Welcome to the third Annual Evidence Update on Acne Vulgaris produced by the NLH Skin Disorders Specialist Library, with the results of a search for new UK national guidelines, systematic reviews and randomised controlled trials published or indexed since the last Annual Evidence Update in March 2008. There is also a "what's new" analysis, discussing the new evidence and its implications for clinical practice.

Introduction by Professor Hywel Williams (Clinical Lead) and Dr Douglas Grindlay (Information Specialist), NLH Skin Disorders Specialist Library

Spot the new evidence
Welcome to the NLH Skin Disorders Specialist Library's 2009 Annual Evidence Update on Acne Vulgaris — a summary of all important evidence published or indexed since the 2008 Annual Evidence Update. Although the Skin Disorders Specialist Library is aimed at healthcare professionals, we hope that many people with acne will also find some of our material interesting.

So what's in our Annual Evidence Update on Acne?
The Annual Evidence Update is basically "what it says on the tin" — a haul of new UK national guidelines and evidence on acne that has appeared over the last year. The key resources that we found have been listed under relevant headings in our Results, with links to PubMed if you want to read more deeply into the original articles. For those of you who are interested, we also describe how we have searched and sorted the evidence included for this year's Annual Evidence Update in our Methodology.

In our other Annual Evidence Updates — on psoriasis, atopic eczema and skin cancer — we have only included systematic reviews in our search, since they offer an opportunity to look at all the evidence in a systematic fashion and because single randomised controlled trials (RCTs) can be hazardous when viewed in isolation. However, just as with our 2008 Annual Evidence Update on Acne, there seems to be a dearth of new systematic reviews. So rather than just discuss the one systematic review that we had found by our search date, we have again this year chosen to extend our search to RCTs and have found 25 new RCTs to be included in the Annual Evidence Update. Whilst it is not possible for us to do a Cochrane-style systematic review of all these new RCTs, we have provided a commentary and guide for busy health care professionals on what might be clinically important developments in our "What's new?" commentary, with suitable health warnings about the limitations of the data when viewed in isolation. We would like to express our thanks to Dr John Ingram (Specialist Registrar and UK Dermatology Clinical Trials Network Fellow) for helping us to put the "What's new" section together. It has to be said that the new evidence base for informing in acne treatment has been rather disappointing, dominated by industry-sponsored trials all trying to get a foothold in the "me too" market, but there are some pearls lurking in there too.

Filling important research gaps
We hope you enjoy this Annual Evidence Update, but if you feel that important questions about acne have not been answered, please send these to us using our DUETs submission form so that we can consider including them in DUETs, the UK Database of Uncertainties about the Effects of Treatments (http://www.library.nhs.uk/DUETs). Such uncertainties can be about side effects as well as treatment benefits, and they can also include over-the-counter products or non-drug interventions such as education. Documenting such uncertainties will help future researchers and funders to prioritise and fill those important gaps — and as you see from this year's Annual Evidence Update, there are lots of important gaps to fill.

Hywel Williams and Douglas Grindlay, 2nd March 2009
Searches were carried out to identify UK national guidelines, systematic reviews and randomised controlled trials relating to acne vulgaris (common acne) and its treatment that were published or indexed since the 2008 Annual Evidence Update on Acne Vulgaris. The date of the searches was 15th January, 2009.

Please note that the inclusion of citations in this list does not imply endorsement. The NLH Skin Disorders Specialist Library does not accept responsibility for the content or quality of included or excluded studies.

**UK guideline**


[Link to full text (PDF)]

**Systematic review**


[Link to PubMed Abstract]

**Causes and exacerbating factors**


[Link to PubMed Abstract]


[Link to PubMed Abstract]

**Patient education**


[Link to PubMed Abstract]

**Topical retinoids**


Pariser D, Colon LE, Johnson LA, Gottschalk RW. Adapalene 0.1% gel compared to tazarotene 0.1% cream in the treatment of acne vulgaris. Journal of Drugs in Dermatology. 2008;7(6 Suppl):s18-23.

Thiboutot D, Arsonnaud S, Soto P. Efficacy and tolerability of adapalene 0.3% gel compared to tazarotene 0.1% gel in the treatment of acne vulgaris. Journal of Drugs in Dermatology. 2008;7(6 Suppl):s3-10.

**Topical dapsone**


**Other single agent topical treatments**


**Topical combination treatments**


Link to PubMed Abstract

Tanghetti E, Kircik L, Wilson D, Dhawan S.  
Solubilized benzoyl peroxide versus benzoyl peroxide/clindamycin in the treatment of moderate acne.  
Link to PubMed Abstract

Thiboutot D, Zaenglein A, Weiss J, Webster G, Calvarese B, Chen D.  
An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients.  
Link to PubMed Abstract

**Oral isotretinoin**

Dhir R, Gehi NP, Agarwal R, More YE.  
Oral isotretinoin is as effective as a combination of oral isotretinoin and topical anti-acne agents in nodulocystic acne.  
Link to PubMed Abstract

Tsur L, Kozer E, Berkovitch M.  
The effect of drug consultation center guidance on contraceptive use among women using isotretinoin: a randomized, controlled study.  
Link to PubMed Abstract

**Oral antibiotics**

Ansarin H, Savabynasab S, Behzadi AH, Sadigh N, Hasanloo J.  
Doxycycline plus levamisole: combination treatment for severe nodulocystic acne.  
Link to PubMed Abstract

Toossi P, Farshchian M, Malekzad F, Mohtasham N, Kimyai-Asadi A.  
Subantimicrobial-dose doxycycline in the treatment of moderate facial acne.  
Link to PubMed Abstract

**Oral contraceptives**

Efficacy and safety of 3 mg drospirenone/20 mcg ethinylestradiol oral contraceptive administered in 24/4 regimen in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled trial.  
Link to PubMed Abstract

A combined oral contraceptive containing 3-mg drospirenone/ 20-microg ethinyl estradiol in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled study evaluating lesion counts and participant self-assessment.  
Link to PubMed Abstract
Link to PubMed Abstract

**Phototherapy**

Link to PubMed Abstract

**Laser treatment**

Link to PubMed Abstract

**Treatments for scarring and keloids**

Link to PubMed Abstract

**EXCLUDED CITATIONS**

Link to PubMed Abstract
(Provocation study in healthy volunteers)

Link to PubMed Abstract
(No indication of randomisation in abstract or full text)

Link to PubMed Abstract
(Full text indicates patients not randomised)

Leyden JJ, Wortzman M. A novel gel formulation of clindamycin phosphate-tretinoin is not associated with acne flaring.
Loesche C, Pernin C, Poncet M. Adapalene 0.1% and benzoyl peroxide 2.5% as a fixed-dose combination gel is as well tolerated as the individual components alone in terms of cumulative irritancy. European Journal of Dermatology. 2008;18(5):524-6. Link to PubMed Abstract (Post hoc analysis of three previously published RCTs)


2009 Annual Evidence Update on Acne Vulgaris - Commentary

"What's new?" — a tour of the 2009 Annual Evidence Update on Acne Vulgaris with the busy clinician in mind

Professor Hywel Williams, Clinical Lead for the NLH Skin Disorders Specialist Library and Coordinating Editor of the Cochrane Skin Group, and Dr John Ingram, Dermatology Registrar, University Hospital of Wales, Cardiff

Purpose of this commentary

Our task in this “What’s new” commentary on the 2009 Annual Evidence Update on Acne Vulgaris is to read through the citations in the Results, the haul of new evidence that we have found, and then to provide you with a summary of the 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 will also try to highlight some of the more subtle ways in which biases can creep into the reporting of trials, and we hope that you find some of these insights educational.

Our tour is necessarily superficial at times as it covers a lot of material – one guideline, one systematic review and 25 randomised controlled trials (RCTs). The evidence being reviewed is what was published or indexed in the period from the 2008 Annual Evidence Update on Acne Vulgaris up until
this year’s search date of 15th January, 2009. Our Annual Evidence Updates normally only include systematic reviews of the available evidence, but since we found only one systematic review for acne in the last year, we have also included individual RCTs to make it more interesting and informative for you. We include such RCTs with a strong “general health warning” that they may represent only a selected part of the totality of evidence that should ideally be picked up in future systematic reviews, and their conclusions may be modified by subsequent research [1].

In our commentary we have tried to pull out the key results from the included studies and then provide some comment on what they might mean for everyday clinical practice. The opinions expressed are ours, and you may have a different take on the evidence for good reasons. For those who wish to explore the evidence in more depth, we strongly recommend that you read the abstracts or the original papers to decide on the clinical utility of the studies for yourself – we have linked to the PubMed abstracts in the list of citations on the Results page to help you.

Our guide is written for all UK health care professionals who see people with acne, including dermatologists, associate specialists, specialist nurses, general practitioners, practice nurses, paediatricians, community pharmacists, and those in training. Our ultimate aim, as always, is to improve the quality of care for people with acne by ensuring that they benefit from treatments that are based on high quality evidence.

So let the evidence begin…

An updated UK Guideline

We have found just one new UK guideline actually, and then only a bit of it, as it refers to a section on acne treatment within an update of the British Association of Dermatology/British Photodermatology Group guidelines on the rapidly developing field of photodynamic therapy or PDT ([Link to full text - PDF]). The guideline developers have made good efforts to describe the quantity and strength of evidence of ALA and MAL photodynamic therapy for acne. Several RCTs have been published, but most are rather small, short-term, and susceptible to bias because of their unblinded nature. The studies do suggest that PDT can improve acne on the face and back (especially inflammatory lesions), but at the cost of considerable exfoliation and post-inflammatory pigmentation, which can be a big problem for patients. No specific guidance for practice is given, but instead a general concluding statement that “optimization of protocols, to sustain response while minimizing adverse effects, is awaited”. This seems like sensible advice which we interpret as “don’t use PDT for acne yet until better quality studies clarify the long-term benefits and trade off with adverse effects”. The area is crying out for a systematic review, and if any readers are interested, then suggestions can be made to the Cochrane Skin Group: [http://www.csg.cochrane.org/en/needreviews.html](http://www.csg.cochrane.org/en/needreviews.html)

Just the one systematic review, then

Although it was disappointing to find just one systematic review by our search date, this review by Barratt et al. ([Link to PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29388183/)) on investigator-assessed outcome measures on acne was excellent. We could not detect any clear biases in the review. However, it is not clear if the team only searched for English language studies (we suspect so from the reference list), and the search dates of the three databases searched are not given. A previous review had found 25 different methods for assessing acne severity and 19 for counting lesions [2]. The emphasis in this new systematic review was evaluation of nine newly proposed methods for investigator assessment of acne, to document the extent they had been constructed properly and whether they had been tested adequately for inter-rater reliability, responsiveness to change and validity. As in a recent systematic review on outcome measures for atopic eczema [3], the results were found to be a mess. None of the nine scales provided satisfactory statistical results for reliability, responsiveness and validity. Other aspects of the review by Barratt et al. were reliability of lesion counting, and how lesion counts do correlate to global investigator scores, with variable results, as well as some guidance on the pros and cons of lesion counting versus global grading systems. This systematic review has highlighted the need for future research, and signals a stop to others proposing yet more acne scales unless they have been developed and tested properly. It also highlights the difficulties in interpreting some of the existing scales in the clinic – for example, a 50% reduction in lesion count may sound impressive, but it may not impress the patient if they still have severe acne. The message for the busy clinician from this important systematic review is to (i) ask yourself what the outcome measure in a reported trial means to you, and (ii) check with the systematic review whether the tool is up to the job – chances are it may not be.
And so to the potentially hazardous single randomised controlled trials

**Causes and exacerating factors**

Short et al. ([Link to PubMed Abstract](#)) set out to address the commonly-held belief amongst teenagers that exercise may affect acne severity. They prospectively compared truncal acne counts in boys randomised to avoid or perform exercise, the latter group further divided into those who showered 1 hour or 4 hours later. The study illustrates the importance of standard deviation estimates in power calculations – 30 participants were recruited and no significant differences were observed, but the large standard deviations of the data demonstrated that the study was underpowered. It could, however, serve as a pilot to inform a larger RCT.

Another RCT by Smith et al. ([Link to PubMed Abstract](#)) looked at the fatty acid composition of triglycerides on the skin surface as a result of a low glycaemic load diet. This was done in a subgroup of patients previously reported in a duplicate publication that was highlighted in the commentary for last year’s Annual Evidence Update ([Link](#)). The authors do reference the previous two publications, but only indirectly. Perhaps not surprisingly, the subgroup analysis shows that those participants given a low glycaemic diet had changes in skin sebum (with increases in the ratio of saturated to monounsaturated fatty acids of skin surface triglycerides), when compared to controls. We are not sure what these changes mean clinically, although they do correlate with some of the lesion counts reported in the previous publications. A dietary approach for acne is interesting, but we would like to see the original study replicated elsewhere before recommending its application to clinical practice.

**Patient education**

A study by Koch et al. ([Link to PubMed Abstract](#)) looked at ways of improving knowledge about acne by randomising 101 adolescents who were waiting to see a dermatologist (21 from a pilot study and 80 in a revised larger study) to receive information either from a written handout or from a computer presentation which might have been considered to be “cool” by this age group. Knowledge compared to baseline improved in both groups after the intervention and was sustained one month later, but the study failed to show any superiority for the computer presentation. The abstract reports “At the 1-month follow-up, patients in the pilot study randomized to receive the computerized presentation still showed significant gain in knowledge from baseline (P < .05), while those in the handout group did not”, implying that one group had a sustained effect whilst the other did not. Such reporting is misleading – the correct test statistic (not highlighted in the abstract) is the difference in change of score between the two groups; this was not significant either immediately after the intervention or one month later (P=0.21 and P=0.30 respectively). The study might have been underpowered, but it certainly did not provide any evidence to support investment and use of a new computer presentation, so we will be continuing with our good old-fashioned and “uncool” written handouts for now.

**Topical retinoids**

This section is dominated by a recent supplement in the *Journal of Drugs in Dermatology*. In many cases, such supplements can seem more a vehicle for drug company marketing than a significant advance in the scientific literature, with emphasis on “me too” products assessed in non-inferiority studies citing better tolerability. This is rather the case for three commercial studies examining adapalene gel. Two of the studies, by Pariser et al. ([Link to PubMed Abstract](#)) and Gold et al. ([Link to PubMed Abstract](#)), are “salami slices” of the same trial. This 12 week trial contained three arms: adapalene 0.1% gel, tazarotene 0.1% cream, and six weeks of adapalene 0.1% gel followed by six weeks of tazarotene 0.1% cream (“switch therapy”). The paper by Pariser et al. reports the comparison of adapalene gel and tazarotene cream, while Gold et al. consider the comparison of adapalene gel and switch therapy. In both cases, adapalene gel was “not inferior” to the comparator and had a better tolerability profile. The drug company is to be applauded for giving prospective details of the study on a clinical trials register, ClinicalTrials.gov [4]; however, details of the 15% non-inferiority margin are not included so we cannot be sure if this was chosen prospectively. Neither publication references the other and, given that it would have been straightforward to report the results of all three arms in a single publication, we feel that this represents a form of covert duplicate publication that could artificially raise the impact of the study [5]. Interestingly, the study is registered as a single trial on the clinical trials register.

The challenge of tazarotene by adapalene continues in the study by Thiboutot et al. ([Link to PubMed Abstract](#)), who compared a higher concentration of adapalene gel, 0.3%, with tazarotene 0.1% gel. Again, the majority of the authors are drug company employees associated with adapalene. The trial may have been performed in response to a previous study that reported greater efficacy of tazarotene.
0.1% gel compared to adapalene 0.1% gel [6]. The 0.3% adapalene gel was found “not inferior” in efficacy to tazarotene and was better tolerated. However, the bottom line is that both products are quite well tolerated, with trial discontinuation due to adverse events of the order of 1-2%, and so from a doctor’s and patient’s perspective the debate is perhaps not terribly important. The most surprising aspect of the vehicle-controlled study of adapalene 0.1% gel by Kawashima et al. (Link to PubMed Abstract) in Japanese patients is that topical retinoids, at the time of this article’s publication, were still not licensed in Japan. We suspect that this study was performed to aid in the licence application process and, unsurprisingly, it found that adapalene gel is superior to vehicle for acne in Japanese patients.

**Topical dapsone**

Two publications evaluate 5% topical dapsone gel for acne. The first, an industry-funded study by Piette et al. (Link to PubMed Abstract) evaluated topical dapsone versus vehicle in 64 people with acne who also had G6PD deficiency, by means of a crossover design with a two week washout period. Reassuringly, no significant haemolysis was shown in the topical dapsone group after two weeks of use, with a mean decrease in haemoglobin of 0.32g/dl (the largest reduction being 1.5 g/dl in any treated individual). No efficacy data were presented.

The second study, by Raimer et al. (Link to PubMed Abstract), was also company-funded and described two RCTs in a total of 1,125 people with acne. Two studies were presumably needed for FDA licensing. The combined study results showed that topical dapsone does have an effect on acne – the proportion of participants with a global acne score of 0 (none) or 1 (minimal) was 40.1% in the dapsone group and 28.2% in the vehicle gel-only group. Another way of putting this is that on average eight people with acne would need to be treated with the dapsone gel in order to see one extra “success” when compared with gel alone. The problem is that few of us use vehicle gel in clinical practice, so it is difficult to guess how this new product compares to the thirty or so existing active acne products listed in the BNF [7]. The two studies also look suspiciously similar to two others that were published in 2007 [8, 9].

**Other single agent topical treatments**

Given the increasing problem of antibiotic resistance, it was very encouraging to learn of a potential new non-antibiotic topical therapy, taurine bromamine cream. This has anti-inflammatory and antioxidant properties and also exerts bactericidal activity in vitro against P. acnes. Marcinkiewicz et al. (Link to PubMed Abstract) reported a pilot study of 40 patients randomised to receive taurine bromamine cream or clindamycin 1% gel for six weeks. In both groups the total lesion count was reduced by about two-thirds. It would be interesting to see how the new product performs against benzoyl peroxide, given that this is probably the most widely used topical agent in this class. There are a couple of caveats to this study. First, patients with comedonal acne were excluded and second, the study was not double-blind as reported, because patients would have been able to distinguish the cream from the gel comparator.

The study by Sharquie et al. (Link to PubMed Abstract) from Baghdad, Iraq comparing 2% tea lotion with 5% zinc sulphate solution certainly caught our attention. A check of the paper confirmed that tea lotion, rather than tea tree oil, was under investigation. Zinc sulphate solution is an unusual comparator but has been used in other skin conditions for its anti-inflammatory effect. There was greater improvement for the 2% tea lotion subjects but only within-group comparisons were made. Without the correct between group comparison, it is difficult to say whether the observed changes may have been due to the natural history of disease flares. Too early to put those tea bags on your spots just yet then, although progression to a formal placebo-controlled RCT would be nice.

**Topical combination treatments**

Combination therapies that contain two or more active topical substances seem to have become more popular over recent years, as they may offer slightly better efficacy when compared with monotherapy. With so many monotherapies on the market, the potential number of possible combinations is bewildering. Four new RCTs deal with a variety of combination therapies. The first RCT by Goshal et al. (Link to free full text) described a comparison of topical adapalene gel versus oral azithromycin versus a combination of the two for 12 weeks, in 61 Indian participants with inflammatory acne. There was no evidence of a difference in treatment response for inflammatory lesions between the three groups. The authors did state that non-inflammatory lesion reduction was greater in the two groups using topical adapalene, but no data were given – just a bald P value and a selection of clinical images. The study is poorly reported, and encouraging more use of oral antibiotics is probably undesirable if we are to reduce bacterial resistance in the community.
An RCT from Thailand by Ruamrak et al. (Link to PubMed Abstract) evaluated the combination of an ascorbic acid derivative (5% sodium ascorbyl phosphate lotion) plus 0.2% retinol cream versus each agent used singly in 45 young adults with moderate acne vulgaris. Although described as double blind, it is likely that irritation from the retinol might have cause some unblinding, and only 30 participants were included in the final comparisons at week 8. They reported that the combination product was better than either agent alone, with a 63% reduction of lesion count in the combination product compared with 49% in either monotherapy alone.

A poorly reported crossover RCT of 23 acne patients by Tanghetti et al. (Link to PubMed Abstract) claimed that a solubilized form of benzoyl peroxide gel used twice daily results in better efficacy than a combination product containing 5% benzoyl peroxide and 1% clindamycin phosphate. Further scrutiny of the results suggests that superior efficacy was only shown for non-inflammatory lesions, which was not specified as a primary outcome amongst the eight outcomes listed.

The last RCT in this section, by Thiboutout et al. (Link to PubMed Abstract), is also worthy of closer scrutiny. This industry-funded paper includes the results of two identical RCTs conducted mainly in the US that were used for FDA licensing approval. The two studies compared a new formulation of clindamycin phosphate 1.2% combined with benzoyl peroxide 2.5% in a gel against each component as monotherapy and vehicle gel alone (i.e. four groups). Good points of the studies include the large combined sample size (2,813 patients with moderate to severe acne), high follow-up rates, and an intention to treat analysis. However, concealment of the randomisation sequence was not well described, and blinding is also suspect, given that benzoyl peroxide can bleach hair and clothing. It is also worth noting that the monotherapy active comparators were used only once daily and not twice daily as is recommended in normal clinical practice, thereby enhancing the chances of finding a beneficial effect of the combined product. The study showed that the combination product was better than either agent alone when used once daily, yet the magnitude of benefit was modest (number needed to treat 12 compared with each single agent alone). Although the combined studies have probably played a pivotal role for licensing purposes, we are unsure how these studies inform clinical practice. Few clinicians use once daily topical monotherapy in the UK, and it is unclear whether this “me too” product offers any advantage over an existing very similar combination product that is already available in the UK, which contains clindamycin phosphate 1% and benzoyl peroxide 5%. It is also possible that prescribing the two components separately in generic form (one in the morning and the other in the evening) might achieve equivalent results at much less cost to the NHS.

**Oral isotretinoin**

Dhir et al. (Link to PubMed Abstract) report an Indian study that compared oral isotretinoin with a combination of oral isotretinoin and topical therapy, claiming equivalence between the two groups. With only 60 recruited patients (of whom 50 completed the treatment course and 35 completed six months of follow up), the study was hopelessly underpowered for demonstrating equivalence. Pregnancy prevention for women of child-bearing age prescribed oral isotretinoin remains a thorny subject, so we were very pleased to find an Israeli RCT of an intervention to minimise such a risk. Tsur et al. (Link to PubMed Abstract) inserted a note with the contact details of a drug consultation centre in each isotretinoin package that encouraged patients to make contact for further information. The 108 women of reproductive age who did so were all given information about teratogenicity and the need for contraception. The “active” group had further written information posted to them as well as mobile telephone text messages, whereas no further advice was given to the control group. Unfortunately the intervention did not increase the use of contraception. The headline figures make rather alarming reading: only half of patients used any form of contraception, only two women used two methods of contraception, and pre-treatment and during-treatment pregnancy tests were performed in 20% and 5% of the patients respectively, although many of these women were not sexually active.

**Oral antibiotics**

The study by Ansarin et al. (Link to PubMed Abstract) is particularly interesting because it seeks to provide data on a very pertinent question: what treatment should be given for a person with severe acne in whom oral isotretinoin is contraindicated? The authors performed a RCT in 60 Iranian patients (mostly women) with severe nodulocystic acne to assess the synergistic effect of levamisole in addition to doxycycline. Participants were randomised to receive either doxycycline 100mg daily plus oral levamisole 2.5 mg/kg/week, or doxycycline 100mg daily plus a weekly placebo for 6 months. The primary endpoint was not clearly stated but is presumed to be percentage decrease in total lesion count; data for individual lesion subtypes were also given. At six months, total lesion count had decreased by 80% in the combined therapy group and 69% in the doxycycline group (P=0.001), and
significant improvement was present two months after commencing therapy. One patient in the levamisole group had to discontinue due to reversible leukopaenia – apparently this occurs in 1-2% of patients. All trial subjects required fortnightly blood tests. It is easy to be seduced by impressive P values, but the modest reduction of 11% in total lesion count would possibly not represent a meaningful benefit to a patient, particularly when weighed against the risk of serious side effects.

In another Iranian study, Toossi et al. (Link to PubMed Abstract) compared low dose oral doxycycline 20mg twice daily with the standard doxycycline dose of 100mg once per day in 100 patients with moderate acne, 71 of whom completed three months of treatment. This was essentially a non-inferiority study, but a non-inferiority margin was not pre-specified and the trial, which concluded that there was no difference in efficacy between the two doses, was underpowered and therefore inconclusive.

Oral contraceptives

Three papers were found reporting on RCTs that evaluated the efficacy and safety of a new oral contraceptive containing 3 mg drospirenone (an anti-androgen progestin) combined with 20 mcg ethinylestradiol, against placebo. It took a little while for us to work it out, but it is now clear that the three papers refer to two very similar RCTs conducted by the manufacturer for licensing purposes. The study by Koltun et al. (Link to PubMed Abstract) looks as if it is the first paper, with main outcome data reported on 534 women. The odds of improvement (clear or almost clear on the investigator global assessment scale) were 4.3 times greater in the active treatment group. Rate ratios rather than odds ratios should have been used, as odds ratios will overestimate risk when event rates are common [10]. The relative benefit sounds impressive, until one looks at the actual proportion of women who were deemed to be clear or almost clear by investigators - just 16% of women achieved such a status in the active group. The same team (with Lucky and Koltun swapping places as first author) then published the same study again (Link to PubMed Abstract), this time claiming to focus on patient assessed outcomes, although they presented the main outcomes in several different ways again. The second, almost identical, RCT by Maloney et al. (Link to PubMed Abstract) of 538 women showed similar results including a reasonable safety profile. So this new oral contraceptive pill does help women with acne more than a placebo, but not a lot, and it remains unclear whether the addition of drospirenone offers further benefits above traditional oestrogen oral contraceptive pills alone.

Phototherapy, photodynamic therapy & laser treatment

Development of therapies in this area might offer very useful, non-invasive treatments that reduce the potential for antibiotic resistance. On the flip side, such treatment approaches tend to be expensive, available in only a few centres with the appropriate technology, labour intensive, and lacking long-term recurrence rate data. We found two new RCTs. Sami et al. (Link to PubMed Abstract) compared pulsed dye laser with intense pulsed light or blue-red combination light-emitting diode phototherapy. The study was small, with only 15 patients in each group and there was no sham control group. Pulsed dye laser was most effective, requiring four treatment sessions for disease remission, but there were no data on the duration of remission.

Haedersdal et al. (Link to PubMed Abstract) compared long-pulsed dye laser (LPDL) treatment to long-pulsed dye methylaminolevulinic acid photodynamic therapy (MAL-LPDL) in 15 patients. MAL was applied to one side of the face for 3 hours and then the whole face was treated with long-pulsed dye laser to allow a side-to-side comparison. The MAL-LPDL side did best, with an 80% reduction in inflammatory lesions at twelve weeks compared to 67% for the control group. These results seem fairly impressive but three treatments were required at two week intervals, each of which involved 580 laser pulses. Moderate to severe pain was frequently reported. Also, we are aware that MAL took up a considerable proportion of our Departments’ drug budgets last year, and the cost of this treatment should not be overlooked. This type of treatment modality still does not seem to be a practical or cost-effective option for general use at present.

Treatments for scarring and keloids

Keloids can become a significant problem in acne, so we have included a small RCT by Berman et al. (Link to PubMed Abstract) that compared etanercept injections (which might block the profibrotic actions of TNF alpha) against triamcinolone injections for the treatment of keloids. The triamcinolone group improved in 11 out of 12 keloid parameters compared with 5 out of 12 parameters for etanercept, although the differences between the two groups were not statistically significant. The study is essentially inconclusive, although it perhaps rules out a very dramatic beneficial effect of etanercept on keloid regression.
The bottom line – will we be changing our practice on acne?

We were very disappointed with the new evidence on acne treatments over the last year in terms of the potential of those studies to inform clinical practice. The RCTs seem to be dominated by industry studies fronted by conflicted clinicians evaluating “me too” products with marginal benefits, in a market crowded with many existing therapies, none of which work very well. Quality of reporting is, with a few exceptions, poor, and most studies have been too small to exclude even large treatment differences. There is a lack of declaration of primary outcomes, over-egging of significant findings in abstracts, and overt and covert duplicate publication and “salami” publication. Like we found last year, there is a lack of active comparator studies, along with examples of using active comparators at a suboptimal frequency. There is also a lack of long-term data, and patient-reported outcomes and quality of life data are scarce.

Perhaps our disappointment was our fault for agreeing to look at single RCTs rather than systematic reviews. The one systematic review was informative and pointed to the desperate need to sort out the mess of outcome measures for acne, by suggesting a minimum list of reliable, responsive, valid outcomes that mean something to clinicians and patients. Who will revive these research needs for acne? If only there was another Bill Cunliffe out there...

In relation to whether the evidence would change our clinical practice in any way, the answer has to be “not very much”. It is likely that we will:

• Not recommend photodynamic therapy as an acne therapy until better studies are done that show clear benefits and minimal post inflammatory pigmentation
• Treat the many objective and scientific-sounding outcome measures that are used in clinical trials with a pinch of salt until better validation studies are done
• Look forward to more independent studies of low glycaemic load and other dietary interventions as a means of reducing acne severity
• Continue to provide written information about acne to our acne patients
• Keep our eyes open for studies that compare topical dapsone against other active commonly used therapies
• Continue to use current combination products such as clindamycin with benzoyl peroxide, until new products demonstrate clear advantages in terms of efficacy, tolerability and cost
• Not use oral levamisole in combination with oral antibiotics
• Eagerly await further trials that compare a combination of drospirenone and 20 mcg ethinylestradiol against other active acne therapies, rather than placebo
• Continue to stress the importance of pregnancy prevention in women of reproductive age who are taking isotretinoin
• Keep an open mind with regards to phototherapy and laser therapy, especially if good long term data emerge and costs come down
• Not use etanercept for the treatment of keloids
• Continue to be confused about which treatments are best for acne because so few treatments have been compared directly to one another on a level playing field [11].

John Ingram and Hywel Williams, 2nd March 2009

Additional references

   Link to PubMed Abstract
   Link to PubMed Abstract
   Link to PubMed Abstract
   Link to PubMed Abstract


### 2009 Annual Evidence Update on Acne Vulgaris - Methodology

A literature search was carried out to identify UK national guidelines, systematic reviews and randomised controlled trials (RCTs) relating to acne vulgaris (common acne) that have been published or indexed since the last Annual Evidence Update in March 2008. The results are the NLH Skin Disorders Specialist Library's 2009 Annual Evidence Update on Acne Vulgaris.

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

#### Search period

The search for the 2009 Annual Evidence Update on Acne Vulgaris was for citations published or indexed in 2007-9 and not included in the 2008 Annual Evidence Update.

In the case of PubMed, the search was refined by searching for records indexed in the database in 2008 and 2009 (using the "edat" command), which would find any citations published before 2007 but indexed late and not found in last year’s search.

All the searches were carried out for the last time on 15th January, 2009.

#### Databases and search strategies

*PubMed*

`acne AND 2008 : 2009[edat]`

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

1. `acne vulgaris.mp. [mp=title, original title, abstract, name of substance word, subject heading word]`
2. `limit 1 to yr="2007 - 2009"`

*Ovid EMBASE*

1. `acne vulgaris.mp. [mp=title, original title, abstract, name of substance word, subject heading word]`
2. `limit 1 to yr="2007 - 2009"`

*NLH Skin Disorders Specialist Library*

`acne`
Note: For PubMed 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 randomised controlled trials and inclusion criteria

All citations found in the database searches were scanned by reading the titles and abstracts to identify potential systematic reviews and randomised controlled trials relevant to acne vulgaris. Where there was doubt, the full texts were then read if available to ensure that they were indeed systematic reviews or randomised controlled trials.

To reduce the chances of missing eligible citations while scanning titles and abstracts, the search in PubMed was first of all combined with the PubMed Clinical Queries systematic review filter to find potential systematic reviews using the following search string:

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.”

The definition of randomised controlled trials used to guide selection was also taken from the Glossary of Cochrane Collaboration Terms:
“An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body).”

Healthy volunteer studies were excluded as being insufficiently relevant for everyday clinical practice. The final decision on whether to include a citation as being a valid systematic review or randomised controlled trial, was made by Professor Hywel Williams, Clinical Lead for the NLH Skin Disorders Specialist Library and Co-ordinating Editor of the Cochrane Skin Group.

A list of candidate citations that were excluded in the final appraisal is given at the end of the Annual Evidence Update results page, along with the reasons for exclusion.

Systematic reviews on acne vulgaris - INDEX PAGE

This is the index page for a mapping by topic of systematic reviews on acne vulgaris published from 1999 onwards (the last search date for the comprehensive review of management of acne by Lehmann et al., 2001). The systematic reviews were found in the searches for the Annual Evidence Updates on Acne Vulgaris in 2007, 2008, 2009, 2010 and 2011.

Systematic reviews on acne vulgaris - Epidemiology

This is a mapping by topic of systematic reviews on the epidemiology of acne vulgaris that have been published from 1999 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Acne Vulgaris. The links given are to the PubMed abstract or free full text where available.

<table>
<thead>
<tr>
<th>Diet</th>
<th>2009</th>
<th>Diet and acne: a review of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2005</td>
<td>A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight</td>
</tr>
<tr>
<td>Hygiene</td>
<td>2005</td>
<td>A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight</td>
</tr>
<tr>
<td>Sunlight</td>
<td>2005</td>
<td>A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight</td>
</tr>
<tr>
<td>Outcome</td>
<td>2009</td>
<td>Outcome measures in acne vulgaris: systematic review</td>
</tr>
</tbody>
</table>
### Systematic reviews on acne vulgaris - Topical treatments

This is a mapping by topic of systematic reviews on topical treatments for acne vulgaris that have been published from 1999 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Acne Vulgaris. The links given are to the PubMed abstract or free full text where available.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical retinoids</td>
<td>2009</td>
<td>Do topical retinoids cause acne to “flare”?</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Treatment of acne vulgaris</td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td>Topical antibiotics</td>
<td>2005</td>
<td>Treatment of acne with topical antibiotics: lessons from clinical studies</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Treatment of acne vulgaris</td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td>Antibiotic resistance</td>
<td>2003</td>
<td>Is antibiotic resistance in cutaneous propionibacteria clinically relevant?: implications of resistance for acne patients and prescribers</td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>2004</td>
<td>Treatment of acne vulgaris</td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>2010</td>
<td>Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne</td>
</tr>
<tr>
<td></td>
<td>2009</td>
<td>Advancement in benzoyl peroxide-based acne treatment: methods to increase both efficacy and tolerability</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Treatment of acne vulgaris</td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td>Cleansers</td>
<td>2005</td>
<td>A systematic review of the evidence for ‘myths and misconceptions’ in acne management: diet, face-washing and sunlight</td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td>Dapsone</td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td>Glycolic acid</td>
<td>None found</td>
<td></td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td>Sulphur</td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td>Zinc treatments</td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td>Combination therapies</td>
<td>2010</td>
<td>Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Treatment of acne vulgaris</td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>Management of acne</td>
</tr>
</tbody>
</table>

### Systematic reviews on acne vulgaris - Systemic treatments

This is a mapping by topic of systematic reviews on systemic treatments for acne vulgaris that have been published from 1999 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Acne Vulgaris. The links given are to the PubMed abstract or free full text where available.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tetracyclines</td>
<td>2008</td>
<td>Efficacy of tetracyclines in the treatment of acne vulgaris: a review</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Safety of doxycycline and minocycline: a systematic review</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>Use of macrolides and tetracyclines for chronic inflammatory diseases</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Treatment of acne vulgaris</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>Minocycline for acne vulgaris: efficacy and safety (Cochrane Review)</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>Acne: comparing hormonal approaches to antibiotics and isotretinoin</td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>Management of acne</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>Minocycline-induced lupus. A systematic review</td>
</tr>
<tr>
<td>Other oral antibiotics</td>
<td>2005</td>
<td>Use of macrolides and tetracyclines for chronic inflammatory diseases</td>
</tr>
</tbody>
</table>
Systematic reviews on acne vulgaris - Physical therapies
This is a mapping by topic of systematic reviews on physical therapies for acne vulgaris that have been published from 1999 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Acne Vulgaris. The links given are to the PubMed abstract or free full text where available.
### Systematic reviews on acne vulgaris - Complementary and alternative therapies

This is a mapping by topic of systematic reviews on complementary and alternative therapies for acne vulgaris that have been published from 1999 onwards. The systematic reviews were found in the searches for the Annual Evidence Updates on Acne Vulgaris. The links given are to the PubMed abstract or free full text where available.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscellaneous</td>
<td>2010</td>
<td>Botanicals in dermatology: an evidence-based review</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Topical and oral CAM in acne: a review of the empirical evidence and a consideration of its context</td>
</tr>
<tr>
<td>Tea tree oil</td>
<td>2010</td>
<td>Botanicals in dermatology: an evidence-based review</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>Topical and oral CAM in acne: a review of the empirical evidence and a consideration of its context</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>Tea tree oil: a systematic review of randomized clinical trials</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>2009</td>
<td>Evaluation of therapeutic effect and safety for clinical randomized and controlled trials of treatment of acne with acupuncture and moxibustion</td>
</tr>
</tbody>
</table>