

2011 - 2012 Annual Evidence Update on Acne vulgaris

Introduction

Welcome to the sixth **Annual Evidence Update on Acne Vulgaris** from the Centre of Evidence-Based Dermatology at the University of Nottingham where we search for new UK national guidelines and systematic reviews of randomised controlled trials published or indexed since the last Annual Evidence Update in February 2011. In addition to collating new resources, we also include a "what's new" analysis, discussing the new evidence and its implications for clinical practice. This update is aimed at healthcare professionals, but we also hope that many people who have acne will find at least some of the information interesting.

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, the results of which tend to be contradicted with time. ([TV Pereira et al](#)). If you want to delve more deeply into the topic areas, we recommend that you read the original articles and come to your own decisions about their utility.

In previous years, our annual evidence updates were produced in collaboration with NHS Evidence-skin disorders, managed by the National Institute of Health and Clinical Excellence (NICE). However, NICE have decided to reorganise the specialist libraries which has meant that NHS Evidence-skin disorders and its annual evidence updates no longer exist. Whilst one of us (HW) continues to work with NICE as its expert advisor for NHS Evidence <https://www.evidence.nhs.uk/nhs-evidence-content/medicines-information> (accessed August 12th 2013), we have taken the decision at our Centre of Evidence-Based Dermatology to try and continue our updates on acne and eczema under our own steam based on the fantastic feedback we have had from you, our readers.

2011 – 2012 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 2011 Annual Evidence Update on Acne Vulgaris. The result of this search is the **2012 Annual Evidence Update on Acne Vulgaris**.

Search period

January 2010 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 February 2011).

All the searches were carried out for the last time on 22nd August, 2012.

Sources Searched

The following sources were searched:

Ovid MEDLINE (using SIGN MEDLINE systematic review filter)

Ovid EMBASE (using SIGN EMBASE systematic review filter)

PubMed (using PubMed Clinical Queries systematic review filter)

Cochrane Library

NHS Evidence – www.evidence.nhs.uk

All citations found in the searches were hand searched by reading the titles and abstracts to identify guidelines and potential systematic reviews relevant to acne vulgaris. For all

potential systematic reviews where there was still some doubt, the full texts were then read to ensure that they were indeed systematic reviews.

The definition of a systematic review from the Glossary of Cochrane Collaboration Terms on the Cochrane Collaboration website was used:

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

RESULTS

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

Please note that the inclusion of citations in this list does not imply endorsement. We not accept responsibility for the content or quality of included studies.

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

European Guideline

Nast A, Dréno B, Bettoli V, Degitz K, Erdmann R, Finlay AY, Ganceviciene R, Haedersdal M, Layton A, López-Estebanz JL, Ochsendorf F, Oprica C, Rosumeck S, Rzany B, Sammain A, Simonart T, Veien NK, Zivković MV, Zouboulis CC, Gollnick H; European Dermatology Forum.

European evidence-based (S3) guidelines for the treatment of acne.

J Eur Acad Dermatol Venereol. 2012 Feb;26 Suppl 1:1-29.

[Link to PubMed abstract](#)

Systematic Reviews

Zhao YE, Hu L, Wu LP, Ma JX.

A meta-analysis of association between acne vulgaris and Demodex infestation.

Journal of Zhejiang University SCIENCE B. 13(3):192-202, 2012 Mar.

[Link to PubMed abstract](#)

Note: MEDLINE and Web of knowledge searched

Veith WB, Silverberg NB.

The association of acne vulgaris with diet.

Cutis. 88(2):84-91, 2011 Aug.

[Link to PubMed abstract](#)

Note: PubMed only searched.

Dunn LK, O'Neill JL, Feldman SR.

Acne in adolescents: quality of life, self-esteem, mood and psychological disorders.

Dermatology Online Journal. 17(1):1, 2011.

[Link to PubMed abstract](#)

Note: Medline only searched

Alharithy R.

Adolescent's acne: scarring inside out!

Journal of the Saudi Society of Dermatology & Dermatologic Surgery (2011) 15, 43–46.

[Link to abstract](#)

Note: Medline, PsychINFO, EMBASE and CINHALL searched.

Crijns HJ, Straus SM, Gispen-de Wied C, de Jong-van den Berg LT.

Compliance with pregnancy prevention programmes of isotretinoin in Europe: a systematic review

British Journal of Dermatology. 164(2):238-44, 2011 Feb.

[Link to PubMed abstract](#)

Note: Medline and EMBASE searched

Shapiro S, Heremans A, Mays DA, Martin AL, Hernandez-Medina M, Lanes S.

Use of topical tretinoin and the development of noncutaneous adverse events: evidence from a systematic review of the literature

J Am Acad Dermatol. 2011 Dec;65(6):1194-201.

[Link to pubmed abstract](#)

Note: Medline, embase and Current Contents for relevant studies of any design including case reports searched

Siedler EM and Kimball AB.

Meta-analysis of randomised controlled trials using 5% benzoyl peroxide and clindamycin versus 2.5% benzoyl peroxide and clindamycin topical treatments in acne.

Journal of the American Academy of Dermatology. 65(4):e117-9, 2011 Oct.

[Link to PubMed abstract](#)

Note:L PubMed and FDA summaries searched.

Brandsetter AJ and Maibach HI.

Topical dose justification: benzoyl peroxide concentrations.

J Dermatolog Treat. 2011 Dec 27.

[Link to PubMed abstract](#)

Note: PubMed, Embase and a science citation index were searched.

Mohd Nor NH and Aziz Z.

A systematic review of benzoyl peroxide for acne vulgaris.

J Dermatolog Treat. 2012 July 25

[Link to PubMed abstract](#)

Note: Cochrane library, Medline, EBSCohost and PubMed, CINAHL and Science direct was searched.

Gamble R, Dunn J, Dawson A, Petersen B, McLaughlin L, Small A, Kindle S, Dellavalle RP.

Topical antimicrobial treatment of acne vulgaris: an evidence-based review.

Am J Clin Dermatol. 2012 Jun 1;13(3):141-52.

[Link to PubMed abstract](#)

Note: Ovid, MEDLINE, EMBASE and Cochrane library searched.

Webster GF.

Evidence-based review: fixed-combination therapy and topical retinoids in the treatment of acne.

J Drugs Dermatol. 2011 Jun;10(6):636-44

[Link to PubMed abstract](#)

Note: PubMed only searched.

Purdy S and de Berker D.

Acne vulgaris.

Clinical evidence, 2011.

[Link to PubMed abstract](#)

Note: MEDLINE, EMBASE, the Cochrane database of systematic reviews, the US food and drug administration (FDA) alerts and the Medicines and healthcare products regulatory agency (MRHA) were searched.

Ong MW and Bashir SJ.

Fractional laser resurfacing for acne scars: a review.

British Journal of Dermatology. 166(6):1160-9, 2012 Jun.

[Link to PubMed abstract](#)

Note: PubMed and Scopus searched.

Dreno B, Fischer TC, Perosino E, Poli F, Viera MS, Rendon MI, Berson DS, Cohen JL, Roberts WE, Starker I, Wang B.

Expert opinion: efficacy of superficial chemical peels in active acne management – what can we learn from the literature today? Evidence-based recommendations.

[Link to PubMed abstract](#)

Note: PubMed only searched.

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

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

[Link to Cochrane abstract](#)

Garner SE, Eady A, Bennett C, Newton JN, Thomas K, Popescu CM.

Minocycline for acne vulgaris: efficacy and safety.
Cochrane

[Link to Cochrane abstract](#)

Arowojolu AO, Gallo MF, Lopez LM, Grimes DA

Combined oral contraceptive pills for treatment of acne. Cochrane

[Link to Cochrane abstract](#)

Excluded references

Zeichner JA

Optimizing topical combination therapy for the treatment of acne vulgaris

J Drugs Dermatol. 2012 Mar;11(3):313-7

[Link to pubmed abstract](#)

Note: No methods section and no details of systematic search strategy

Gold MH

Photodynamic therapy

Curr Probl Dermatol. 2011;42:181-92

[Link to pubmed abstract](#)

Note: No detailed methods sections and no systematic search strategy

Szczepaniak D, Treadwell P.

Acne Therapy in primary care: Comprehensive review of current evidence based interventions and treatments.

Adolesc Med State Art Rev. 2011 Apr;22(1):77-96.[Link to PubMed abstract](#)

Note: No systematic search and incomplete methodology reporting.

Gannon M, Underhill M, Wellik KE.

Clinical enquiries. Which oral antibiotics are best for acne?

J. Fam. Pract. 2011 May;60(5):290-2

[Link to full text](#)

Note: No clear method described and no systematic search strategy

Feldman SR, Tan J, Poulin Y, Dirschka T, Kerrouche N, Manna V.

The efficacy of adapalene-benzoyl peroxide combination increases with number of acne lesions.

J Am Acad Dermatol. 2011 Jun;64(6):1085-91.

[Link to pubmed abstract](#)

Note: No search strategy, so unclear how the 3 pooled trials were identified and therefore at risk of publication bias.

Gold MH

Clindamycin Phosphate 1.2% and Benzoyl Peroxide 2.5% Gel for the Treatment of Moderate to severe Acne: An update

The Journal of Clinical & Aesthetic Dermatology. 5(1):30-5, 2012 Jan

[Link to pubmed abstract](#)

Note: no methodology and no search strategy

Williams HC, Dellavalle RP, Garner S.

Acne vulgaris

Lancet. 2012 Jan 28;279(9813):361-72

[Link to pubmed abstract](#)

Note: systematic searching however the methods of synthesising evidence was not explicit.

Woolery-Lloyd H, Viera MH, Valins W.

Laser therapy in black skin.

Facial Plastic Surgery Clinics of North America. 19(2):405-16, 2011 May

[Link to pubmed abstract](#)

Note: No clear methodology

Pierard-Franchimont C, Paquet P, Pierard GE

New approaches in light/laser therapies and photodynamic treatment of acne

Expert Opin Pharmacother. 2011 Mar; 12(4):493-501

[Link to pubmed abstract](#)

Note: No clear method outlined

Comin AF, de Albuquerque Santos ZE

Relationship between diet's glycemic load and acne. <Relacao entre carga glicemica da dieta e acne.>

Scientia Medica. 21(1) (pp37-43), 2011.

[Link to full text](#)

Note: No methodology and no details of search in main text

Leyden JJ, Del Rosso JQ

Oral Antibiotic therapy for Acne Vulgaris. Pharmacokinetic and Pharmacodynamic perspectives.

J Clin Aesthet Dermatol. 2011 February; 4(2):40-47

[Link to pubmed abstract](#)

Note: No clear method or systematic search

Arora MK, Yadav A, Sani V.

Role of hormones in acne vulgaris.

Clinical Biochemistry. 44(13):1035-40, 2011 Sep.

[Link to PubMed abstract](#)

Note: No outline of methodology and no systematic search strategy.

2012 Annual Evidence Update on Acne Vulgaris – Commentary

"What's new?" — a tour of the 2012 Annual Evidence Update on Acne Vulgaris with the busy clinician in mind

Dr Ketaki Bhate, Academic Clinical Fellow in Dermatology , Nottingham University Hospitals NHS Trust, and Professor Hywel Williams, Director of the Centre of Evidence-Based Dermatology at the University of Nottingham .

What this guide is all about

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

In the 2011 Annual Evidence Update on Acne Vulgaris ([link](#)), we found two guidelines and five articles that fall within our definition of a systematic review. The quality of those systematic reviews was rather disappointing, with only one out of the five reviews searching more than one electronic database. The current 2012 update included one guideline and 17 systematic reviews. You will see that we have excluded lots of articles that were initially picked up as possible systematic reviews by our searches, in most cases due to an absence of details of any systematic review methodology in the full articles.

Guidelines

European evidence based (S3) guidelines for the treatment of acne

One new guideline was found in our search in 2011 to 2012: a guideline in acne composed by nominated experts from the European Dermatology Forum and The European Academy of Dermatology and Venereology working in the acne field. It is the first of its kind stemming from Europe. Most well known acne therapies were discussed including topical, systemic and light based therapies and these therapies were divided into treatments for comedonal acne, papulopustular acne and nodular/conglobate acne. Overall, after reviewing the clinical trials found in their searches the authors recommended a topical retinoid for comedonal acne (but this was not a strong recommendation), adapalene or clindamycin in combination with benzoyl peroxide topically for mild to moderate papulopustular acne and isotretinoin orally for severe papular-pustular acne, moderate nodular acne or severe nodular/conglobate acne. Systemic antibiotics were not recommended for comedonal acne and were not strong recommendations for papulopustular or nodular/conglobate acne. Hormonal therapies were recommended as an alternative for female patients with papulopustular/nodular/conglobate acne. These guidelines highlight the lack of evidence for light based or laser therapies at present particularly with regard to side effect profiles.

Search criteria were thorough and recommendations were agreed in a consensus by a panel of experts, and the strength of recommendations took into consideration the level of evidence the recommendations stemmed from; overall making this a sturdy guideline which can be relied upon. Over 300 references were included. The only aspect that let down this otherwise thorough guideline was that potential conflicts of interest of the authors were not declared, and several are known to work for the industry. Often acne therapy begins in primary care by general practitioners and the introduction of these guidelines will be useful particularly to those GPs initiating therapy but also to practising dermatologists dealing with more severe forms of acne. They are valid until 2015 at which point they are due to be updated.

Systematic reviews

Acne vulgaris and Demodex infestation

Demodex mites are colonisers of human skin found on the nose, cheeks, forehead, temples, chin, external ear, scalp and upper chest and principally reside around sebaceous glands. The mite has been associated with several other skin conditions such as rosacea. The authors of this meta-analysis set about to collate evidence from case-control studies to confirm the link between demodex infestation and acne vulgaris. Their search strategy dated back to 1950 and involved 2 English databases – MEDLINE and Institute of scientific information Web of Knowledge and one Chinese database – China National Knowledge infrastructure. The study employed definitive inclusion and exclusion criteria which allowed them to isolate studies which would be included into a meta-analysis. All in all, 60 Chinese and just 3 English papers were included in the analysis. A χ^2 test was applied to all papers with 43 of them finding an association and 15, with no association. The pooled odds ratio (OR) of an association between demodex infestation and the development of acne was significant at 2.80 (95% CI 2.34-3.36). Fail safe number formulae were applied to reduce publication bias – this number was 18,477 meaning that many papers with negative conclusions would be required before the conclusion that demodex and acne were related could be doubted. The authors presented data appropriately in forest plots allowing easy readability and concluded that acne vulgaris is significantly related to Demodex infestation but not as closely as the relationship between demodex and rosacea. Overall this is a thorough systematic review which indicates surprisingly large literature on demodex and acne from China. The main drawback of the review is that there is too much emphasis on quantitative meta-analysis without enough consideration of the risk of bias associated with the observational studies found. In terms of affecting our practice however, these findings are unlikely to influence our clinical work other than letting our patients know demodex may be implicated should they ask. The studies to date cannot separate cause from effect. If causal, it is unclear whether it is the demodex or demodex-associated bacteria at this stage. This study highlights the need for further studies looking into manipulating demodex species as a therapeutic target.

Diet and acne

The topic of diet and acne has become quite controversial with an influx of new studies and hypotheses over the last 10 years. The authors of this article aimed to systematically

summarise the relevant evidence. They searched PubMed and included English articles only. They excluded non-systematic reviews and anecdotal reports and included 23 studies overall. There is no flow diagram to help us follow their search and processes of exclusion and inclusion although included studies were tabulated. The articles were only minimally critiqued and there were some opinions of the authors thrown in which didn't seem to fully correlate to the evidence presented. Based on objectively limited evidence regarding dairy or milk and acne the authors advised that 'for now, an acne patient could be advised to limit dairy intake while supplementing his/her diet with calcium and vitamin D'. They concluded that those with disfiguring acne should be guided to avoid high glycaemic index foods, limit milk consumption and maintain a healthy weight. They also point out that more studies are needed to investigate specific dietary components such as casein and saturated fats. Overall the commentary on the individual studies could have been critiqued more and the results of the review should be treated with some caution as recommendations were being made on limited evidence. It is too early to say whether a dietary approach is effective in acne ([Link to review in the epidemiology of acne vulgaris](#)).

Quality of life, self-esteem, mood, and psychological disorders and Adolescent's acne

Quality of life and the psychological aspects of acne is an important area which has lacked systematic reviews. The psychological effects of suffering acne are often underestimated or sometimes overlooked by clinicians and they have a devastating effect on the individual given the potential for residual scarring. There were two systematic reviews this year examining the evidence in this area.

The first systematic review was published in the Dermatology online journal. Medline was searched and studies in adolescents between the ages of 13 and 18 only were included. Sixteen studies were deemed appropriate for inclusion and of these, 5 dealt with quality of life, 4 with self esteem, 2 with personality and mood and 5 with psychological disorders. All included studies were semi-quantitative analyses in response to questionnaires and one was a qualitative analysis in response to interviews. Some of the included studies touched upon the possible link between isotretinoin and psychological morbidity which we have covered in the 2011 Evidence Based Update ([Link](#)). The authors critiqued included studies as a whole rather than individually and commented that bias associated with self reporting was the predominant flaw. Study data was presented in an easy to follow table and an appropriate flow of the search strategy and included studies was provided. A more rigorous search of more databases would have ensured no papers being missed. Although a meta-analysis was not possible due to the variety of included studies, the authors concluded that the presence of acne can negatively affect the quality of life, self-esteem and mood in adolescents, acne is associated with an increased risk of anxiety, depression and suicidal ideation and treatment with isotretinoin qualitatively decreases depressive symptoms and improves quality of life.

The second systematic review had a more sound search strategy and included more databases – Medline, PsychINFO, EMBASE and CINHALL were all searched. Only studies undertaken in the last 10 years were included and these had to be cross-sectional or cohort studies.

Seven cross-sectional and 1 cohort study were identified confirming that acne negatively impacts upon depressive symptoms, self esteem and quality of life when compared to individuals without acne. Unfortunately, the review was not framed by a clear question and it was not absolutely clear how the studies came to be included as they were incompletely described and there was no flow presented diagram like the previous study.

These are, to our knowledge, the only up to date systematic reviews of psychological effects of acne, and despite their flaws, they emphasise and help to quantify the psychological burden and reduced quality life that individuals suffer with this predominantly adolescent disease. Such a message reinforces the need to question acne patients about psychological factors including symptoms of depression and the potential value of early intervention.

Compliance of isotretinoin pregnancy prevention programmes in Europe

This systematic review investigated adherence to the pregnancy prevention programme (PPP) when using isotretinoin in Europe. Medline and EMBASE were searched with no language restriction, and manual searches in relevant journals was also undertaken.

Their 17 included studies were made up of eight database studies, 2 surveys involving dermatologists or pharmacists and 7 case reports of exposed pregnancies despite the employment of a PPP. All included studies concluded that compliance with and implementation of the pregnancy prevention programme (PPP) was insufficient and that it should be strengthened by the use of explicit instructions, monitoring and adjusting as necessary.

This study was well conducted and methods were clearly described. Limitations of the observational data were acknowledged, including the potential for response bias in surveys. The study underlines the fact that despite having a PPP in place, errors can occur along the way, underscoring the need for full implementation of the programme throughout the course of treatment but little suggestion was made for improvement.

Topical therapies

Topical tretinoin and non-cutaneous adverse events

In 2005, the Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) trial was terminated early. The study set out to investigate whether topical tretinoin 0.1% twice daily could prevent the development of non-melanoma skin cancer in 1131 elderly patients during a 2- year follow up. The trial was stopped due to higher mortality rate in the tretinoin group – 82 in intervention group vs. 53 in placebo group, $p=0.01$). Deaths were predominantly a result of pulmonary disease and non-small-cell lung cancer. The authors conducted this systematic review to assess the rate of non-cutaneous adverse events in those receiving topical tretinoin in studies prior to the VATTC trial. Cochrane research methods were used and the search protocol was written prospectively. MEDLINE, Embase and Current Contents for relevant studies of any design including case reports were searched and methodology was clearly described. Twenty studies were included (14 evaluating tretinoin) and 27.9%

(n=742) of those on treatment with topical tretinoin developed a non-cutaneous adverse event and 25.2% (n=428) of those in the placebo groups developed a non-cutaneous adverse event. Most of these adverse events were 'non-specific' and included headaches and respiratory symptoms and there were no 'clinically significant' adverse events. Authors concluded that there was no evidence that an association existed between the use of topical retinoids and mortality before the VATTC study. Limitations of this study included the shorter follow up time of 24 months compared to 72 months in the VATTC study. In addition, a higher strength tretinoin (0.1%) in a twice daily regime was used in the VATTC trial with the studies in this review using 0.02-0.05% strength tretinoin in a once daily regime. It would also have been pertinent to include non English papers in case some major studies were missed.

Overall this is a useful study collating the evidence of non-cutaneous adverse events prior to the well publicised study by Weinstock et al. However, studies of a longer follow up period and those using higher strength tretinoin in a twice daily regime are needed before any hard conclusions can be made.

Combination of topical clindamycin with 2.5% or 5% benzoyl peroxide

Topical combination products are commonly prescribed in the treatment of acne. The authors of this review had previously published a study comparing 5% benzoyl peroxide (BPO), 1-2% clindamycin (CL), a combination of both, or a combination of 5% BPO and salicylic acid, which we discussed last year. They then chose to do this follow up systematic review comparing 5% BPO/CL and 2.5% BPO/CL. Their search strategy followed Cochrane guidelines searching PubMed from 1987 to the time of study, the Food and Drug Administration (FDA) summaries as well as posters. They identified 16 randomised controlled trials (RCTs) and found that at weeks 10-12, the percentage reduction in non-inflammatory lesion count was statistically greater with 2.5% BPO/CL than other treatments with non-overlapping 95% confidence intervals. 2.5% BPO/CL and 5%BPO/CL had similar percentage inflammatory lesion count reductions with overlapping confidence intervals.

One of the authors is a researcher for Stiefel which produces a clindamycin and 2.5% benzoyl peroxide product. Furthermore, the work was funded by CORIA laboratories a company dealing in the research, development and marketing of dermatology products, though they do not make benzoyl peroxide products. There was no study flow diagram. There was a risk of bias as methods of randomisation, blinding and an intention to treat analysis were not described. It is also unclear whether the comparator groups were included more than once in the comparisons between treatments, giving rise to potential bias by attributing undue weight to a particular study.

The authors concluded that 2.5% BPO/CL is comparable to other topical products containing 5% BPO/CL in reducing lesion counts and may have an advantage in treating non-inflammatory lesions, due to less skin irritation and great compliance.

Although the review was probably funded by the drug company responsible for launching a new clindamycin/benzoyl peroxide product and although there are flaws in the methodology of this SR particularly in terms of the reporting of methodology, the findings of this study

suggest that a lower strength of benzoyl peroxide (2.5%) may be optimal for combination with clindamicin.

Benzoyl peroxide concentrations

This review was inspired by the US Foods and Drug Administration who have declared benzoyl peroxide (BPO) as generally safe and effective. The authors set out to establish the difference in efficacy and toxicity between the available concentrations of BPO and vehicles commonly used. They searched PubMed, EMBASE and a Science citation index but there was unfortunately no breakdown of filtered results and no study flow diagram. Of 10 included studies, one included relevant data comparing 2.5%, 5% and 10% BPO. The authors concluded that there was not enough data to justify the use of a higher concentration of BPO over lower doses and that the 2.5% BPO concentrations had a better side effect profile, a similar conclusion to that in another review included in the 2010 Annual Evidence Update ([link](#)).

Benzoyl peroxide for acne vulgaris

Sticking to the subject of BPO, this well conducted systematic review conducted by Noor *et al* which searched the Cochrane library, Medline, EBSCOhost, PubMed, CINAHL and Science direct, aimed to summarise the effectiveness of benzoyl peroxide containing products. Their search strategy was thorough and tabulated appropriately. They employed clear inclusion/exclusion criteria including only RCTs and they included studies from all languages. 22 studies were included of which only 5 had numerical data. Details of the study characteristics are presented along with a clear documentation of risks of realised and potential bias. Overall 7 trials reported BPO to be useful in acne and 13 trials showed it to have no superiority over an active control. The overall quality of trials included was relatively poor however, which did not allow the authors to draw a clear conclusion. They did however, report that they were in agreement with the systematic review by Siedler and Kimball in our last acne update in 2010 that BPO did significantly reduce both inflammatory and non-inflammatory lesions counts. This review was well reported however it was a little contradictory in interpretation.

It adds little to previous reviews apart from confirming the efficacy of BP in treating acne.

Topical antimicrobial treatment of acne

This systematic review addressed topical antimicrobial therapy and which to use when. A well conducted and clearly documented search of Medline, EMBASE and Cochrane was performed and the various topical antimicrobial therapies were discussed in turn.

The authors found that combination of antibiotics with benzoyl peroxide and retinoids resulted in the best efficacy and side effect profile. Alternative therapies such as dapsone and zinc are also effective although are lacking in definitive well conducted studies. This

study illustrated the lack of studies comparing various combination products with one another i.e. comparative effectiveness research.

There was no flow chart which would have made the results slightly easier to follow although data was tabulated well in a supplement. Searches dated back to 2004 only which was the last time a similar review was undertaken in the publishing journal. This work was funded by the government, however, in 2010, one of the authors received an unrestricted grant from Galderma who manufacture Epiduo, a combination of adapalene and benzoyl peroxide. Overall this was a useful review that has underlined the message that combination topical therapies are potentially better than monotherapies for treating mild to moderate acne.

Fixed combination therapy and topical retinoids in the treatment of acne

This systematic review sought to answer the question of whether topical fixed combination products or monotherapy with topical retinoids are more efficient choice in reducing non-inflammatory and inflammatory lesion counts after 12 weeks of treatment in mild to moderate acne. The methods were sound and documented clearly but only one database (PubMed) was searched. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to guide the selection of included studies. 43 studies, all with acne lesion counts as an outcome measure were included but these studies were not all necessarily RCTs. It was difficult to perform meta-analyses due to the degree of varying methods and comparators used in the individual trials. All but one of the studies found fixed combination therapy more effective than retinoid monotherapy for inflammatory lesions. Percentage lesion count reduction for non-inflammatory lesions were similar in both groups. Editorial support for the study was funded by a pharmaceutical company which produces a fixed combination therapy but not surprisingly, they do not manufacture a retinoid as monotherapy. Results should be interpreted with caution and further work to answer this question is recommended.

Clinical evidence - Skin disorders: Acne vulgaris

Topical agents and oral antibiotics are quite often prescribed by general practitioners before dermatologists see patients with acne in their clinics. But, do they really work and are there any side effects? This well conducted systematic review aimed to collate the evidence of the effects of topical and oral treatment used in acne vulgaris. The authors searched MEDLINE, EMBASE, the Cochrane database of systematic reviews, the US food and drug administration (FDA) alerts and the Medicines and healthcare products regulatory agency (MRHA). 69 systematic reviews, RCTs and observational studies were found in total.

Collating the evidence, the authors could make some useful recommendations. Topical benzoyl peroxide monotherapy should be considered as first line in mild acne and topical benzoyl peroxide and azaleic acid can reduce both inflammatory and non-inflammatory acne lesions but they both do have side effects of burning, itching and erythema. Topical antibiotics like erythromycin and clindamycin with or without zinc help people with inflammatory acne but not those with non-inflammatory acne so much. Topical tetracyclines

may reduce overall acne severity. Topical isotretinoin, adapalene and tretinoin may reduce inflammatory and non-inflammatory lesions but the well documented side effects and risks have to be considered when prescribing these. The review was more circumspect about the usefulness of oral antibiotics and some having side effects. This is a well documented evidence summary which has a good search strategy and presents data in tables with summary sections alongside. The review is well indexed so that finding what you need when you need is not too difficult.

A systematic review in this topic is helpful as the choice of which topical agent/oral antibiotic to use in the clinic tends to be based on personal preferences. This review highlights clearly what is known in the case of benzoyl peroxide and what we are unsure about in the case of oral antibiotics and also it identifies key areas that would benefit from further well designed trials. More importantly, this independent review has recommended that benzoyl peroxide monotherapy should be considered as the first line treatment. Even though combination topical treatment is probably more effective than monotherapies, the cost of combination products is much more, and they are only available from a doctor. Given that mild acne almost universal, the potential financial gains for manufacturers of combination products if combination products are recommended as first line therapy is enormous. Given that benzoyl peroxide is cheap and available and over the counter, it is hard to see how marginal superiority of combination products could ever be cost-effective as a first line treatment.

Fractional laser resurfacing for acne scars

Acne vulgaris often results in scarring which many, particularly adolescents and those in their 20's find distressing. Relatively new therapies for scarring such as fractionated lasers have been introduced but it is unclear exactly how effective they are in relation to existing technologies. Ong *et al* conducted a systematic review to establish the current evidence on treating acne scars using fractional photothermolysis (FP) with ablative and non-ablative techniques. The methods were clear but no flow diagram was included. Two databases (PubMed and scopus) were searched and a manual search was also undertaken. Excluding duplicates, 428 papers were shortlisted and 26 papers were finally included. Searches ranged from 2003 (when the technique was introduced) until 2011. The authors paid careful consideration to the trial methodologies used by the included studies pointing out that only 4 of the included studies were split face Randomised Controlled Trials (RCTs). No studies included a quality of life measure as an outcome and only one study followed their patients up to 2 years. There was also a great deal of variability between studies so collating them was difficult. They showed that ablative FP had a short-term acne scar improvement in both subjective and objective measurements between 26-83% and non-ablative FP had an improvement range of 26-50%. Non ablative FP has a better and shorter side effect profile than ablative but this was to be expected. The authors critiqued the included studies sufficiently – there was a lot of variability between the design of included studies making collation difficult. This was the first review to evaluate FP lasers so it was an overall useful insight. It summarises the key side effects of this technique and highlights the need for future studies with a longer follow up period. The study also highlighted the recommendation of giving antiviral prophylaxis to avoid reactivation of herpes simplex infection in unknown cases.

Efficacy of superficial chemical peels in active acne management

Chemical peels are used in the cosmetic industry in an attempt to smooth out the skin surface and give an even skin tone. Many different agents can be used in the peels: glycolic acid, salicylic acid and pyruvic acid being the main ones. This was a systematic review conducted using only the PubMed database, between 1990 and 2009. Included studies were grouped into the chemical agent used for peeling: salicylic acid, glycolic acid and pyruvic acid as well as the NHS classification of clinical trials - levels of evidence A to D (broadly speaking A being a randomised controlled trial or a prospective cohort study, B a retrospective or an exploratory cohort study, C a case series and D expert opinion). Overall 13 randomised controlled trials or open label studies of superficial chemical peels in acne were included and critiqued. Salicylic acid and glycolic acid had a significant benefit in the treatment of comedonal acne in 4 studies with reduction of comedones ranging between 35-50% though in the majority of these studies, individuals were allowed to use other acne medications alongside the peels. Authors did not always specify if this reduction was in terms of appearance, lesion count or symptoms which made interpretation difficult. There is very little evidence of positive benefit in inflammatory acne and the peels may even exacerbate inflammatory lesions. The authors conclude that peels are a safe treatment but they do not give data to back this up. They acknowledge the studies included were too weak to offer definitive conclusions. All 11 authors declared a conflict of interest with a pharmaceutical/cosmetic organisation. In addition the authors had only searched one database and therefore may have missed some key studies, so the results should be interpreted cautiously. They do call for further trials particularly to look for the synergistic effect of peels used alongside topical/systemic medications in mild to moderate acne and also comparing the treatment effects of traditional topical anti-acne medication with chemical peels. There is a real need to assess treatments that purport to improve the appearance of facial skin that is affected by acne in a rigorous and independent way.

Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne (Cochrane review)

Extensive Cochrane searches yielded only one trial of spironolactone for acne, the remainder focusing on hirsutism. The one included study by Muhlemann (1985) included just 29 patients (8 of which withdrew), and no evidence of effectiveness was demonstrated. With so few patients, a larger study is needed to establish whether spironolactone is of any use in acne as no evidence of effect in small study is not the same as evidence of no effect.

Minocycline for acne vulgaris: efficacy and safety (Cochrane review)

This Cochrane review update found 13 new trials resulting in 39 in total (6013 participants). The new trials were small and of low quality. There were no new conclusions drawn. Minocycline is effective in moderate-severe acne vulgaris but it has not been shown to be superior to other commonly used topical or oral acne treatments. The review also found that

minocycline has a significantly worse profile compared to other tetracyclines (a lupus-like reaction has also been noted with minocycline only). The meta-analysis conducted found there is some evidence for minocycline having a more rapid onset of action but this efficacy is not sustained and overall the treatment effect does not last longer than other tetracyclines upon stopping treatment. There is no clear evidence to preferentially prescribe minocycline over other acne therapies. Overall, this was a well conducted review with a very thorough analysis into a relatively controversial topic producing a clear clinical message that minocycline does not appear to offer any advantage over other oral antibiotics and that it might be less safe.

Combined oral contraceptive (COC) pills for the treatment of acne (Cochrane review)

This review update identified 6 new trials, giving a total of 31 trials with 12,579 individuals. 24 of the 31 trials were comparison trials, 6 compared a COC to a placebo, 17 to another COC and one to an antibiotic. As usual, strict Cochrane methodology was employed with the computerised databases of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, POPLINE and LILACS being searched as well as clinical trials registered in clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP). ALL RCTs were assessed for the risk of bias. No new conclusions were drawn from the last review: COCs are useful in reducing both inflammatory and non-inflammatory lesions. Comparisons between various COCs were inconsistent and only one trial compared a COC to another form of acne therapy. The authors of this review found it hard to compare the effects of different COCs due to a lack of appropriate data. No single COC appeared to be superior. More importantly, only one trial had compared COCs to other forms of acne treatment, calling for trials in this area. A validated and universally used outcome measure would be of benefit.

Implications for practice

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

- There are now well formulated treatment algorithms from guidelines such as the S3 European Guidelines that clinicians can refer to when prescribing anti-acne medication;
- There is a consistent modest association between demodex infestations and acne but it is unclear if this has any therapeutic implications.
- There may be a link with certain dietary components such as a low glycaemic index diet being beneficial in acne, but the evidence is not clear enough to change practice at present
- Acne bears a significant psychological burden and reduced quality of life upon some patients that needs to be elicited during an acne consultation;
- Despite having a pregnancy prevention programme in place for patients receiving isotretinoin, errors can still occur along the way emphasising that when in place, the pregnancy prevention programme should be as stringent as possible;
- Although topical combination therapy with an antimicrobial and benzoyl peroxide probably offers the most beneficial side effect profile and efficacy, it is probably best to start treatment of mild acne with 2.5% benzoyl peroxide alone;
- Due to the side effect profile of higher strengths of benzoyl peroxide, it may be prudent to begin with the 2.5% dose in order to increase concordance;
- There is no high quality evidence of efficacy of spironolactone as an effective therapy for acne vulgaris at present;
- There is no evidence of any clear benefit of minocycline over tetracyclines or other commonly prescribed acne medications and some evidence that it may result in more harm;
- Combined oral contraceptives are an effective therapy in acne but there is no evidence of superiority of one type over the other or to other standard acne therapies due to lack of comparative studies

2012 Annual Evidence Update on Acne Vulgaris - UK DUETs uncertainties update

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) ([link to website](#)).

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 upon 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.

This DUETs uncertainties update discusses the implications for treatment uncertainties of the new systematic reviews found in the 2012 Annual Evidence Update on Acne Vulgaris.

Update on treatment uncertainties on acne vulgaris

The systematic reviews found in the Results of the 2012 Annual Evidence Update on Acne Vulgaris have been reviewed for new uncertainties to add to DUETs, and to determine if they have any implications for existing uncertainties in the DUETs database.

No existing uncertainties have been removed as a result of the systematic reviews found in the 2012 Annual Evidence Update.

Three new uncertainties have been added to the DUETs database:

- The long term benefit of chemical peels in the treatment of acne vulgaris
- Cost effectiveness of benzoyl peroxide versus combination topical products for the first line treatment of mild acne
- The therapeutic benefit of targeting demodex

The systematic reviews looking into chemical peels and laser resurfacing for treating acne scars included in this update did not sufficiently answer the uncertainties and so have been added as references to existing DUETs (laser resurfacing for treating acne scars, 2009 and topical glycolic acid for acne, 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.

2011 Annual Evidence Update on Acne Vulgaris – Methodology

A literature search was carried out to identify **new guidelines and systematic reviews** relating to acne vulgaris (common acne) that have been published or indexed since the 2011 Annual Evidence Update on Acne Vulgaris. In addition other important studies on acne published in the last year were identified by the Annual Evidence Update team. The result of this search is the **2012 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 2012 Annual Evidence Update on Acne Vulgaris was for citations published or indexed in 2010-12 and not included in the 2011 Annual Evidence Update. January 2010 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 February 2011).

In the case of PubMed, the search was refined by searching for records *indexed* in the database in 2011 and 2012 (using the "edat" command), which would find any citations published before 2010 but indexed late and not found in last year's search. All the searches were carried out for the last time on 22nd August, 2012.

Sources searched

The following sources were searched:
Ovid MEDLINE (using SIGN MEDLINE systematic review filter) Ovid EMBASE (using SIGN EMBASE systematic review filter) PubMed (using PubMed Clinical Queries systematic review filter) Cochrane Library NHS Evidence - skin disorders.

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

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

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

Systematic review filters

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

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

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

http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html

http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_sources.html

Search strategies

SIGN MEDLINE systematic review filter:

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

1. Meta-Analysis/
2. meta analy\$.tw.
3. metaanaly\$.tw.
4. meta analysis.pt.
5. (systematic adj (review\$1 or overview\$1)).tw.
6. exp Review Literature/
7. or/1-6
8. cochrane.ab.
9. embase.ab.
10. (psychlit or psyclit).ab.
11. (psychinfo or psycinfo).ab.
12. (cinahl or cinhal).ab.
13. science citation index.ab.
14. bids.ab.
15. cancerlit.ab.
16. or/8-15
17. reference list\$.ab.
18. bibliograph\$.ab.
19. hand-search\$.ab.

20. relevant journals.ab.
21. manual search\$.ab.
22. or/17-21 23. selection criteria.ab.
24. data extraction.ab.
25. 23 or 24
26. review.pt.
27. 25 and 26
28. comment.pt.
29. letter.pt.
30. editorial.pt.
31. animal/
32. human/
33. 31 not (31 and 32)
34. or/28-30,33
35. 7 or 16 or 22 or 27
36. 35 not 34
37. acne.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
38. 36 and 37
39. limit 38 to yr="2009 - 2011"

SIGN EMBASE systematic review filter:

Ovid EMBASE

1. exp Meta Analysis/
2. ((meta adj analy\$) or metaanalys\$).tw.
3. (systematic adj (review\$1 or overview\$1)).tw.
4. or/1-3
5. cancerlit.ab.
6. cochrane.ab.
7. embase.ab.
8. (psychlit or psyclit).ab.
9. (psychinfo or psycinfo).ab.
10. (cinahl or cinhal).ab.
11. science citation index.ab.
12. bids.ab.
13. or/5-12
14. reference lists.ab.
15. bibliograph\$.ab.
16. hand-search\$.ab.
17. manual search\$.ab.
18. relevant journals.ab.
19. or/14-18
20. data extraction.ab.
21. selection criteria.ab.
22. 20 or 21
23. review.pt.
24. 22 and 23

25. letter.pt.
26. editorial.pt.
27. animal/
28. human/
29. 27 not (27 and 28)
30. or/25-26,29
31. 4 or 13 or 19 or 24
32. 31 not 30
33. limit 32 to yr="2009 - 2011"
34. acne.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
35. 33 and 34

PubMed using Clinical Queries systematic review filter:
acne AND systematic[*sb*] AND 2010 : 2011[*edat*]

Cochrane Library and NHS Evidence - skin disorders:
acne

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

Identification of systematic reviews and inclusion criteria

All citations found in the database searches were scanned by reading the titles and abstracts to identify guidelines and potential systematic reviews relevant to acne vulgaris and its treatment. A particularly careful analysis of the methods was made to identify citations with a systematic review methodology. For all potential systematic reviews where there was still some doubt, the full texts were then read to ensure that they were indeed systematic reviews.

To determine systematic reviews, the definition of a systematic review from the Glossary of Cochrane Collaboration Terms was used:

‘A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies’.
Using this definition (which was also used in the recent PRISMA statement on reporting of systematic reviews), reviews that only searched one database have been included, but a note has been added to this effect.

The final decision on whether to include a citation as being a valid guideline or systematic review was made by Professor Hywel Williams, Director of the Centre of Evidence-Based Dermatology 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 2012 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.