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What's new in acne? An analysis of systematic reviews and clinically significant trials published in 2010–11

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Summary

This review summarizes important clinical developments in acne treatment identified in five systematic reviews and two significant primary research studies, published between March 2010 and February 2011. Although evidence showing a direct link between development of bacterial resistance and oral antibiotic therapy for acne is not convincing, prescribers can still tailor their practice to minimize future risks by stopping treatment when appropriate, using benzoyl peroxide, and avoiding combining topical and systemic antimicrobials. A systematic review evaluating combination products containing benzoyl peroxide did not show convincing evidence that such products are superior to monotherapies. A systematic review of combined oral contraceptives confirmed their efficacy for acne in women. However, another systematic review of botanical products for acne failed to provide any good-quality evidence of benefit. A large, well-reported retrospective cohort study attempted to clarify the potential link between isotretinoin and depression/suicide. Although suicide risk peaked 6 months after isotretinoin treatment, an increased risk was present before initiation of isotretinoin, making it difficult to attribute the increased risk to isotretinoin alone. However, those with a history of suicide attempts before treatment made fewer new attempts than those whose behaviour started during treatment. This suggests that patients with severe acne with a history of attempted suicide should not automatically be refused isotretinoin. Another randomized controlled trial of 60 patients from Korea suggested that low-dose isotretinoin dose than might provide a better long-term outcome with minimal side-effects for people with moderate acne.

Background

This paper summarizes five systematic reviews dealing with the treatment of acne, which were indexed in bibliographic databases from March 2010 to February 2011 and included in the *2011 Annual Evidence Update on Acne Vulgaris* from NHS Evidence – Skin Disorders, available on the NHS Evidence website (http://www.evidence.nhs.uk/search?g=evidence+update+acne).

Because of the paucity of systematic reviews, two primary research studies from the previous year with potentially important clinical implications for treating acne are also considered. Similar articles from the 2008–09 and 2009–10 Annual Evidence Updates on Acne Vulgaris have previously been published in this journal.[1,2]

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Systematic reviews

Antimicrobial resistance: an effect of acne treatment?

The potential association between antibiotic use in acne and development of antimicrobial resistance has been examined in a systematic review[3] using English-language articles identified through MEDLINE. Inclusion criteria were not specified, and in conjunction with a narrow search strategy, this raises concerns of selection bias. There appeared to be little evidence to implicate directly the use of oral antibiotics in acne to community resistance to antibiotics; however, there is still a compelling argument to re-examine current practices and the use of long-term oral antibiotics. To minimize the risk of *Propionibacterium acnes* developing resistance, antibiotics should be limited to the shortest possible period, and discontinued when further improvement of acne is unlikely. Simultaneous use of topical and oral antibiotics should be avoided; instead, the evidence suggests that antibiotic monotherapy should be combined with retinoids or benzoyl peroxide (BPO) to make use of their useful synergistic properties.

Benzoyl peroxide and combination products

A meta-analysis comparing efficacy of topical BPO in combination with clindamycin or salicylic acid (SA) against BPO and clindamycin alone[4] included 23 of 124 studies initially identified from PubMed, the Food and Drug Administration, posters and unpublished data. It should be noted that one of the authors worked as a consultant for two companies that manufacture topical acne treatments. Assessment of the risk of bias was not presented, and it is unclear whether the comparator groups were included more than once in the various comparisons between treatments, a procedure that can lead to bias.

The authors concluded that at 2–4 weeks, a 5% BPO + SA combination was most effective at reducing inflammatory and noninflammatory lesions. At later time points, of 10–12 weeks, 5% BPO + SA was similar to BPO + clindamycin. The magnitude of the benefit of combination over monotherapy was questionable, and outcomes of clinical relevance (e.g. clear/almost clear) were not included. In conclusion, longer-term trials with patient-oriented outcomes are needed to establish any real superiority between the products.

Use of botanicals?

A review on the use of botanicals for the treatment of dermatological conditions including acne[5] was based on a PubMed search over a short duration from December 2007 to March 2010. A level of evidence (LOE) was assigned to each cited work, and predictably, most studies were LOE grade D. Two studies of LOE grade A criteria in acne led the authors to conclude that topical tea-tree oil 5% gel and gluconolactone (obtained from *Saccharomyces bulderi*) are efficacious in mild to moderate disease, with the latter comparable with BPO 5%. However, no data were provided to support these claims, and one of the studies was published in 1992, outside the initial designated search criteria. One LOE grade B study comparing tea-tree oil 5% against BPO 5% (without placebo group) concluded that, although tea-tree oil provided slower relief from acne, it caused less discomfort.

The lack of appropriate data, absence or quality assessment, and inconsistencies in search methodology suggests that this review is of limited value for informing practice.

Pharmacoeconomy in acne: evaluation of benefit and economics

A systematic review estimated the annual cost of treating people with acne in Germany to be > 400 million euros.[6] Although few studies on cost-effectiveness have dealt with topical treatments, the authors of this review suggested that topical combination products may have a better economic outcome. They found oral isotretinoin to have the best cost–benefit ratio for moderate to severe acne.

This work should act as a reminder to consider the costs of treating acne; even small differences in unit costs can significantly add up at a population level. A pharmacoeconomic evaluation for acne treatment in the UK would be useful to inform local commissioning policies.

Hormonal antiandrogens in acne

Another German systematic review evaluated antiandrogen therapies in acne.[7] Three databases (MEDLINE, EMBASE and Cochrane Library) were searched from 1945 to 2009. Although LOEs were tabulated, there was no description of the flow of studies after identification, and no commentary on the quality of included trials.

The authors recapped the function of androgens in acne, and classified antiandrogens depending on their mechanism of action as: (i) receptor blockers; (ii) inhibitors of circulating androgens through acting on ovaries; (iii) inhibitors of circulating androgens through acting on the pituitary gland; (iv) inhibitors of adrenocortical activity; and (v) inhibitors of peripheral androgen metabolism. The authors concluded that ethinyl

estradiol plus cyproterone acetate (the oral contraceptive Dianette), dienogest desogestrel and drospirenone had the best effect and should be continued for a 6–12 month course.

A Cochrane review was also published in 2009 on combined oral contraceptives for acne,[8] which concluded that all types evaluated in placebo-controlled trials were effective in reducing inflammatory and noninflammatory facial-acne lesions, but there was no clear evidence that those containing additional cyproterone offered any further benefit, despite their widespread use for acne in the UK.

Primary research studies

Isotretinoin and risk of suicide

An important retrospective cohort study from Sweden[9] explored the potential link between depression and attempted suicide with isotretinoin. All patients on isotretinoin from 1980 to 1990 (identified through the national Medical Products Agency) were linked to the national patient register of in-hospital care and the registers of cause of death. Standard incidence ratios for attempted suicides were calculated 3 years before, during and up to 15 years after treatment. It was found that risk of suicide attempts gradually increased the year before treatment, peaked 6 months after, and fell back to expected levels 3 years after isotretinoin. The increased risk of suicide attempts 6 months into treatment cannot be attributed solely to isotretinoin, as that risk was already starting to rise before treatment. Furthermore, there were no comparable data on suicide risk and other acne treatment such as antibiotics, which might be relevant comparators. Patients with a history of suicide attempts before treatment made fewer new attempts than those whose behaviour started during treatment, suggesting that patients with severe acne with a history of attempted suicide should not automatically be refused isotretinoin.

From a practical standpoint, as the increased risk of suicide was still apparent up to 6 months after cessation of isotretinoin, patients should be monitored for up to 1 year after treatment has ended, a policy that could have major cost implications for hospital or extended general practitioner (GP) follow-up.

Randomized controlled trial: effectiveness of low-dose and intermittent oral isotretinoin in the treatment of acne

Finally, a Korean study compared efficacy and tolerability of low-dose and intermittent regimens of isotretinoin with conventional dosing[10] in 60 patients with moderate acne. The interventions included isotretinoin 0.5–0.7 mg/kg/day (normal dose), 0.25–0.4 mg/kg/day (low-dose) or an intermittent regimen of 0.5–0.7 mg/kg/day for 1 out of every 4 weeks. The authors found that at 24 weeks, reduction in global acne grading and inflammatory and noninflammatory lesion counts was significantly greater in the conventional/low-dose isotretinoin groups compared with the intermittent regimen. Patient satisfaction was higher in the low-dose group, dose-related known side-effects were more frequent in the conventional group, and relapse rates at 1 year after the end of treatment were lower in the normal/lower dose compared with the intermittent group.

Although this was a small study with limited power and some potential for bias, it does provide some evidence that low-dose isotretinoin over a 6-month period might be a useful treatment option for moderate acne. This needs to be confirmed in larger trials using conventional comparators.

Learning points

- Combined oral and topical antibiotics should not be used together for acne in order to reduce potential resistance problems. Instead, oral antibiotics should be used in conjunction with other topicals such as BPO or retinoids.
- Oral or topical antibiotics should be stopped and switched to an alternative topical preventative measure if improvement fails to occur, rather than carrying on for several months 'just in case'.
- A topical combination product may be better than topical antibiotic monotherapy.
- Patients should not spend large amounts on herbal/botanical preparations, given the lack of current good evidence to support their use.
- Patients requiring isotretinoin should be screened before and during treatment for depression. It might be necessary for GPs to formally review patients for possible mental health problems for up to 1 year after cessation of treatment.
- It is possible that lower-dose isotretinoin (0.25–0.4 mg/kg/day for 24 weeks) offers a good trade-off between efficacy and dose-related side-effects for people with moderate acne.

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CPD questions

Learning objectives

To demonstrate an understanding of the up-to-date evidence relating to acne treatment as discussed in this review.

Question 1

Which of the following acne treatment regimens should be discouraged to limit the development of antimicrobial resistance?
a) Using systemic and topical antibiotics simultaneously
b) Combining ethinyl estradiol and cyproterone acetate
c) Using a limited course of systemic antibiotics simultaneously with topical benzoyl peroxide
d) Using topical retinoic acid only
e) Using topical benzoyl peroxide only

Question 2

Which of the following have been shown to be effective at treating acne?
a) *Glycyrrhiza* extract
b) *Primula*
c) 2.5% benzoyl peroxide
d) *Mahonia aquifolium* (syn *Berberis aquafolium)*, a botanical product
e) None of the above

Question 3

When does the risk of suicide after cessation of isotretinoin peak according to a recent cohort study?
a) 3 months
b) 6 months
c) 12 months
d) 2 years
e) 5 years

Question 4

A low-dose isotretinoin regimen (0.25–0.4 mg/kg/day) is potentially suitable for which of the following groups?
a) Mild acne
b) Moderate acne
c) Severe acne
d) Acne conglobata
e) Hidradenitis suppurativa

Question 5

Which of the following is not a mechanism of action for antiandrogens in the treatment of acne?
a) Receptor blockers
b) Inhibitors of circulating androgens through acting on ovaries
c) Inhibitors of circulating androgens through acting on the pituitary gland
d) Inhibitors of circulating androgens through acting on the hypothalamus
e) Inhibitors of adrenocortical activity

Instructions for answering questions

This learning activity is freely available online at www.wileyblackwellcme.com.

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- Reflect on the article
- Register or login online at www.wileyblackwellcme.com and answer the CPD questions
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