

2010 Annual Evidence Update on Acne Vulgaris

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Welcome to the fourth **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 2009. There is also a "what's new" analysis, discussing the new evidence and its implications for clinical practice.

2010 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 2010 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 least year since our [2009 Annual Evidence Update](#). Although NHS Evidence - skin disorders is aimed at healthcare professionals, we hope that many people who have acne will also find some of the information of interest.

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](#)).

For the last two years, we have extended the searches for our Annual Evidence Update on Acne Vulgaris to randomised controlled trials (RCTs), as only one or two systematic reviews were being published each year. However, this exercise threw up problems in trying to assess issues of quality and reporting, making it difficult to rely on the RCTs as a source of high quality evidence to inform clinical practice, in the absence of a full systematic review of the evidence.

This year we have been gratified to find nine new systematic reviews on the topic of acne, so we have decided to limit the Annual Evidence Update results to new guidelines and systematic reviews, and not include the slightly more hazardous single RCTs. There is still plenty of interesting material for the clinician to read about and we hope that this increase in the number of systematic reviews published in acne will continue in the future.

The new evidence that we have found has been listed under relevant headings on our [Results](#) page, with links to PubMed or free full text, if available, if you want to delve more deeply into the original articles.

We also provide our usual ["What's new" commentary](#), intended as a guide for the busy health care professionals on the significance of the new evidence for clinical practice. We would like to express our thanks to Dr Emma Smith, Specialist Registrar and UK Dermatology Clinical Trials Network Fellow, for helping us to put the "What's new" section together.

Since last year's Annual Evidence Update we have put together a set of uncertainties about acne vulgaris in DUETs, the UK Database of Uncertainties about the Effects of Treatments ([Link here](#)). Do take a look. This list includes uncertainties identified in systematic reviews and submitted by health professionals and patients.

2010 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 [2009 Annual Evidence Update on Acne Vulgaris](#).

The result of this search is the **2010 Annual Evidence Update on Acne Vulgaris** from NHS Evidence - skin disorders.

Search period

January 2008 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 2009). All the searches were carried out for the last time on 8th February, 2010.

Sources Searched

The following sources were searched:

- Ovid MEDLINE
- Ovid EMBASE
- PubMed
- 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, arranged by topic. Within each topic, the citations are presented in reverse chronological order, i.e. most recent first. 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 number of citations were identified as possible systematic reviews for the Annual Evidence Update in the initial sift of the search results, but were subsequently excluded on the grounds of a lack of a clear systematic review methodology. These citations are listed at the end of this page under the heading "Excluded references".

UK Guidelines

Acne Vulgaris, Clinical Knowledge Summaries (CKS)

[Link to full text](#)

Note: Published June 2009 — converted from PRODIGY guidance to CKS topic structure. The evidence-base has been reviewed in detail, and recommendations are more clearly justified and transparently linked to the supporting evidence. There are no major changes to the recommendations.

Diet and acne

Spencer EH, Ferdowsian HR, Barnard ND.

Diet and acne: a review of the evidence.

International Journal of Dermatology 2009 Apr;48(4):339-47.

[Link to PubMed \(no abstract\)](#)

Note: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects (DARE), PsycInfo and CINAHL searched.

Benzoyl peroxide

Fakhouri T, Yentzer BA, Feldman SR.

Advancement in benzoyl peroxide-based acne treatment: methods to increase both efficacy and tolerability.

Journal of Drugs in Dermatology 2009 Jul;8(7):657-61.

[Link to PubMed abstract](#)

Note: Only PubMed searched.

Topical retinoids

Yentzer BA, McClain RW, Feldman SR.

Do topical retinoids cause acne to "flare"?

Journal of Drugs in Dermatology 2009 Sep;8(9):799-801.

[Link to PubMed abstract](#)

Note: Only PubMed and Google searched.

Oral isotretinoin

Kontaxakis VP, Skourides D, Ferentinos P, Havaki-Kontaxaki BJ, Papadimitriou GN.

Isotretinoin and psychopathology: a review.

Annals of General Psychiatry 2009 Jan 20;8:2.

[Link to PubMed abstract](#)

[Link to full text](#)

Note: MEDLINE and EMBASE searched.

Hormones and anti-androgens

Arowajolu AO, Gallo MF, Lopez LM, Grimes DA, Garner SE.

Combined oral contraceptive pills for treatment of acne.

Cochrane Database of Systematic Reviews 2009 Jul 8;(3):CD004425.

[Link to full text](#)

Note: Update of 2007 Cochrane Review.

Brown J, Farquhar C, Lee O, Toomath R, Jepson RG.

Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne.

Cochrane Database of Systematic Reviews 2009 Apr 15;(2):CD000194.

[Link to full text](#)

Note: Update of 2003 Cochrane Review.

Laser and light therapies

Hamilton FL, Car J, Lyons C, Car M, Layton A, Majeed A.

Laser and other light therapies for the treatment of acne vulgaris: systematic review.

British Journal of Dermatology 2009 Jun;160(6):1273-85.

[Link to PubMed abstract](#)

[Link to DARE abstract](#)

Note: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, PsycInfo, LILACS, ISI Science Citation Index and Dissertation Abstracts International searched.

Photodynamic therapy

Riddle CC, Terrell SN, Menser MB, Aires DJ, Schweiger ES.

A review of photodynamic therapy (PDT) for the treatment of acne vulgaris.

Journal of Drugs in Dermatology 2009 Nov;8(11):1010-9.

[Link to PubMed abstract](#)

Note: Only PubMed searched.

Taylor MN, Gonzalez ML.

The practicalities of photodynamic therapy in acne vulgaris.

British Journal of Dermatology 2009 Jun;160(6):1140-8.

[Link to PubMed abstract](#)

Note: MEDLINE, PubMed and EMBASE searched.

EXCLUDED REFERENCES

Li B, Chai H, Du YH, Xiao L, Xiong J.

Evaluation of therapeutic effect and safety for clinical randomized and controlled trials of treatment of acne with acupuncture and moxibustion [in Chinese].

Zhongguo Zhen Jiu 2009 Mar;29(3):247-51.

[Link to PubMed abstract](#)

Note: The English abstract indicates this is a systematic review that searched the Cochrane Library, CBM databank and CNKI databank. However, the full text is in Chinese and we were unable to obtain a copy to confirm the methodology and conclusions in time for the Annual Evidence Update.

Piérard GE, Piérard-Franchimont C, Paquet P, Quatresooz P.

Spotlight on adapalene.

Expert Opinion on Drug Metabolism & Toxicology 2009 Dec;5(12):1565-75.

[Link to PubMed abstract](#)

Note: Abstract states systematic review carried out, but full text has no methodology.

Sagransky M, Yentzer BA, Feldman SR.

Benzoyl peroxide: a review of its current use in the treatment of acne vulgaris.

Expert Opinion on Pharmacotherapy 2009 Oct;10(15):2555-62.

[Link to PubMed abstract](#)

Note: Insufficient indication of systematic review methodology.

Sardana K, Garg VK.

Efficacy of low-dose isotretinoin in acne vulgaris.

Indian Journal of Dermatology, Venereology and Leprology 2010 Jan-Feb;76(1):7-13.

[Link to PubMed abstract](#)

[Link to full text](#)

Note: No new systematic review search, just meta-analysis of existing, historic data up to 1997 from two already published sources.

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 May;60(5 Suppl):S1-50.

[Link to PubMed abstract](#)

Note: Expert opinion/consensus document, with no methodology given.

2010 Annual Evidence Update on Acne Vulgaris - Commentary

"What's new?" — a tour of the 2010 Annual Evidence Update on Acne Vulgaris with the busy clinician in mind

Professor Hywel Williams, Clinical Lead for NHS Evidence - skin disorders and Co-ordinating Editor of the Cochrane Skin Group, and Dr Emma Smith, Dermatology Registrar, University Hospital of Wales, Cardiff.

What this guide is all about

Our task in this "What's new" section of the 2010 Annual Evidence Update on Acne Vulgaris from NHS Evidence - skin disorders is to read through all the new systematic review evidence we have found and listed 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 and educational.

In last year's Annual Evidence Update ([Link](#)), we only had one systematic review to look at, so we also included individual randomized controlled trials (RCTs). That exercise was tricky as many of the individual trials could not be used to generate clear clinical messages because of poor design or reporting. But this year, we have one guideline and nine systematic reviews covering everything from good old fashioned benzoyl peroxide to light therapies for acne, so there should be at least something there to interest everyone.

The opinions expressed in this brief commentary 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 original papers linked to in the [Results](#) to decide on the clinical utility of the studies for yourself.

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, and community pharmacists and for those that are in training. Our ultimate aim, as always, is to improve the quality of care for people who have acne by ensuring that they benefit from treatments that are based on high quality external evidence.

Let the evidence begin...

UK Guidelines

Just one guideline emerged in the last year on acne ([Link to full text](#)), produced by the CKS (Clinical Knowledge Summaries) team and funded by NICE through NHS Evidence. This resource has been derived from the previous PRODIGY guidance and is primarily directed at primary care. The guidance was last updated in August 2009 and is updated as new important studies become available.

We liked this guidance. It is set out in a clear and helpful way, covering practical areas such as assessing a person with acne, and scenarios such as mild, moderate and severe acne, along with detailed prescribing advice. The summary also provides helpful advice on what to cover in the consultation of a young person with acne in terms of self-care and dispelling myths, rather than just going straight into drug therapies. The link between treatment recommendations and the evidence is clear, and a lot of work has gone into compiling evidence based on quality-appraised systematic reviews where possible. We did not see any “new” evidence in the guideline that would change our current practice in any way, but the guidance reflects current thinking, and those in primary care and training in dermatology are likely to find it most useful.

Diet and acne

Many of us tell our patients that acne has nothing to do with diet. Spencer *et al.* ([Link to PubMed - no abstract](#)) undertook a broad systematic review of various dietary influences in acne. They did a thorough search of six databases, and included observational studies (15 cross-sectional studies, two case-controlled studies and four cohort studies) as well as six randomized controlled trials. They also included non-English studies, which is a good sign of a thorough review. They concluded that there was some evidence from observational studies and trials that dairy products (especially milk) are associated with an increased risk of acne and with more severe acne, and that a low glycaemic load diet might improve acne. They concluded that the old question about chocolate worsening acne had not been answered.

Despite the thorough searches, the review was let down by lack of a thorough assessment of study quality. Most of the observational studies they evaluated were rather weak in design and used self-reported data on diet and acne. We have already commented in the [2008](#) and [2009](#) acne Annual Evidence Update commentaries on one trial of a low glycaemic diet in acne carried out by Smith and colleagues in Australia that was published in duplicate [1, 2], followed by a third publication that evaluated sebum production in a subgroup of the same trial [3]. Interestingly, Spencer *et al.* in their systematic review have included two of the reports in their summary as if they were two separate trials, rather than one subset of the other. This just highlights the problem with duplicate publications getting disproportionate impact [4].

Overall, the review added little to a previous systematic review on “myths and misconceptions” in acne [5] that we found in our [2007 Annual Evidence Update](#), despite a more thorough search and narrower focus on diet. Our take-home message for both reviews is clear—don’t be so dogmatic in telling patients that acne has little to do with diet. Better research is needed to see whether things like milk or chocolate can make acne worse and whether certain diets can make it better.

Benzoyl peroxide

Giving topical and oral antibiotics for long periods to young people with acne may be a great way of promoting bacterial resistance in individuals and in the community. Fakhouri *et al.* in their 2009 review ([Link to PubMed abstract](#)) revisit good old fashioned benzoyl peroxide (BP), with its proven efficacy and safety record as a possible saviour for over-reliance on antibiotics. They specifically wished to see whether there are better ways of using BP to increase efficacy and overcome problems with irritancy. Based on a search of just PubMed that revealed 900 reports, the authors concluded that: 2.5%, 5% and 10% BP preparations were equivalent; that BP efficacy may be enhanced by Vitamin E and tertiary amines; that efficacy is enhanced when combined with retinoids; and that new delivery systems using microparticles or urea or a hydrophase increase tolerability without compromising efficacy.

Although we have a lot of sympathy with the notion of revisiting benzoyl peroxide, we have concerns about this systematic review. It is unclear how the authors selected only a small subsection of the 900 study reports to include in their various sections—in some places it looked as if the authors selectively cited those studies that supported their views. No attempt was made at quality rating the studies or meta-analysis. The conclusion that 2.5% BP is equivalent to 5% and 10% BP, for example, was based on just one study that was underpowered to determine such equivalence [6].

One of the authors is conflicted with a company that makes a combination product containing benzoyl peroxide and adapalene, so it is unclear if the overall perspective of this narrow review was simply to give the new combination product a plug. Our take home message is to consider more use of topical benzoyl peroxide, given the background of increasing bacterial resistance. Irritancy problems can often be overcome by adequate patient explanation and by building up gradually. Using BP in combination with other products such as adapalene may enhance efficacy.

Topical retinoids

Yentzer *et al.* from the same team looked at the question of whether topical retinoids initially worsen acne ([Link to PubMed abstract](#)). They state that it is common dogma in the US that topical retinoids cause acne to flare in the first two weeks of therapy. We had not heard of this notion before, but we can understand the authors' motives to examine the claim further with objective evidence. The team looked specifically at clinical studies to see if acne lesion counts increase in the first few weeks of topical retinoid therapy. They did a Google and PubMed search for studies that contained lesion counts recorded at one or two weeks. They did not specify study type or how the quality of studies was assessed, and no flow diagram is presented to outline how many studies they found and how they ended up citing only some studies. From their Google searches, the authors highlighted some sources such as MedlinePlus and Drug Digest that claimed that topical retinoids cause a temporary worsening of acne, but they did not find any evidence of worsening of lesion counts in eight studies that included lesion counts for a range of topical retinoids at 1-2 weeks. One study did suggest a slight worsening of acne in the early stages of treatment. Skin irritation was common in the first few weeks for all topical retinoid preparations, but this normally settled by weeks 8 to 12. So the authors found little in the way of hard evidence to support the notion that acne worsens during the first two weeks of therapy (unlike with oral retinoids), but plenty of evidence that topical retinoids give rise to local irritation.

We thought that the review was a bit contrived—we did not think that topical retinoids worsened acne to begin with, and we all knew that they caused local irritation. The review was not conducted to a high standard, as it was unclear how they included some studies and how they assessed the quality of the studies. We should emphasize again that the team's research centre is supported by Galderma who manufacture a leading topical retinoid, adapalene.

Oral isotretinoin

Something that does worry us a lot in our daily practice is whether oral isotretinoin is linked to psychiatric events such as depression or suicidal thoughts. A systematic review conducted by Kontaxakis *et al.*, a team of psychiatrists in Greece, searched MEDLINE and EMBASE up to March 2008 ([Link to full text](#)). No other aspects of the methodology, such as study types for inclusion and how the data would be quality rated and combined in a meta-analysis, were specified.

Kontaxakis *et al.* present results from 24 case reports and case series that suggested a link between isotretinoin and psychiatric side effects. Some case reports described a clear cessation of mood disturbance when isotretinoin was stopped and recurrence of symptoms on restarting isotretinoin.

However, such case reports are highly prone to publication bias, as a recent review of dermatology case series found [7]. The authors then describe four large database studies, two of which found no association between isotretinoin and depression, and two of which found a slight increased use of antidepressants for people taking isotretinoin. A further case crossover study (a newer type of study design whereby events in the same individuals are compared when they are exposed to a drug and when they are off the drug) of 30,000 people found that those developing depression were 2.68 times more likely to have been exposed to isotretinoin in the preceding five months [8]. The most important studies, i.e. prospective controlled studies, were few. Only two were controlled (i.e. comparing events to a control group taking antibiotics), and neither of these found evidence of an increase in psychiatric side effects, although numbers were small.

The authors follow the results with a long discussion (almost a mini-review article in itself) about the possible mechanisms by which isotretinoin could cause various disturbances in brain physiology, based on animal studies and analogies from people with vitamin A excess. The authors eventually come to a position and state that the evidence in their review *strongly* supports a link between the use of isotretinoin and psychopathology, based on the observation that "there is a great number of reports that support this association". It may well be true that isotretinoin use is associated with depression, but the better quality study designs included in this review were far from conclusive, and it is highly likely that many of the case reports that make up the bulk of studies are the result of publication bias due to increasing awareness of a possible problem. Although the discussion of neurophysiology of

retinoids was interesting, the systematic review was not a high quality one, as it was unclear how the studies were selected, quality assessed and combined.

The review has not really influenced our clinical practice—we remain suspicious that oral isotretinoin can lead to psychiatric symptoms and that all patients taking isotretinoin should be warned of this possibility. We await better prospective controlled studies that are large enough to identify small but important rare adverse effects. Isotretinoin remains a very useful drug for severe acne, which itself is associated with significant depression.

Oral contraceptives and anti-androgens

Some of us recommend oral contraceptives as a potentially useful adjunct in acne therapy, but which is the best one to choose? A Cochrane systematic review by Arowojolu *et al.* updated from 2007 ([Link to full text](#)) examined comparisons of combined oral contraceptives (COCs) with each other, with alternatives and with placebo for treating acne, using data from 8,051 patients who participated in 25 trials. Six of these trials compared COCs to placebo and the authors confirm their superiority in reducing lesion counts. The two studies comparing levonorgestrel (LNG) showed the highest mean reduction of -9.98 (CI -16.51 - -3.45), with those for norgestimate being similar. Whether this translates into an appreciable difference for the patient probably depends on the individual. Despite the fact that COCs containing cyproterone acetate (CPA) are traditionally used for acne, the evidence of benefit over other progestins is based on limited data from just two trials. These compared CPA with LNG, showing that fewer women in the latter group had a 'good' acne self-assessment outcome (OR 0.23, CI 0.09-0.54) in one study and in the other, similarly lowered odds of improved or healed acne. Both show wide confidence intervals. Three other trials comparing CPA with desogestrel were inconclusive.

Of the 13 direct comparisons of two different COCs, most were too methodologically diverse and conflicting to draw any conclusions about which gives greatest clinical benefit. Only one study looked for benefit over standard acne treatment, comparing cyproterone acetate with minocycline 50 mg; this was small and showed similar self-assessments of acne improvement in each group. Analysis in this Cochrane Review was also generally hampered by a high drop-out rate (up to 53%) and by weak design and reporting—only seven studies used intention to treat analysis and just ten described randomization. So, COCs seem to be effective in reducing lesion counts, but which one is most effective and how they compare to other standard acne treatments is still unclear.

A second Cochrane systematic review by Brown *et al.* ([Link to full text](#)), also updated from 2007, considers antiandrogens and spironolactone for the treatment of hirsutism and/or acne. Although the review includes nine trials, only two included studies and one excluded study were relevant for acne. The first trial only evaluated sebum excretion rates [9]. Spironolactone was used topically as a 3% and 5% cream and compared with topical canrenoate (a metabolite with a similar mechanism of action) in a three arm trial of just 31 patients with moderately severe facial acne. At two months none of these treatments produced a reduction in sebum excretion rate. The second trial was a double-blinded RCT that compared oral spironolactone 200 mg with placebo in 29 women with acne using a cross-over design [10]. The trial authors claimed that there was significant reduction in mean inflamed lesion counts after 3 months treatment with spironolactone when compared with placebo, which was also shown for global clinician assessment, patient global assessment and photographic records. One problem with the study was that no intention to treat analysis was done. More importantly, the spironolactone group was much more severe at study entry—an imbalance that was not corrected during analysis, so that much of the reported changes could have been due to a phenomenon known as regression to the mean. The third, excluded, study of 36 men and women compared four different doses of spironolactone against placebo [11], with 26 patients completing three months of treatments. The authors claimed that spironolactone doses of 100 mg or more produced improvements in acne when assessed by three blinded methods, yet they did not present any statistics to back up such a claim. Such differences are likely to be insignificant given the small sample size and multiple groups. The authors also measured sebum excretion rates and failed to demonstrate any difference between the five groups. There really is insufficient evidence to draw any conclusions on the efficacy of spironolactone for acne at present.

Laser and light therapies and photodynamic therapy

Laser and light therapies may improve acne by damaging sebaceous glands and generating reactive oxygen species that destroy *P. acnes*. Although promising in theory, our previous Annual Evidence Updates have not revealed convincing evidence of clear benefit. The first systematic review we found in this field, the 2008 review by Haedersdal *et al.* [12], was evaluated in our [2008 Annual](#)

[Evidence Update commentary](#), and this year there are no less than three new reviews looking at various aspects of laser and light treatment for acne.

The 2009 systematic review by Hamilton *et al.* ([Link to PubMed abstract](#)) was performed by a Cochrane team using Cochrane methods who opted to publish their review in a journal paper before completion of their Cochrane Review. The paper was well reported as one would expect with Cochrane support. They searched eight databases and included data on 694 patients from 25 randomized controlled trials. Most trial participants had mild to moderate acne. Included trials varied widely in design and quality, and meta-analysis was not possible due to the diversity of wavelengths of light examined. Ten RCTs evaluated light treatment versus placebo and those examining green, yellow, and infrared spectrums either showed no difference or only a slight improvement. The trial examining red light claimed significant improvement but was not blinded. There was some evidence for the superiority of blue or blue-red light over placebo in three studies, where reduction in inflammatory lesions was 49-75% in the treated vs. 10-25% in the placebo, with minimal reported side effects.

Only three studies looked at light treatment versus a topical active comparator, two of which were included in the previously mentioned 2008 review by Haedersdal *et al.* [12]. One study showed significant benefit of blue-red light against 5% benzoyl peroxide, reducing lesion counts by 75% in the light group compared to 60% on topical treatment at week 8 ($p=0.02$). A study that compared blue light to topical clindamycin and a comparison of intense pulsed laser versus intense pulsed light plus benzoyl peroxide showed no significant difference in outcomes.

Some forms of light therapy clearly show short-term benefit when compared with placebo, but their performance against simple topical therapies is less convincing to date. We shall watch this area develop with interest.

The review by Hamilton *et al.* also included 12 small trials of light therapy plus light-activated cream (i.e. photodynamic therapy or PDT). The PDT trials showed more consistency in their results, with most suggesting benefit over light therapy alone and better results for multiple rather than single treatments. However, the authors did find that the one active comparator trial showed that PDT was less effective in reducing inflammatory lesions than 1% adapalene gel at 12 week follow-up. Many trial participants experienced side effects such as pain, redness, folliculitis and peeling skin that were severe enough to make them discontinue treatment. Given these drawbacks and lack of superiority over topical adapalene, we would not recommend PDT therapy for acne based on existing data.

The two other new reviews on light therapy focus solely on PDT. The first, by Riddle *et al.* ([Link to PubMed abstract](#)), adds little information to the review by Hamilton and co-authors. Riddle *et al.* undertook a rather uncritical analysis of eight trials and 13 case series following a limited search strategy of just one database, PubMed. All studies reported a reduction in inflammatory lesions, ranging from 25 to 88%, and/or a significant improvement in acne, and as with the review by Hamilton *et al.*, there was consistent superiority of PDT over light source treatment alone. Side effects such as pain, oedema and erythema featured in all the studies, and in a handful of patients, long-term photosensitivity was described. These authors mention an unpublished multi-centre RCT which failed to show a significant difference between ALA and blue light over blue light and vehicle control. One of the authors is a consultant for a laser company.

The other review to consider PDT for acne, by Taylor and Gonzalez ([Link to PubMed abstract](#)), attempted to answer several practical questions, such as choice of photosensitizer, route of administration, treatment intervals, light sources and patient selection—a difficult and expansive task given the findings of the previous reviews. Using a wider search than Riddle *et al.*, Taylor and Gonzalez again acknowledged a scarcity of good quality data, finding only five randomized trials and 16 other reports that included a total of 419 patients. After consideration of the limited evidence available, they favoured topical photosensitisers, shorter contact times, MAL over ALA, and lower light fluences mainly on the basis of more tolerable side effect profiles. The authors struggle to extrapolate further, but do recommend selection of patients with inflammatory and moderately severe acne, of skin types I to III, and treatments at 2-4 week intervals to minimize side effects. They also accept that there is no evidence of superiority of PDT over standard therapies. Whilst an interesting commentary that tried to address practical issues facing those that use PDT for acne, there is limited evidential weight behind its conclusions to offer firm guidance for practice in an area where there is ongoing uncertainty about superiority over conventional treatment.

The bottom line – will we be changing our practice on acne?

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 be quite so dogmatic with patients when it comes to discussing acne and diet; perhaps low glycaemic diet does help and perhaps chocolate does worsen acne but better studies are needed to resolve such uncertainties;
- Promote wider use of more benzoyl peroxide as a means of possible reduction of bacterial resistance due to prolonged use of antibiotics;
- Continue to warn patients that topical retinoids will often result in skin irritation during the first weeks of treatment but we will reassure them that their acne will not worsen;
- Tell patients that oral isotretinoin may be associated with depression, although we are not entirely convinced by the evidence so far—better to be safe than sorry if later evidence produces stronger evidence to support such a notion;
- Prescribe oral contraceptives as they are useful in reducing acne lesion counts, but we will be cautious of favouring those containing cyproterone acetate in view of the limited evidence to show additional benefit;
- Avoid spironolactone as an acne treatment for now, until better quality evidence emerges;
- Tell our patients that light and laser treatments have been shown to be of short-term benefit if they can put up with some initial discomfort;
- Inform our patients that light and laser therapies have not been shown to be better than simple topical treatments and that their long benefits are unknown;
- Not recommend photodynamic therapy (PDT) because of unacceptable local side effects, even though it is better than placebo in the short term;
- Point out to patients thinking about PDT that it is no better than 1% adapalene.

Additional references

1. Smith RN, Mann NJ, Braue A, Mäkeläinen H, Varigos GA. A low-glycemic-load diet improves symptoms in acne vulgaris patients: a randomized controlled trial. *American Journal of Clinical Nutrition* 2007;86:107-15.
[Link to PubMed abstract](#)
2. Smith RN, Mann NJ, Braue A, Mäkeläinen H, Varigos GA. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. *Journal of the American Academy of Dermatology* 2007;57:247-56.
[Link to PubMed abstract](#)
3. Smith RN, Braue A, Varigos GA, Mann NJ. The effect of a low glycemic load diet on acne vulgaris and the fatty acid composition of skin surface triglycerides. *Journal of Dermatological Science* 2008;50:41-52.
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4. Wilhelmus KR. Redundant publication of clinical trials on herpetic keratitis. *American Journal of Ophthalmology* 2007;144:222-6.
[Link to PubMed abstract](#)
5. Magin P, Pond D, Smith W, Watson A. A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight. *Family Practice*. 2005;22:62-70.
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[Link to PubMed abstract](#)

2010 Annual Evidence Update on Acne Vulgaris - DUETs uncertainties update

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.

Now, this DUETs uncertainties update discusses the implications for treatment uncertainties of the new systematic reviews found in the 2010 Annual Evidence Update on Acne Vulgaris that were not available at the time the DUETs uncertainties on acne vulgaris were compiled in summer 2009.

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](#).

Update on treatment uncertainties on acne vulgaris

[DUETs uncertainty: Can modified diet influence acne severity?](#)

[New DUETS uncertainty: Can avoiding chocolate influence acne severity?](#)

The 2010 Annual Evidence Update on Acne Vulgaris includes a review by Spencer *et al.* (2009) on diet and acne ([Link to PubMed - no abstract](#)). While this review concluded that “evidence suggests that components of Western diets, particularly dairy products, may be associated with acne”, it also stated: “in order to test the efficacy of dietary interventions, prospective, randomized trials, including controls for environmental stressors, acne medications, age, pubertal stage, and age at menarche, are essential.” In view of the interest in the role of chocolate and the evidence discussed in this review, we have added a new uncertainty on whether avoiding chocolate can affect acne.

Conclusion: The influence of modified diet on acne remains an uncertainty until tested by high quality randomized trials.

[Potential new DUETs uncertainty: Do topical retinoids cause acne to "flare"?](#)

A review by Yentzer *et al.* (2009) has addressed the question whether topical retinoids cause acne to “flare” ([Link to PubMed abstract](#)). This question has not previously been considered for DUETs. It

should be noted that the review by Yentzer *et al.* only involved a search of PubMed and Google. No reports from clinical trials of acne flare during topical retinoid therapy were found in the literature search. The review concluded: "The clinical evidence did not support the dogma that topical retinoids cause acne to worsen or flare".

Conclusion: No evidence was found that that topical retinoids cause acne to "flare" so this has **not** been added to the DUETs database as an uncertainty. This decision has been made with the caveat that the review in question did not search other databases, such as EMBASE.

[DUETs uncertainty: Is there a causative association between oral isotretinoin and depression and suicidal behaviour in acne patients?](#)

In their 2009 review, Kontaxakis *et al.* ([Link to free full text](#)) concluded that the evidence "strongly suggests a link between the use of isotretinoin and psychopathology". However, they also referred to "the absence of double-blind, placebo-controlled studies, some flaws in the methodology of the current literature and some contradicting results in the studies of animal models" as the reasons for the "lack of an established causal link between isotretinoin use and psychiatric symptoms".

Conclusion: The question of a causative association between oral isotretinoin and depression and suicidal behaviour in acne patients remains an uncertainty.

[DUETs uncertainty: Comparative effectiveness of different combined oral contraceptive pills for acne in women](#)

[DUETs uncertainty: Relative effectiveness of combined oral contraceptive pills in women compared to other acne treatments](#)

[New DUETs uncertainty: The additional benefit of oral contraceptive pills containing cyproterone acetate for acne](#)

The existing Cochrane Review on combined oral contraceptive pills for treatment of acne has been updated in 2009 ([Link to full text](#)), but the conclusions have not changed. While combined oral contraceptive pills containing cyproterone acetate are traditionally used for acne, the Cochrane Review shows that the evidence of benefit over other progestins is poor. Hence, this has been added as a new uncertainty to DUETs.

Conclusion: These questions on combined oral contraceptive pills for treatment of acne remain uncertainties.

[DUETs uncertainty: Spironolactone for treatment of acne in women](#)

The existing Cochrane Review on spironolactone for hirsutism and/or acne has been updated in 2009 ([Link to full text](#)), but the conclusions have not changed.

Conclusion: Spironolactone for treatment of acne in women remains an uncertainty.

[DUETs uncertainty: Efficacy and safety of photodynamic therapy for acne](#)

Three new reviews on photodynamic therapy for acne have appeared in 2009, by Hamilton *et al.* ([Link to PubMed abstract](#)), Taylor & Gonzalez ([Link to PubMed abstract](#)) and Riddle *et al.* ([Link to PubMed abstract](#)). While Riddle *et al.* commented that "Evidence supporting the use of PDT in acne vulgaris is becoming more pronounced", there have been relatively few randomized controlled trials and their review shows that various questions remain to be answered on aspects of this type of therapy. Similar doubts were raised by Hamilton *et al.*, while Taylor & Gonzalez concluded that "the quality of the data was suboptimal in a significant number of articles" and indicated there is a need for "well-designed nonsplit-face randomized controlled trials".

Conclusion: There is still a lack of high quality evidence from clinical trials on various aspects of photodynamic therapy for acne vulgaris, and doubts over its effectiveness. Comparisons with other commonly used active therapies are lacking, long-term benefits are unknown, and how they perform in severe acne is uncertain. Hence this treatment has been retained as an uncertainty.

[New DUETs uncertainty: Acupuncture and moxibustion for acne](#)

There is already an uncertainty in DUETs for "Complementary and alternative therapies for acne". Now, the abstract of a 2009 systematic review in Chinese by Li *et al.* ([Link to PubMed abstract](#)) indicates that evidence was found from randomized and controlled trials that acupuncture and moxibustion were significantly better than conventional Western acne treatments. Moxibustion is a form of fire heat treatment that stimulates specific acupuncture points of the body. However, Li *et al.* indicated that there was still uncertainty about the relative effectiveness of acupuncture and moxibustion because of the poor quality of some of the literature.

Conclusion: While there is some evidence from trials that acupuncture and moxibustion may be better for acne than conventional Western treatments, some of the studies are poor quality. Hence, acupuncture and moxibustion for acne have been added to DUETs as an uncertainty.

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.

Diet	2009	Diet and acne: a review of the evidence
	2005	A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight
Hygiene	2005	A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight
Sunlight	2005	A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight
Outcome measures	2009	Outcome measures in acne vulgaris: systematic review

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.

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

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.

Oral tetracyclines	2008	Efficacy of tetracyclines in the treatment of acne vulgaris: a review
	2005	Safety of doxycycline and minocycline: a systematic review
	2005	Use of macrolides and tetracyclines for chronic inflammatory diseases
	2004	Treatment of acne vulgaris
	2003	Minocycline for acne vulgaris: efficacy and safety (Cochrane Review)
	2003	Acne: comparing hormonal approaches to antibiotics and isotretinoin
	2001	Management of acne
	2000	Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data
	2000	Minocycline-induced lupus. A systematic review
Other oral antibiotics	2005	Use of macrolides and tetracyclines for chronic inflammatory diseases
	2004	Treatment of acne vulgaris
	2001	Management of acne
Antibiotic resistance	2010	The development of antimicrobial resistance due to the antibiotic treatment of acne vulgaris: a review
	2003	Is antibiotic resistance in cutaneous propionibacteria clinically relevant? : implications of resistance for acne patients and prescribers
Isotretinoin	2009	Isotretinoin and psychopathology: a review
	2005	Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review (N.B. This paper was republished unchanged in 2007 in a "best of" compilation in the same journal)
	2005	Isotretinoin, depression and suicide: a review of the evidence
	2004	Treatment of acne vulgaris
	2003	Acne: comparing hormonal approaches to antibiotics and isotretinoin
	2001	Management of acne
	1999	The cost-effectiveness of isotretinoin in the treatment of acne. Part 1. A meta-analysis of effectiveness literature
Oral contraceptives	2010	[Hormonal antiandrogens in acne treatment]
	2009	Combined oral contraceptive pills for treatment of acne (Cochrane Review)
	2007	Metformin versus oral contraceptive pill in polycystic ovary syndrome: a Cochrane review
	2007	Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome (Cochrane Review)
	2004	Hormonal treatment of acne: review of current best evidence
	2004	Treatment of acne vulgaris
	2001	Management of acne
Anti-androgens	2010	[Hormonal antiandrogens in acne treatment]
	2009	Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne (Cochrane Review)
	2004	Hormonal treatment of acne: review of current best evidence
	2004	Treatment of acne vulgaris
	2003	Acne: comparing hormonal approaches to antibiotics and isotretinoin
	2003	Treatment of acne with antiandrogens – an evidence-based review
	2001	Management of acne

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.

Laser therapy	2009	Laser and other light therapies for the treatment of acne vulgaris: systematic review
	2008	Evidence-based review of lasers, light sources and photodynamic therapy in the treatment of acne vulgaris
	2001	Laser resurfacing for facial acne scars (Cochrane Review)
	2000	Laser resurfacing of the skin for the improvement of facial acne scarring: a systematic review of the evidence
Light therapy	2009	Laser and other light therapies for the treatment of acne vulgaris: systematic review
	2008	Evidence-based review of lasers, light sources and photodynamic therapy in the treatment of acne vulgaris
PDT	2009	A review of photodynamic therapy (PDT) for the treatment of acne vulgaris
	2009	The practicalities of photodynamic therapy in acne vulgaris
	2008	Evidence-based review of lasers, light sources and photodynamic therapy in the treatment of acne vulgaris
Grenz rays	2001	Management of acne
Heat therapy		None found

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.

Miscellaneous	2010	Botanicals in dermatology: an evidence-based review
	2006	Topical and oral CAM in acne: a review of the empirical evidence and a consideration of its context
Tea tree oil	2010	Botanicals in dermatology: an evidence-based review
	2006	Topical and oral CAM in acne: a review of the empirical evidence and a consideration of its context
	2000	Tea tree oil: a systematic review of randomized clinical trials
Acupuncture	2009	Evaluation of therapeutic effect and safety for clinical randomized and controlled trials of treatment of acne with acupuncture and moxibustion

2010 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 [2009 Annual Evidence Update on Acne Vulgaris](#).

The result of this search is the **2010 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 2010 Annual Evidence Update on Acne Vulgaris was for citations published or indexed in 2008-10 and not included in the 2009 Annual Evidence Update. January 2008 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 2009). In the case of PubMed, the search was refined by searching for records *indexed* in the database in 2009 and 2010 (using the "edat" command), which would find any citations published before 2008 but indexed late and not found in last year's search. All the searches were carried out for the last time on 8th February, 2010.

Databases and search strategies

PubMed

acne AND 2009 : 2010[edat]

Note: To reduce the chances of missing eligible systematic reviews 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: acne AND 2009 : 2010[edat] AND systematic[sb]

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

1. acne.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. limit 1 to yr="2008 - 2010"

Ovid EMBASE

1. acne vulgaris.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. limit 1 to yr="2008 - 2010"

Cochrane Library

acne

NHS Evidence - skin disorders

acne

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 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 done to find new guidelines and also gave a confirmatory search for new Cochrane Reviews and DARE abstracts.

As the number of results was reasonably small, systematic review filters were not used in the searches, except for initial scoping.

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 2010 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.