid (adapalene) | 379 | £15 969 | 0.816 | £162 | £349 | 6.33 (2–11) |
| Topical monotherapy | BPO | 80 | £15 798 | 0.804 | £97 | £280 | 8.22 (2–14) |
| Physical treatment | Photodynamic therapy | 298 | £15 755 | 0.835 | £705 | £945 | 9.26 (2–16) |
| Oral isotretinoin | Oral isotretinoin; total cumulative dose < 120 mg/kg | 938 | £15 715 | 0.827 | £726 | £827 | 9.84 (2–17) |
| Oral antibiotic monotherapy | Oral tetracycline (lymecycline) | 1386 | £15 600 | 0.796 | £106 | £313 | 10.69 (7–14) |
| Physical treatment | Photochemical therapy (red light) | 53 | £15 547 | 0.814 | £473 | £727 | 11.46 (2–17) |
| Topical treatment combination | BPO + topical lincosamide (clindamycin) | 276 | £15 539 | 0.795 | £157 | £352 | 11.43 (4–16) |
| Topical treatment combination | BPO + topical lincosamide (clindamycin) + topical retinoid (tretinoin) | 600 | £15 534 | 0.795 | £155 | £360 | 11.29 (4–16) |
| Topical treatment combination | BPO + topical macrolide (erythromycin) | 365 | £15 511 | 0.793 | £148 | £346 | 11.70 (6–15) |
| Topical monotherapy | Topical retinoid: adapalene | 3570 | £15 219 | 0.779 | £120 | £359 | 14.97 (12–16) |
| Treatment with placebo | Treatment with placebo | 4122 | £15 006 | 0.766 | £68 | £319 | 16.62 (15–17) |

BPO, benzoyl peroxide; CI, confidence interval; Int, intervention; NMB, net monetary benefit; QALY, quality-adjusted life year. aClasses are ordered by NMB (highest NMB indicates highest cost-effectiveness); bNMB and ranking estimated using a cost-effectiveness threshold (willingness to pay) of £20 000/QALY; c n, number of observations across randomized controlled trials included in the network meta-analysis of efficacy that informed the economic analysis.
inconsistency between the direct and indirect evidence synthesized in the NMA, possibly reflecting heterogeneity in populations, treatments or study design across the included RCTs. However, NMA conclusions were robust to potential bias in the evidence. The RCTs included in the NMAs were of moderate to very low quality. The strengths and limitations of the source NMA and included RCTs should be considered when interpreting the cost-effectiveness results.

The size of the evidence differed considerably across the examined treatments. Topical treatments had the largest evidence base on efficacy (several topical treatments had > 500 observations each), followed by oral treatments alone or combined with topical treatments, whereas the evidence for physical therapies (chemical peels, photochemical therapies, PDT) was based on < 300 observations for each treatment class.

Figure 2 Cost-effectiveness planes. Results for 1000 people with acne vulgaris. In each graph, the points for each treatment show its incremental quality-adjusted life years (QALYs) (horizontal axis) and costs (vertical axis) vs. treatment with placebo, which is placed at the origin. The slope of the dotted line indicates the National Institute for Health and Care Excellence lower cost-effectiveness threshold of £20 000/QALY. Moving towards the right of the horizontal axis, treatments result in more QALYs. For both acne severity levels, all treatments produce more QALYs compared with treatment with placebo. Moving towards the top of the vertical axis, treatments become more costly. For both acne severity levels, all treatments are more costly than treatment with placebo, with the exception of BPO in mild-to-moderate acne, and with the exception of BPO, topical clindamycin, combined topical tretinoin with clindamycin, oral lymecycline, and azelaic acid combined with oral lymecycline in moderate-to-severe acne. In all three graphs, treatments lie on the right side of the dotted line, suggesting that in all three analyses all assessed treatments are cost-effective compared with treatment with placebo.
Model input parameters were obtained from sources of varying quality (ranging from RCTs through to large retrospective analyses to expert opinion), depending on data availability. The time horizon of the analysis (1 year) was considered adequate to capture longer-term outcomes and costs associated with a course of

Figure 3 Cost-effectiveness acceptability frontier. Each graph shows the most cost-effective treatment of each analysis, over a range of values of willingness to pay for a quality-adjusted life year (QALY), which was varied between £0 and £40 000 per QALY (horizontal axis) and the probability that this treatment is the most cost-effective of those assessed, reflecting the uncertainty in the results (vertical axis).
acne treatment, but some long-term effects, such as potential subsequent scarring and associated management costs were not captured because of insufficient evidence. Costs and utility decrements associated with side effects of treatment were not considered; however, we did incorporate the impact of intolerable side effects on HRQoL and costs. Antimicrobial resistance associated with antibiotic use was not considered. These omissions constitute limitations of our analysis.

We carried out probabilistic analyses to handle uncertainty around model parameters and deterministic sensitivity analyses to address gaps in the evidence. The results were characterized by some uncertainty; however, they were overall robust to scenarios tested through deterministic sensitivity analysis.

Our analysis was conducted from the perspective of the NHS in England. The results may be generalizable to other settings with similar funding and structure of healthcare services and comparable care pathways for people with acne. Conclusions on cost-effectiveness ultimately rely on the cost-effectiveness threshold adopted, and this depends on the policymakers' willingness to pay for treatment benefits, which may vary across countries and health systems.

The results of this economic analysis, along with clinical evidence from the NMA and other considerations, informed the NICE national guidance on the management of acne vulgaris. These considerations included concerns about antibiotic resistance, current regulations regarding oral isotretinoin, long-term harms of chemical peel use outside specialist settings (e.g. risk for significant skin damage from inappropriate strength or type of peel) and limited availability and use of some treatments in NHS routine practice (e.g. chemical peels, photochemical therapies, PDT, topical antifungals). Doxycycline was considered a suitable alternative to lymecycline, as they have similar efficacy, AE profile and acquisition cost.

Fixed topical treatment combinations (adapalene with benzoyl peroxide (BPO); clindamycin with BPO; tretinoin with clindamycin) were recommended as first-line treatments of mild-to-moderate acne. Fixed topical treatment combinations (adapalene with BPO; tretinoin with clindamycin), or oral tetracyclines (doxycycline or lymecycline) combined with topical treatments (azelaic acid, or a fixed combination of adapalene with BPO) were recommended as first-line treatments of moderate-to-severe acne. Where oral lymecycline or doxycycline are contraindicated or not tolerated, alternative oral antibiotics (trimethoprim or an oral macrolide such as erythromycin) might be considered. BPO might be considered across both severity levels if other recommended first-line treatments are contraindicated (e.g. during pregnancy) or if there is a patient preference against their use. PDT might be considered for adults with moderate-to-severe acne if other treatments are ineffective, not tolerated or contraindicated.

Conclusion

This economic analysis allowed estimation of the relative cost-effectiveness of a range of topical pharmacological, oral pharmacological, physical and combined treatments for acne stratified by severity level. The results informed the NICE national guidance on the management of acne vulgaris. There remains a need for well-conducted studies that examine the long-term clinical efficacy and cost-effectiveness of the full range of acne treatments.

What's already known about this topic?
- Acne vulgaris is the eighth most common disease globally.
- In a previous NMA, topical treatment combinations, chemical peels and photochemical therapies were most effective for mild-to-moderate acne; and topical treatment combinations, oral antibiotics combined with topical treatments, oral isotretinoin and PDT were most effective for moderate-to-severe acne.
- Evidence on the cost-effectiveness of acne vulgaris treatments is lacking.
- Identifying acne vulgaris treatments that ensure efficient healthcare resource use is needed.

What does this study add?
- All treatments are more cost-effective than treatment with placebo, modelled as GP visits without active treatment.
- For mild-to-moderate acne, the most cost-effective treatments include topical treatment combinations and photochemical therapy (combined blue/red light).
- For moderate-to-severe acne, the most cost-effective treatments include topical treatment combinations, oral antibiotics combined with topical treatments, and oral isotretinoin.
- These findings, combined with NMA findings and other clinical considerations, informed NICE guidance on the management of acne vulgaris.
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Conflict of interest
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Ethics statement
Ethics approval and informed consent not applicable.

Data availability
Data are available in the supplementary files.

References
1. Tan JK, Bhate K. A global perspective on the epidemiology of acne. Br J Dermatol 2015; 172(Suppl 1): 3–12.
2. Buldewin HE. The interaction between acne vulgaris and the psyche. Cutis 2002; 70: 133–9.
3. Tun JK. Psychosocial impact of acne vulgaris: evaluating the evidence. Skin Therapy Lett 2004; 9: 9.
4. Layton AM, Thiboutot D, Tan J. Reviewing the global burden of acne: how could we improve care to reduce the burden? Br J Dermatol 2021; 184: 219–25.
5. Mavranezouli I, Daly CH, Welton NJ et al. A systematic review and network meta-analysis of topical, oral, physical and combined treatments for acne vulgaris. Br J Dermatol 2022. https://doi.org/10.1111/bjd.21739
6. National Institute for Health and Care Excellence. Acne vulgaris: management. NICE, 2021. Available at: https://www.nice.org.uk/guidance/ng198 (accessed 16 March 2022).
7. Dikicier BS. Topical treatment of acne vulgaris: efficiency, side effects, and adherence rate. J Int Med Res 2019; 47: 2987–92.
8. Gerlinger C, Städtler G, Götzelmann R et al. A non-inferiority margin for acne lesion counts. Drug Inf J 2008; 42: 607–15.
9. Klassen AF, Newton JN, Mallon E. Measuring quality of life in people referred for specialist care of acne: comparing generic and disease-specific measures. J Am Acad Dermatol 2000; 43: 229–33.
10. Al Robaee AA. Assessment of general health and quality of life in patients with acne using a validated generic questionnaire. Acta Dermatovenerol Alp Pannonica Adriat 2009; 18: 157–64.
11. Ara R, Brazier J. Deriving an algorithm to convert the mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value Health 2008; 11: 1131–43.
12. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Discussion paper 172. York: Centre for Health Economics, University of York, 1999.
13. Francis NA, Entwistle K, Santer M et al. The management of acne vulgaris in primary care: a cohort study of consulting and prescribing patterns using the Clinical Practice Research Datalink. Br J Dermatol 2017; 176: 107–15.
14. Curtis L, Burns A. Unit costs of health and social care 2019. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019 (accessed 30 July 2022).
15. NHS England and NHS Improvement. National Schedule of NHS costs – Year 2018–19 – NHS trusts and NHS foundation trusts. NHS England and NHS Improvement, 2020. Available at: https://www.england.nhs.uk/publication/2018-19-national-cost-collection-data-publication (accessed 15 March 2022).
16. NHS Business Services Authority. NHS Prescription Services. NHS England and Wakes. Electronic Drug Tariff. Issue: July 2020. Compiled on the behalf of the Department of Health and Social Care. NHS Business
Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Data S1. Description of economic model structure and assumptions.

Supplementary Data S2. Relative effects on efficacy and discontinuation used in the economic analysis.

Supplementary Data S3. Methods of estimation of absolute effects for the reference treatment.

Supplementary Data S4. Distribution around the mean percentage change in total acne lesion count from baseline (%CFB) in the economic model.

Supplementary Data S5. Methods of estimation of utility values used in the economic analysis.

Supplementary Data S6. Intervention costs of treatments for acne vulgaris used in the economic analysis.

Supplementary Data S7. Estimation of the average acne care cost.

Supplementary Data S8. Model input values, probability distributions and scenarios tested in deterministic sensitivity analysis.

Supplementary Data S9. Results of deterministic sensitivity analysis.

Supplementary Data S10. Published economic assessments of acne treatments.

Supplementary Table S1. Cost-effectiveness results for treatments for moderate-to-severe acne in males.