

## **2011 Annual Evidence Update on Acne Vulgaris**

Welcome to the fifth **Annual Evidence Update on Acne Vulgaris** produced by NHS Evidence - skin disorders, with the results of a search for new guidelines and systematic reviews on acne published or indexed since the last Annual Evidence Update in March 2010. There is also a "what's new" analysis, discussing the new evidence and its implications for clinical practice.

### **2011 Annual Evidence Update on Acne Vulgaris – Introduction**

**Introduction by Professor Hywel Williams (Clinical Lead) and Dr Douglas Grindlay (Information Specialist), NHS Evidence - skin disorders**

Welcome to the 2011 Annual Evidence Update on Acne Vulgaris from NHS Evidence - skin disorders. The Annual Evidence Update is a summary of important new evidence published or indexed over the last year since our 2010 Annual Evidence Update. Although NHS Evidence - skin disorders is aimed at healthcare professionals, we also hope that many people who have acne will find at least some of the information interesting.

Our Annual Evidence Updates search for new evidence in the form of systematic reviews and guidelines. We use systematic reviews as our core evidence source for Annual Evidence Updates because of the well-known hazards in interpreting the results of single research studies (see, for example, [Ioannidis 2005](#)).

This year we have found fewer systematic reviews than last year, and those that we found were generally disappointing in quality. The new evidence that we have found has been listed under relevant headings in our Results, with links to PubMed or free full text, if available.

We also provide our usual "What's new" commentary, intended as a guide for the busy health care professional on the significance of the new evidence for clinical practice. We would like to express our thanks to Dr Rosalind Simpson, Specialist Registrar and UK Dermatology Clinical Trials Network Fellow, for taking the lead in writing the "What's new" section.

If you want to delve more deeply into the topic areas, we recommend that you read the original articles and come to your own decisions about their utility.

Readers should be aware that this will be the last Annual Evidence Update produced in this way by the team at the Centre of Evidence of Based Dermatology. At the beginning of April 2011, the National Institute of Health and Clinical Excellence (NICE) and Bazian will be taking over the running of the specialist collections and producing Evidence Updates under new procedures. For more information about the changes, keep an eye on the main [NHS Evidence website](#). We would like to thank all our readers for their support for our Annual Evidence Updates over the last five years.

## 2011 Annual Evidence Update on Acne Vulgaris – Results

A literature search was carried out to identify **new guidelines and systematic reviews** relating to acne vulgaris (common acne) that have been published or indexed since the 2010 Annual Evidence Update on Acne Vulgaris. This year a selection of **other important new studies** has also been included. These studies were identified by the Evidence Update team from their current awareness activities and dermatology news alerts, and from a PubMed search using the Cochrane RCT filter.

The result of this search is the **2011 Annual Evidence Update on Acne Vulgaris**.

### Search period

January 2009 was set as the limit for earliest publication date in this year's searches, to allow for any delays in indexing of citations in the bibliographic databases used (which might mean the citations were not found in the searches for the previous Annual Evidence Update in March 2010).

All the searches were carried out for the last time on 11th February, 2011.

### Sources Searched

The following sources were searched:

- Ovid MEDLINE (using SIGN MEDLINE systematic review filter)
- Ovid EMBASE (using SIGN EMBASE systematic review filter)
- PubMed (using PubMed Clinical Queries systematic review filter)
- Cochrane Library
- NHS Evidence - skin disorders

All citations found in the searches were hand searched by reading the titles and abstracts to identify guidelines and and potential systematic reviews relevant to acne vulgaris. For all potential systematic reviews where there was still some doubt, the full texts were then read to ensure that they were indeed systematic reviews.

The definition of a systematic review from the [Glossary of Cochrane Collaboration Terms](#) on the Cochrane Collaboration website was used:

“A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.”

## RESULTS

New guidelines and citations for new systematic reviews judged of direct relevance to the topic of acne vulgaris and its treatment are listed below. Links to PubMed abstracts or free full text, where available, are provided.

**Please note that the inclusion of citations in this list does not imply endorsement. NHS Evidence - skin disorders does not accept responsibility for the content or quality of included studies.**

A large number of citations were identified as possible systematic reviews for the Annual Evidence Update in the initial search results, but were subsequently excluded on the grounds of a lack of a clear systematic review methodology or for other reasons. These citations are listed at the end of this page under the heading "Excluded references".

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### UK guideline

Goodfield MJD, Cox NH, Bowser A, McMillan JC, Millard LG, Simpson NB, Ormerod AD.

Advice on the safe introduction and continued use of isotretinoin in acne in the U.K. 2010.

British Journal of Dermatology 2010 Jun;162(6):1172–9.

[Link to full text \(PDF\)](#)

### Overseas guideline

Nast A, Bayerl C, Borelli C, Degitz K, Dirschka T, Erdmann R, Fluhr J, Gieler U, Hartwig R, Meigel EM, Möller S, Ochsendorf F, Podda M, Rabe T, Rzany B, Sammain A, Schink S, Zouboulis CC, Gollnick H; German Society of Dermatology (DDG) and the Association of German Dermatologists (BVDD).

[S2k-guideline for therapy of acne].

Journal der Deutschen Dermatologischen Gesellschaft 2010 Jul;8 Suppl 2:s1-59.

[Link to PubMed abstract](#)

*Note: Full text in German with English abstract.*

### Systematic reviews

Patel M, Bowe WP, Heughebaert C, Shalita AR.

The development of antimicrobial resistance due to the antibiotic treatment of acne vulgaris: a review.

Journal of Drugs in Dermatology 2010 Jun;9(6):655-64.

[Link to PubMed abstract](#)

*Note: MEDLINE only searched.*

Radtke MA, Schäfer I, Augustin M.  
[Pharmacoeconomy in acne — evaluation of benefit and economics].  
Journal der Deutschen Dermatologischen Gesellschaft 2010 Mar;8 Suppl 1:S105-14.  
[Link to PubMed abstract](#)

*Note: PubMed only searched. Full text in German with English abstract.*

Reuter J, Merfort I, Schempp CM.  
Botanicals in dermatology: an evidence-based review.  
American Journal of Clinical Dermatology 2010;11(4):247-67.  
[Link to PubMed abstract](#)

*Note: PubMed only searched.*

Seidler EM, Kimball AB.  
Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne.  
Journal of the American Academy of Dermatology 2010 Jul;63(1):52-62.  
[Link to PubMed abstract](#)

*Note: PubMed only searched.*

Zouboulis CC, Rabe T.  
[Hormonal antiandrogens in acne treatment].  
Journal der Deutschen Dermatologischen Gesellschaft 2010 Mar;8 Suppl 1:S60-74.  
[Link to PubMed abstract](#)

*Note: MEDLINE, EMBASE and Cochrane Library searched. Full text in German with English abstract.*

### **Other important studies identified by the Annual Evidence Update team**

Lee JW, Yoo KH, Park KY, Han TY, Li K, Seo SJ, Hong CK.  
Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: a randomized, controlled comparative study.  
British Journal of Dermatology 2010 Nov 29. [Epub ahead of print]  
[Link to PubMed abstract](#)

Sundström A, Alfredsson L, Sjölin-Forsberg G, Gerdén B, Bergman U, Jokinen J.  
Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study.  
BMJ 2010 Nov 11;341:c5812.  
[Link to full text](#)

## EXCLUDED REFERENCES

Babilas P, Schreml S, Szeimies RM, Landthaler M.  
Intense pulsed light (IPL): a review.  
Lasers in Surgery and Medicine 2010 Feb;42(2):93-104.  
[Link to PubMed abstract](#)

*Note: Abstract states there was a systematic search of several electronic databases, but there is no methods section and no details of a systematic search methodology.*

Bayerl C, Degitz K, Meigel E, Kerscher M.  
[Adjuvant dermato-cosmetic acne therapy].  
Journal der Deutschen Dermatologischen Gesellschaft 2010 Mar;8 Suppl 1:S89-94.  
[Link to PubMed abstract](#)

*Note: No indication of a systematic review methodology. Full text in German with English abstract.*

Callender VD, Preston N, Osborn C, Johnson L, Gottschalk RW.  
A meta-analysis to investigate the relation between Fitzpatrick skin types and tolerability of adapalene-benzoyl peroxide topical gel in subjects with mild or moderate acne.  
Journal of Clinical and Aesthetic Dermatology 2010 Aug;3(8):15-9.  
[Link to PubMed abstract](#)

*Note: No indication that selection of trials for the meta-analysis was based on a systematic literature search, so risk of selection bias.*

Davidovici BB, Wolf R.  
The role of diet in acne: facts and controversies.  
Clinics in Dermatology 2010 Jan-Feb;28(1):12-6.  
[Link to PubMed abstract](#)

*Note: No indication of a systematic review methodology.*

Dessinioti C, Katsambas AD.  
The role of Propionibacterium acnes in acne pathogenesis: facts and controversies.  
Clinics in Dermatology 2010 Jan-Feb;28(1):2-7.  
[Link to PubMed abstract](#)

*Note: No indication of a systematic review methodology.*

Ferdowsian HR, Levin S.  
Does diet really affect acne?  
Skin Therapy Letter 2010 Mar;15(3):1-2, 5.  
[Link to full text](#)

*Note: Not a systematic review but a brief narrative review referring to findings of a previous (2009) systematic review.*

Fluhr JW, Degitz K.  
[Antibiotics, azelaic acid and benzoyl peroxide in topical acne therapy].  
Journal der Deutschen Dermatologischen Gesellschaft 2010 Mar;8 Suppl 1:S24-30.  
[Link to PubMed abstract](#)

*Note: No indication of a systematic review methodology. Full text in German with English abstract.*

Jansen T, Podda M.  
[Therapy of acne scars].  
Journal der Deutschen Dermatologischen Gesellschaft 2010 Mar;8 Suppl 1:S81-8.  
[Link to PubMed abstract](#)

*Note: PubMed was searched but there are no details of a systematic review methodology. Full text in German with English abstract.*

Karimipour DJ, Karimipour G, Orringer JS.  
Microdermabrasion: an evidence-based review.  
Plastic and Reconstructive Surgery 2010 Jan;125(1):372-7.  
[Link to PubMed abstract](#)

*Note: No indication of systematic review methodology.*

Lopez LM, Grimes DA, Gallo MF, Schulz KF.  
Skin patch and vaginal ring versus combined oral contraceptives for contraception.  
Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD003552.  
[Link to full text](#)

*Note: Marginal relevance and insufficient data relating to acne.*

Ochsendorf F.

[Systemic antibiotic therapy of acne vulgaris].

Journal der Deutschen Dermatologischen Gesellschaft 2010 Mar;8 Suppl 1:S31-46.

[Link to PubMed abstract](#)

*Note: Paper republished from 2006, so out of date. Not based on a full systematic review, but used results of previous systematic reviews supplemented by a search for recent trials. Full text in German with English abstract.*

Rigopoulos D, Larios G, Katsambas AD.

The role of isotretinoin in acne therapy: why not as first-line therapy? facts and controversies.

Clinics in Dermatology 2010 Jan-Feb;28(1):24-30.

[Link to PubMed abstract](#)

*Note: No indication of a systematic review methodology.*

Sakamoto FH, Lopes JD, Anderson RR.

Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice: part I. Acne vulgaris: when and why consider photodynamic therapy?

Journal of the American Academy of Dermatology 2010 Aug;63(2):183-93.

[Link to PubMed abstract](#)

*Note: No indication of a systematic review methodology.*

Sakamoto FH, Torezan L, Anderson RR.

Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice: part II. Understanding parameters for acne treatment with photodynamic therapy.

Journal of the American Academy of Dermatology 2010 Aug;63(2):195-211.

[Link to PubMed abstract](#)

*Note: No indication of a systematic review methodology.*

Sherling M, Friedman PM, Adrian R, Burns AJ, Conn H, Fitzpatrick R, Gregory R, Kilmer S, Lask G, Narurkar V, Katz TM, Avram M.

Consensus recommendations on the use of an erbium-doped 1,550-nm fractionated laser and its applications in dermatologic laser surgery.

Dermatologic Surgery 2010 Apr;36(4):461-9.

[Link to PubMed abstract](#)

*Note: Round table consensus document with no indication of a systematic review methodology.*

Webster GF.

Light and laser therapy for acne: sham or science? facts and controversies.  
Clinics in Dermatology 2010 Jan-Feb;28(1):31-3.

[Link to PubMed abstract](#)

*Note: No indication of a systematic review methodology.*

Youn SW.

The role of facial sebum secretion in acne pathogenesis: facts and controversies.  
Clinics in Dermatology 2010 Jan-Feb;28(1):8-11.

[Link to PubMed abstract](#)

*Note: No indication of a systematic review methodology.*

## 2011 Annual Evidence Update on Acne Vulgaris – Commentary

### "What's new?" — a tour of the 2011 Annual Evidence Update on Acne Vulgaris with the busy clinician in mind

*Dr Rosalind Simpson, Dermatology Specialist Registrar, Nottingham University Hospitals NHS Trust, and Professor Hywel Williams, Clinical Lead for NHS Evidence - skin disorders and Co-ordinating Editor of the Cochrane Skin Group.*

#### What this guide is all about

Our task in this “What’s new” section of the 2011 Annual Evidence Update on Acne Vulgaris from NHS Evidence - skin disorders is to read through all the new guidelines and systematic review evidence we have found in the Results section in order to provide you with a summary of important developments in acne research that might *change your practice* — either by stopping something ineffective or harmful, or encouraging you to adopt a new treatment approach that might be beneficial. Sometimes the evidence will just reinforce what you do already, which can also be useful if, like us, you are worried that you might be missing something new and important. We also highlight some methodological issues in the published studies. We hope that you find some of these insights interesting, educational and useful.

In last year’s Annual Evidence Update on Acne Vulgaris, we found only one guideline and nine new systematic reviews to comment upon. On the whole, the quality of those included systematic reviews was poor. This year we have found even less — two guidelines and five articles that fall within our definition of a systematic review. Again the quality of these systematic reviews was rather disappointing, with only one out of the five reviews searching more than one electronic database. You will see that we have excluded lots of articles that were initially picked up as possible systematic reviews by our searches, in most cases due to an absence of details of any systematic review methodology in the full articles.

As part of a trial of procedures for future Evidence Updates, and due to the paucity new systematic reviews in this year’s Annual Evidence Update, we have decided to include and comment on two other primary research studies that have emerged over the last year with important clinical implications for acne treatment.

#### Guidelines (and a relevant new retrospective cohort study)

Two new national guidelines on acne were published in the last year. The British Association of Dermatologists (BAD) has issued updated national guidance on the safe introduction and continued use of isotretinoin in acne in the UK ([Link to full text, PDF](#)). The German Society of Dermatology and Association of German Dermatologists have also published guidelines for acne treatment ([Link to PubMed abstract](#)).

The updated BAD guideline by Goodfield *et al.* ([Link to full text, PDF](#)) focuses mainly on the contraindications and side effects of isotretinoin. A brief overview of the recognised side effect profile is followed by a more in depth discussion regarding teratogenicity, the pregnancy prevention program (PPP), PPP exemptions, and the risk of mood change. The latter issue has continued to raise significant concern amongst clinicians given the lack of clear cut evidence of such a link, as we will discuss later in relation to a new cohort study published after the BAD guideline emerged.

The BAD guideline authors concluded that isotretinoin *may* lead to mood change and in the absence of a defining study recommend that: (i) clinicians should specifically ask about past psychiatric history (screening questions are suggested); (ii) clinicians should warn patients/family members about potential mood change when counseling prior to isotretinoin therapy; and (iii) direct enquiry about psychological symptoms should be made at each follow up visit. It is important that these points be clearly documented in the notes. The guidance states that those with a history of psychiatric disease should be assessed by a psychiatrist prior to therapy. There is also helpful advice on what to do when someone taking isotretinoin does develop mood changes — a default position of discontinuation or continuation with psychiatric support or immediate psychiatric referral if serious psychiatric disease is suspected. The guideline appendices include printed aids for ensuring the safe introduction and monitoring of isotretinoin for use in clinical practice. Overall, the guideline is up to date, practical and easy to read and we recommended that all practising dermatologists take the time to familiarise themselves with this document.

As we are on the vexed topic of a possible link between depression and attempted suicide with isotretinoin treatment, now would be an appropriate time to comment on a new and important retrospective cohort study in Sweden by Sundström *et al.* that explored this topic ([Link to full text](#)). Since all isotretinoin prescriptions in Sweden must be approved through their national Medical Products Agency, it was possible to retrospectively link all patients on the medication over a 10 year period (1980-90) to the national patient register of in-hospital care and cause of death registers. Sundström *et al.* calculated standard incidence ratios for attempted suicides (observed number divided by expected number of attempts) for young men and women up to 3 years before treatment, during treatment, and up to 15 years after treatment. They found that standard incidence ratios of suicide attempts gradually increased in the year before treatment, peaked six months after commencement and fell back to expected levels 3 years after cessation of isotretinoin. Unfortunately, it is not possible to attribute the raised risk of suicide attempts 6 months into treatment solely to isotretinoin because that risk was already starting to rise prior to isotretinoin treatment. Furthermore, there were no comparable data on suicide risk and other acne treatment such as antibiotics which might have helped to disentangle non-specific acne-associated mood changes from those associated with specific treatments. Interestingly, the study suggested that patients with a history of suicide attempts *before* treatment ended up making less new attempts at suicide than those who started such behaviour in connection with treatment, suggesting that patients with severe acne with a history of attempted suicide should not automatically be refused isotretinoin treatment. From a practical standpoint, the study also suggested that because the increased risk of suicide was still apparent up to 6 months after cessation of isotretinoin, patients receiving

isotretinoin 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 follow-up, and which needs to be considered urgently by the BAD acne guidelines group.

The new German acne therapy guideline by Nast *et al.* ([Link to PubMed abstract](#)), produced jointly by the German Society for Dermatology and the Association of German Dermatologists, summarises induction and maintenance therapies, and treatment of post acne scarring. The full text of this guideline is in German, but with an English abstract. The recommendations were developed by an expert group following a thorough literature review and finalised during an interdisciplinary consensus conference. Their main treatment algorithm suggestions include:

- (i) comedonal acne — topical retinoids;
- (ii) mild papular/pustular acne — fixed or sequential combinations of benzoyl peroxide (BPO) and topical retinoids or of BPO and topical antibiotics;
- (iii) moderate papular/pustular acne — oral antibiotic plus BPO or plus topical retinoid or in a fixed combination;
- (iv) acne papulo-pustulosa nodosa and acne conglobata — oral antibiotic plus topical retinoid plus BPO or oral isotretinoin.
- (v) maintenance treatment — topical retinoid or its combination with BPO.

It is interesting that only combination products are being suggested as first line therapy for mild acne these days rather than monotherapy with benzoyl peroxide, an assertion which might benefit from further research, as highlighted in our updated DUETS (UK Database of Uncertainties of the Effects of Treatments) module on acne ([Link](#)). The recommendations in the German guideline are more or less the same as those recommended by the Global Alliance to Improve Outcomes in Acne published in 2009 [1] and they provide a useful guide to general practitioners commencing treatment for milder cases of acne.

## **Systematic reviews**

### *Antimicrobial resistance an effect of acne treatment?*

Antimicrobial resistance is a topic that concerns all clinicians especially when prescribing antibiotics. Patel *et al.* ([Link to PubMed abstract](#)) have undertaken a potentially very important review of the literature surrounding antibiotic use for acne and the development of antimicrobial resistance, both in cutaneous and non-cutaneous environments. Unfortunately their search strategy was less than thorough and only included articles in English identified through MEDLINE. The search period was long (1960–June 2009) and their search criteria would have drawn out many reports over this period, but they only discussed references that they considered 'significantly contributory to the current understanding of the subject', without specifying what criteria their decisions were based on. They cited 69 references in total, without illustrating in a flow chart how many were actually identified through their search criteria and why some were discarded, prompting concerns of selection bias.

The review text itself is interesting and educational. It discusses the potential mechanisms of development of bacterial resistance, the role and usual habitation sites of normal microbial flora (including *P. acnes*, coagulase-negative staphylococci, *S. aureus* and group A streptococci), and the pathogenic effects they may exert if resistance occurs, or in immunocompromised individuals. Although there was little direct evidence to implicate oral antibiotics used for acne in contributing to community resistance of antibiotics, the circumstantial evidence and evidence of *P. acnes* resistance in individuals made a compelling argument to re-examine current practices and the use of long-term oral antibiotics in acne. Patel *et al.* concluded that it is imperative to take steps to minimise the risk of *P. acnes* developing resistance, and advised that antibiotics should be limited to the shortest possible period and discontinued when further improvement of acne is unlikely. They also suggested *simultaneous* use of topical and oral antibiotics should be avoided; instead, antibiotic monotherapy should be combined with retinoids/benzoyl peroxide to make use of their useful synergistic properties (anti-comedogenic, comedolytic and anti-inflammatory for retinoids; bactericidal and keratolysis for benzoyl peroxide). These treatment mantras *are* important and are worth remembering when managing acne.

### *Benzoyl peroxide and combination products*

A meta-analysis comparing efficacy of topical benzoyl peroxide (BPO) in combination with clindamycin or salicylic acid (SA) against BPO and clindamycin alone has been carried out by Seidler & Kimball ([Link to PubMed abstract](#)). Their aim was to test if combining BPO with SA or clindamycin reduces inflammatory and non-inflammatory lesions more than using the treatments alone. It should be noted that one of the authors works as a consultant for two companies that manufacture topical acne treatments.

Seidler & Kimball searched PubMed and studies used by the Food and Drug Administration, along with posters and unpublished data, and included studies only if they met a pre-defined set of criteria. A total of 124 potentially relevant studies were retrieved, of which 23 satisfied the inclusion criteria. The authors provide a helpful study flow diagram. All included studies were assessed for validity, but unfortunately the results of the risk of bias assessment for included studies in terms of method and concealment of randomization, blinding, and whether an intention to treat analysis was done, were not presented. Thus it is difficult for the reader to separate the well-reported from the poorly-reported studies. It is also unclear whether the comparator groups were included more than once in the various comparisons between treatments, a procedure that can give rise to bias by attributing undue weight to a particular study.

All the studies were randomized control trials with at least one arm containing 5% BPO, 1-2% clindamycin, a combination of both, or a combination of 5% BPO with SA. The authors concluded that at 2-4 week time points, the 5% BPO + SA combination was the most effective at reducing acne lesions (inflammatory and non-inflammatory), and at later time points (10-12 weeks), 5% BPO + SA was similar to BPO + clindamycin, albeit with overlapping confidence intervals with the respective

monotherapies. The magnitude of the benefit of combination over monotherapy was questionable, e.g. a weighted mean change in inflammatory lesion count from baseline of 11.6 for BPO/CL versus 11.5 for BPO alone, a difference which is unlikely to be clinically important. Whilst it is fine to include reduction in spots in acne because they can be counted and because they are easy to combine statistically in a meta-analysis, we have yet to meet a teenager in our clinic who is satisfied with a 11 spot reduction compared with their first assessment. What most acne sufferers want is to be clear or mostly clear of spots, or for their quality of life to improve — outcomes which were not included in this systematic review. The authors concluded that more trials at later time points are needed to establish any real superiority between the products. They also noted that clindamycin was similar to placebo in non-inflammatory lesion reduction after 2-4 weeks (this was not statistically significant), but was statistically superior at 10-12 weeks. Following this they stated in the discussion that clindamycin should rarely be used alone, due to its relatively inferior performance and risk of resistance.

### *Use of botanicals?*

Patients often ask about 'herbal remedies' to treat their health problems. Many alternative therapies may have been tried for acne prior to a medical consultation based on recommendations from friends or relatives. We may be quick to dismiss such 'treatments' in clinic, but it is likely that few of us have reviewed the literature to investigate their use. Reuter *et al.* ([Link to PubMed abstract](#)) have published a paper entitled 'Botanicals in dermatology: an evidence-based review', the abstract of which indicates a focus on controlled clinical trials with botanicals (preparations derived from herbs, spices, roots, stems and other material of plant origin) in the treatment of certain dermatological conditions, including acne. They claim that *Mahonia*, tea tree oil and *Saccharomyces* may have the potential to become standard acne treatments.

Reuter *et al.* searched PubMed between December 2007 and March 2010 and identified 1263 articles. They did not state how many of these were relevant to acne. Although they did not comment directly on the quality of reporting on any of the included studies, they did at least attempt to assist the reader by assigning a level of evidence (LOE) to each cited work. As might be expected, the majority of studies were LOE-D (expert opinion without explicit critical appraisal), which gives little weight or credibility to the work. For the other studies of higher LOE, no attempt of critical appraisal was made, which suggests the overall quality was low. There were two studies of LOE-A criteria: a randomised, double-blind placebo-controlled trial that 'proves the efficacy of topical tea tree oil 5% gel in mild to moderate acne' (no data given), and a double blind study of 150 acne patients comparing gluconolactone (obtained from *Saccharomyces bulderi*) against BPO which claimed gluconolactone was 'significantly superior' to placebo and comparable to BPO 5% (again no data given). Interestingly, the latter study was published in 1992, which falls well outside the initial designated search criteria! One LOE-B study was included: a 3 month single-blinded trial with 124 patients comparing tea tree oil 5% against BPO 5% (without placebo group) which concluded that although tea tree oil provided slower relief from acne, it caused less discomfort. Given the lack of data and lack of an

apparent attempt to assess quality of any of these trials, in conjunction with inconsistencies in search methodology, the results of this review are unreliable for informing practice. Three previous systematic reviews have evaluated complementary and alternative (CAM) therapies in acne ([Link to mapping of systematic reviews](#)). The bottom line is that although it is still possible that some CAM treatments may work in acne, there is no good quality positive evidence of benefit yet — larger and better designed and clearly reported studies are needed.

### *Pharmacoeconomy in acne – evaluation of benefit and economics*

Given that acne is a common skin disease, it is surprising that so little is known about the costs of treatment from a societal perspective. Radtke *et al.* ([Link to PubMed abstract](#)) performed a literature search to estimate the annual cost of treating people with acne in Germany 'according to Cochrane criteria', yet searched only PubMed. Note that the full text of this paper is in German, but with an English abstract. The authors estimated the annual cost of treating acne in Germany to be greater than 400 million Euros. They commented that there are few studies on cost effectiveness of topical treatments, but believed that topical combination products may have a better economic outcome. They found that oral isotretinoin to have the best cost-benefit ratio for moderate-severe acne.

This work addresses an important aspect of acne treatment and should act as a reminder to us all to consider costs when prescribing therapies. Even small differences in unit costs can add up to a lot at a population level because acne is so common. The review concludes by suggesting that higher initial treatment costs are countered by high quality outcomes (i.e. early and effective improvement to quality of life), and that patient benefit should be prioritized over the final total cost. A pharmacoeconomic evaluation for acne treatment in the UK would be a useful exercise to inform local commissioning policies.

### *Hormonal antiandrogens in acne*

Another article in German, with abstract in English, by Zouboulis & Rabe ([Link to PubMed abstract](#)), looked at the use of anti-androgen therapies in acne. The authors searched three databases (MEDLINE, EMBASE and Cochrane Library) from 1945-2009 for all review and original publications of hormonal anti-androgen treatment for acne (either monotherapy or in combination). They assigned levels of evidence to each article and tabulated this, although there is no description of the flow of studies following identification from the databases, and no commentary on the quality of included trials. The criteria used to decide which studies were to be included in the final analysis were not stated, raising concerns about possible selection bias.

The authors begin with a recap of the function of androgens on the pilosebaceous unit and its role in pathogenesis of acne. They categorize anti-androgens into: (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.

Overall, Zouboulis & Rabe concluded that anti-androgens are helpful for acne in women, but suggested that they are not effective enough to be used as a monotherapy in uncomplicated acne. They stated that ethinyl estradiol + cyproterone acetate (Dianette), dienogest desogestrel and drospirenone have the best effect and should be continued for a 6-12 month course. They did not find any good evidence to support the use of oestrogen or progesterone alone, spirinolactone, flutamide or gonadotrophin releasing hormone agonists. There are alternative cyproterone acetate containing products, but these are not available in the UK. The authors stated that antiandrogens are a valid treatment for acne, particularly for females with hyper-androgenism or who do not want to commence isotretinoin.

A more comprehensive systematic review on this topic using pre-defined criteria for inclusion of studies and with formal critical appraisal of the individual papers is needed. It should be noted that a previous Cochrane Review on combined oral contraceptives for acne published in 2009 [2] concluded that all four types evaluated in placebo-controlled trials were effective in reducing inflammatory and non-inflammatory facial acne lesions, and that there was no clear evidence that those containing additional cyproterone offered any further benefit, despite their widespread use for acne in the UK.

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

Finally, Lee *et al.*, a group from Korea, have performed an interesting randomized controlled trial comparing the efficacy and tolerability of low-dose and intermittent regimens of isotretinoin with conventional dose isotretinoin ([Link to PubMed abstract](#)). They randomised 60 patients with moderate acne (as defined by a newly devised GAGS score - a Global Acne Grading Score) using a computer-generated schedule into equal groups to receive isotretinoin 0.5-0.7mg/kg per day for 24 weeks (normal dose), 0.25-0.4 mg/kg per day for 24 weeks (low-dose), or an intermittent regimen consisting of 0.5-0.7 mg/kg per day for 1 week out of every 4 weeks for a total of 24 weeks (i.e. 6 weeks isotretinoin in total). At the end of 24 weeks, they found that reduction in GAGS, inflammatory and non-inflammatory lesion counts was significantly greater in the conventional and low-dose isotretinoin groups compared to the intermittent regimen (but with no statistical difference between conventional and low-dose groups). Patient satisfaction was statistically higher in the low-dose group and dose-related known side effects were more frequent in the conventional group. The authors also measured relapse rates 1 year after the end of treatment — 2/16 in the normal dose group relapsed compared with 3/17 in the lower dose group and 9/16 in the intermittent group. The authors concluded that for treating moderate acne, low-dose isotretinoin provides the most tolerable, efficient regimen and has the highest patient satisfaction.

In terms of study reporting quality, the randomization method was mentioned but not how the allocation sequence was concealed. Only the study assessor was blinded to

the intervention group, so information bias could have crept in if the degree of cheilitis (which is dose-related) was discernible between the three groups. Patient satisfaction outcomes could also have been subject to information bias given that patients were not blinded to their treatment allocation. It should also be noted that 11 patients (18%) did not complete the study period (documented as 9 for personal reasons and 2 due to side effects, and there was no attempt to account for these dropouts with an intention to treat analysis. It is also worth pointing out that the GAGS has not been validated against other global acne scores or lesion counts, nor has it been evaluated for reliability, and its clinical interpretation is unclear. The study places undue emphasis on which differences between the groups were statistically significant, rather than commenting on the *magnitude* of differences between the groups and whether they were clinically worthwhile. The power of the study to claim equivalence between the conventional and low dose groups regimens is limited given that less than 20 patients were included in each group, and no confidence intervals are used to assist the reader in determining a range of plausible treatment effects between the groups.

Nevertheless, the study is interesting from two standpoints. First, the study does provide reasonable evidence that using intermittent monthly cycles of isotretinoin is considerably less effective than continuous low or higher dosing over a 6 month period. Second, there is a signal that a lower dose of isotretinoin may be almost as good as the higher dose over 6 months and in terms of relapse rates, but with less adverse effects and better patient satisfaction. Lower dose isotretinoin is quiet commonly used in the Far East, and they may be right to do so. It should be noted that the patients enrolled in this study had moderate severity acne and that the implied equivalence between higher and lower doses may not apply for those with more severe acne. Some clinicians in the UK also use a higher dose of isotretinoin (up to 1mg/Kg/day) rather than the 0.5 to 0.7 mg/Kg/day 'higher' dose described in this study. The study is a small one, and a much larger and better designed study comparing low versus standard dose is worth pursuing since it could change the way we prescribe isotretinoin in the future.

### **Implications for practice**

Will our practice of treating acne change as a result of these data? There are unlikely to be any major changes in the way we practise, but we will be more vigilant in the following ways:

- Screening patients for depression prior to, and during, treatment with isotretinoin;
- Asking general practitioners to formally review patients for possible mental health problems for up to 1 year after cessation of isotretinoin;
- Never using topical and oral antibiotics for acne at the same time (as it may increase bacterial resistance);
- Combining oral antibiotics with topical acne treatments such as benzoyl peroxide or retinoids;

- Stopping oral or topical antibiotics and switching to an alternative topical preventative measure if improvement fails to occur rather than carrying on for several months 'just in case';
- Prescribing a topical combination product rather than topical antibiotic monotherapy;
- Informing patients not to spend large amounts on herbal/botanical preparations given the lack of current good evidence to support their use;
- Being open minded about the possibility that lower dose isotretinoin (0.25 to 0.4mg/Kg/day for 24 weeks) may offer the best trade-off between of efficacy and dose-related side effects;
- Encouraging authors of new acne trials and non-Cochrane systematic reviews to include outcome that can be interpreted more widely by a clinical readership, to publish their study protocol beforehand and to report their study using widely accepted [CONSORT](#) (for trials) or [PRISMA](#) (for systematic review) reporting guidelines.

### **Additional references**

1. Thiboutot D, Gollnick H, Bettoli V, Dréno B, Kang S, Leyden JJ, Shalita AR, Lozada VT, Berson D, Finlay A, Goh CL, Herane MI, Kaminsky A, Kubba R, Layton A, Miyachi Y, Perez M, Martin JP, Ramos-E-Silva M, See JA, Shear N, Wolf J Jr; Global Alliance to Improve Outcomes in Acne.

New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group.

Journal of the American Academy of Dermatology 2009;60(5 Suppl):S1-50.

[Link to PubMed abstract](#)

2. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA, Garner SE.

Combined oral contraceptive pills for treatment of acne.

Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD004425

[Link to full text](#)

## **2011 Annual Evidence Update on Acne Vulgaris - UK DUETs uncertainties update**

*Dr Douglas Grindlay, Information Specialist, NHS Evidence - skin disorders*

### **Introduction**

NHS Evidence – skin disorders is involved in collecting and collating uncertainties about the effects of treatments for skin disorders, to be added to the [UK Database of Uncertainties about the Effects of Treatments \(DUETs\)](#).

DUETs has been established to publish treatment uncertainties that cannot currently be answered reliably by referring to up-to-date systematic reviews of existing research evidence. These uncertainties can then be used to inform future research.

DUETs draws on three main sources to identify uncertainties about the effects of treatments:

- Patients', carers' and clinicians' questions about the effects of treatments;
- Research recommendations in reports of systematic reviews and clinical guidelines;
- Ongoing research, both systematic reviews in preparation and new 'primary' studies.

In summer 2009 a set of uncertainties was added to the DUETs database on acne vulgaris, derived from published systematic reviews and from research questions submitted by health professionals and patients. Please [click here](#) to view the UK DUETS module on acne vulgaris. This set of uncertainties was then reviewed and added to in the 2010 Annual Evidence Update on Acne Vulgaris.

Now, this DUETs uncertainties update discusses the implications for treatment uncertainties of the new systematic reviews found in the 2011 Annual Evidence Update on Acne Vulgaris.

### **Update on treatment uncertainties on acne vulgaris**

The systematic reviews found in the Results of the 2011 Annual Evidence Update on Acne Vulgaris have been reviewed for new uncertainties to add to DUETs, and to determine if they have any implications for existing uncertainties in the DUETs database.

**No existing uncertainties have been removed** as a result of the systematic reviews found in the 2011 Annual Evidence Update.

**Two new uncertainties have been added to the DUETs database:**

[Monotherapy with benzoyl peroxide or topical retinoids versus combination topical therapy in the initial treatment of mild acne](#)

[Low dose versus standard dose isotretinoin for acne](#)

The meta-analysis by [Seidler and Kimball \(2010\)](#) comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin has been added as a reference to the existing DUETs uncertainty on [Which topical combination therapy is best for mild to moderate facial acne?](#) However, it was not judged sufficient to answer the uncertainty, as it only dealt with two combination treatments (which are not available in the UK).

Please note that DUETs is a work in process. If you have identified any uncertainties on acne vulgaris or other skin disorders—clinical questions that are not answered by existing systematic reviews—then do please let us know. You can contact us via our [DUETs feedback form](#).

## **2011 Annual Evidence Update on Acne Vulgaris – Methodology**

A literature search was carried out to identify **new guidelines and systematic reviews** relating to acne vulgaris (common acne) that have been published or indexed since the 2010 Annual Evidence Update on Acne Vulgaris. In addition other important studies on acne published in the last year were identified by the Annual Evidence Update team.

The result of this search is the **2011 Annual Evidence Update on Acne Vulgaris** from NHS Evidence - skin disorders.

This page describes the search strategies used and the criteria for inclusion in the Annual Evidence Update.

### **Search period**

The search for the 2011 Annual Evidence Update on Acne Vulgaris was for citations published or indexed in 2009-11 and not included in the 2010 Annual Evidence Update.

January 2009 was set as the limit for earliest publication date in most of the searches, to allow for any delays in indexing of citations in the bibliographic databases used (which might mean the citations were not found in the searches for the previous Annual Evidence Update in March 2010).

In the case of PubMed, the search was refined by searching for records *indexed* in the database in 2010 and 2011 (using the "edat" command), which would find any citations published before 2010 but indexed late and not found in last year's search.

All the searches were carried out for the last time on 11th February, 2011.

### **Sources searched**

The following sources were searched:

Ovid MEDLINE (using SIGN MEDLINE systematic review filter)  
Ovid EMBASE (using SIGN EMBASE systematic review filter)  
PubMed (using PubMed Clinical Queries systematic review filter)  
Cochrane Library  
NHS Evidence - skin disorders

The search of PubMed was carried out as an insurance to ensure that no systematic reviews were missed using MEDLINE and EMBASE, especially as PubMed tends to be more up to date than and so is better for finding new citations.

The search of the Cochrane Library was also carried out as an insurance, to find relevant citations in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment Database. The intention was to confirm that nothing of relevance was missed in the searches of MEDLINE, EMBASE and PubMed.

The search of NHS Evidence - skin disorders was to find new guidelines and also gave a confirmatory search for new Cochrane Reviews and DARE abstracts.

### **Systematic review filters**

The SIGN systematic review filters developed for Ovid implementations of MEDLINE and EMBASE were used as they provide a reasonable balance between specificity and sensitivity. Details of the SIGN systematic review filters can be found on the following webpage:

<http://www.sign.ac.uk/methodology/filters.html>

Details of the PubMed Clinical Queries systematic review filter and its validation can be found via the following links:

[http://www.nlm.nih.gov/bsd/pubmed\\_subsets/sysreviews\\_strategy.html](http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html)

[http://www.nlm.nih.gov/bsd/pubmed\\_subsets/sysreviews\\_sources.html](http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_sources.html)

### **Search Strategies**

SIGN MEDLINE systematic review filter:

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations & Ovid MEDLINE

1. Meta-Analysis/
2. meta analy\$.tw.
3. metaanaly\$.tw.
4. meta analysis.pt.
5. (systematic adj (review\$1 or overview\$1)).tw.
6. exp Review Literature/
7. or/1-6
8. cochrane.ab.
9. embase.ab.
10. (psychlit or psyclit).ab.

11. (psychinfo or psycinfo).ab.
12. (cinahl or cinhal).ab.
13. science citation index.ab.
14. bids.ab.
15. cancerlit.ab.
16. or/8-15
17. reference list\$.ab.
18. bibliograph\$.ab.
19. hand-search\$.ab.
20. relevant journals.ab.
21. manual search\$.ab.
22. or/17-21
23. selection criteria.ab.
24. data extraction.ab.
25. 23 or 24
26. review.pt.
27. 25 and 26
28. comment.pt.
29. letter.pt.
30. editorial.pt.
31. animal/
32. human/
33. 31 not (31 and 32)
34. or/28-30,33
35. 7 or 16 or 22 or 27
36. 35 not 34
37. acne.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
38. 36 and 37
39. limit 38 to yr="2009 - 2011"

SIGN EMBASE systematic review filter:

Ovid EMBASE

1. exp Meta Analysis/
2. ((meta adj analy\$) or metaanalys\$).tw.
3. (systematic adj (review\$1 or overview\$1)).tw.
4. or/1-3
5. cancerlit.ab.
6. cochrane.ab.
7. embase.ab.
8. (psychlit or psyclit).ab.
9. (psychinfo or psycinfo).ab.
10. (cinahl or cinhal).ab.
11. science citation index.ab.
12. bids.ab.

13. or/5-12
14. reference lists.ab.
15. bibliograph\$.ab.
16. hand-search\$.ab.
17. manual search\$.ab.
18. relevant journals.ab.
19. or/14-18
20. data extraction.ab.
21. selection criteria.ab.
22. 20 or 21
23. review.pt.
24. 22 and 23
25. letter.pt.
26. editorial.pt.
27. animal/
28. human/
29. 27 not (27 and 28)
30. or/25-26,29
31. 4 or 13 or 19 or 24
32. 31 not 30
33. limit 32 to yr="2009 - 2011"
34. acne.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
35. 33 and 34

PubMed using Clinical Queries systematic review filter:

acne AND systematic[*sb*] AND 2010 : 2011[*edat*]

Cochrane Library and NHS Evidence - skin disorders:

acne

For PubMed and MEDLINE the search term used was "acne" rather than "acne vulgaris" to allow for In-Process records that had not yet been tagged to subject headings and that did not contain the term "vulgaris" in their title or abstract.

### **Identification of systematic reviews and inclusion criteria**

All citations found in the database searches were scanned by reading the titles and abstracts to identify guidelines and potential systematic reviews relevant to acne vulgaris and its treatment. A particularly careful analysis of the methods was made to

identify citations with a systematic review methodology. For all potential systematic reviews where there was still some doubt, the full texts were then read to ensure that they were indeed systematic reviews.

To determine systematic reviews, the definition of a systematic review from the [Glossary of Cochrane Collaboration Terms](#) was used:

“A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.”

Using this definition (which was also used in the recent [PRISMA statement](#) on reporting of systematic reviews), reviews that only searched one database have been included, but a note has been added to this effect.

The final decision on whether to include a citation as being a valid guideline or systematic review was made by Professor Hywel Williams, Clinical Lead for NHS Evidence - skin disorders and Co-ordinating Editor of the Cochrane Skin Group.

Lists of the relevant systematic reviews found by combining the results of the different searches are given in the [Results](#) page of the 2011 Annual Evidence Update on Acne Vulgaris. Also included at the end of the Results page is a list of excluded references that were identified as possible candidates in the initial sift of the search results, but were subsequently rejected on the grounds of incomplete evidence of a systematic review methodology.

### **Identification of other important studies**

This year an attempt has been made to identify other new important studies on acne vulgaris, with a focus on high quality randomised controlled trials (RCTs). These were identified from news alerts and the current awareness activities of the Annual Evidence Update team. In addition a search of PubMed was carried out with the Cochrane RCT filter, using the following search strategy:

```
((clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (dt[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (humans[mh]))) AND acne AND 2010 : 2011[edat]
```