Assessment and recommended treatment options for acne

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Acne can have a significant social and psychological impact, and early and appropriate treatment is key to reducing the risk of permanent scarring. Our Drug review provides a brief overview of clinical assessment and discusses the available treatment options, followed by sources of further information and an analysis of the prescription data.

Acne is a common inflammatory dermatosis affecting the pilosebaceous unit. Typically, it is a condition associated with adolescence but it can develop in infancy (see Figure 1) or even begin in adulthood. It is estimated that acne affects up to 80 per cent of young adults aged 11 to 30 years of age.¹ There can be wide variation between individuals with regards to the type of acne lesions experienced and their distribution as well as severity. Practitioners not only have to take into account the physical manifestations of the condition but also manage the significant social and psychological impact that acne can have on an individual. Management strategies must be tailored to each patient to take these factors into account. Early intervention is key to ensure the best outcome for the patient and reduce chances of permanent scarring. This article aims to give an overview of treatments currently available for acne taking into account the most up-to-date evidence and guidelines.²

Clinical assessment

Several key questions should be asked when assessing a patient with acne (see Table 1). Assessment of acne lesions type should be the first step. These can be classified as inflammatory or non-inflammatory. Inflammatory lesions include papules, pustules, cysts and nodules (see Figure 2). Non-inflammatory lesions include open comedones, closed comedones, macrocomedones and submarine comedones (see Figure 3). Greasy skin (seborrhoea) is a common finding (see Figure 4).

At the initial assessment it should also be identified if a patient has already begun to develop scarring as this would warrant a more aggressive approach to treatment. Scarring can take several forms including ice-pick, atrophic, perifollicular elastolytic and keloidal. Pigmentary changes may also be occurring. Thought should also be given to possible underlying medical causes for acne such as polycystic ovarian syndrome or other endocrine disorders such as Cushing syndrome, congenital...
adrenal hyperplasia (CAH), androgen-secreting tumours and acromegaly.

Many medications can induce acne, such as topical or oral steroids, contraceptive agents and anabolic steroids. Severe acne can be seen in body builders due to anabolic steroid abuse (see Figure 5). Assessment of the psychological impact the acne is having on the individual should be undertaken. This is done more formally with scoring systems such as assessment of psychological and social effects of acne (APSEA) and the Cardiff acne disability index (CADI).

**Topical treatments**

With such a wide variety of topical agents available, what to prescribe can be bewildering. Topical treatments include monotherapies and combined topical treatments (see Table 2 for a summary). These are generally suitable for mild to moderate acne.

**Topical monotherapies**

Benzoyl peroxide is the most time honoured of topical treatments. It is available in concentrations ranging from 2.5 to 10 per cent. It is recommended to start at a lower concentration due to irritancy. The concentration can be gradually increased if tolerated, although efficacy is not greater at the higher concentrations. It is relatively inexpensive option when compared with other treatments available, with prices starting at just under £2 for a 40g tube. Benzyl peroxide is not only effective against the skin commensal *Propionibacterium acnes* but also tackles both inflammatory and noninflammatory acne lesions. Also in its favour is that it does not promote bacterial resistance. Its main drawbacks are irritancy and bleaching, which may limit use.

Azelaic acid is effective for both inflamed and noninflamed acne lesions. It is available in two concentrations, a 15 per cent gel (Finacea) and a 20 per cent cream (Skinoren). It is a twice-daily application and is less irritant than benzoyl peroxide. Azelaic acid has also has the added benefit that it may reduce pigment change, so may be valuable in darker skin types where acne is leading to postinflammatory hyperpigmentation.

There is insufficient evidence to support the use of topical nicotinamide as a monotherapy treatment for acne.

**Antibiotics**

Topical antibiotics include clindamycin and erythromycin. Clindamycin is available in two forms, a 1 per cent aqueous/alcohol solution (Dalacin T) and a zinc-based gel (Zindaclin). Dalacin T is a twice-daily application whereas Zindaclin is recommended for once-daily application. Topical erythromycin is available as 2 per cent solution (Stiemycin).

Topical antibiotics are not recommended as first-line treatment for acne. Topical clindamycin has some evidence to support its use in acne treatment; however, in their recent draft guidelines the British Association of Dermatologists felt there was insufficient evidence to recommend topical erythromycin in isolation. It may be argued that topical antibiotics could be helpful for individuals who suffer from sensitive skin and would potentially find other topical treatments too irritant.

The BNF makes several suggestions on the use of topical antibacterials with regard to increasing resistance to *P. acnes*. Firstly, where possible use nonantibiotic antimicrobials such as benzoyl peroxide or azelaic acid. If a topical antibacterial is effective for acne, use it for repeat courses with short intervening courses of benzoyl peroxide or azelaic acid. Do not use any topical treatment for longer than necessary (however, treatment with a topical preparation should be continued for at least six months). Finally, a topical and systemic antibiotic should not be used in unison.

**Retinoids**

Two topical retinoids are available in the UK – adapalene (Differin) and isotretinoin (Isotrex). Tretinoin as a monotherapy is not currently available. Retinoids have been showed to reduce both noninflamed and inflammatory lesions. Care should be given to prescribing these for woman of childbearing age, especially if sexually active. Contraception is currently recommended. One reasonably large study suggests that exposure to topical retinoids in the first trimester of pregnancy does not...
increase the rate of spontaneous abortion or birth defects. However, the rate of elective termination in the retinoid-exposed cohort was three times higher than the control group. Overall, topical retinoids should be avoided during pregnancy or in women attempting pregnancy as their risk/benefit ratio is questionable. Topical retinoids may also cause photosensitivity to UVB light or sunlight.

Topical isotretinoin, an isomer of tretinoin, is available as 0.05 per cent gel and is applied once to twice daily. Isotretinoin has similar efficacy to benzoyl peroxide but the latter was found to be quicker at reducing inflamed lesions. Adapalene is available as a 0.1 per cent cream or gel. It should be applied once at night. Adapalene is comparable to topical isotretinoin; however, the latter may be more irritant.

To minimise irritancy with topical retinoids, it is often helpful to initiate a twice-weekly regimen and then increasing the frequency of application to daily.

**Combination treatments**

Duac Once Daily gel is a combination of clindamycin 1 per cent plus benzoyl peroxide 3 or 5 per cent. It is applied at night. The combination of these two ingredients is more effective than either ingredient used alone. Epiduo (adapalene 0.1 per cent plus benzoyl peroxide 2.5 per cent) is also a once-daily product. Again the combination of the two ingredients is slightly more effective than benzoyl peroxide or adapalene alone. Due to these products containing benzoyl peroxide patients should be warned regarding risks of irritation and bleaching. Duac and Epiduo have been found to be similar in their efficacy. However, they are both more costly than noncombination benzoyl peroxide preparations.

Zineryt (erythromycin 4 per cent plus zinc acetate 1.2 per cent) is a twice-daily application. In two placebo-controlled trials it reduced both inflamed and noninflamed lesions. As previously mentioned with erythromycin, there is evidence to suggest antibiotic resistance will emerge over time with this combination.

Unfortunately, data is limited on benefit of changing between different topical agents.

**Oral antibiotics**

Systemic antibacterial treatment is useful for inflammatory acne if topical treatments are not effective or if they are inappropriate due to location or severity of the acne lesions. See Table 3 for a full list of available antibiotics. Tetracycline, oxytetracycline, doxycycline, lymecycline and minocycline all very similar in their terms of efficacy to treat acne. However, oral lymecycline or oxytetracycline are both good first-line options, taking efficacy and cost into consideration. Lymecycline has the slight advantage of once-a-day administration, which may be helpful with adherence. Side-effects of tetracyclines include dyspepsia, colic, diarrhoea and vaginal candidiasis. Tetracyclines must be avoided in those under 12 years of age due to staining of the teeth. They should also be avoided in pregnant and breast-feeding mothers. Tetracyclines can also induce benign intracranial hypertension and doxycycline in particular can lead to photosensitivity.

It is usual to prescribe a systemic antibiotic with topical therapy as this combination is more effective than monotherapy. A concomitant use of a systemic and topical antibiotic is best avoided; azelaic acid, benzoyl peroxide or a topical retinoid are preferred.

Antibiotics that can be used but not for first-line treatment include minocycline, erythromycin and trimethoprim. Minocycline should not be first line due to its cost and side-effect profile. It is associated with rare but significant side-effects when compared with other antibiotics and the BNF recommends monitoring for hepatotoxicity, pigmentation and systemic lupus erythematosus on a three-monthly basis if the medication is continued for longer than six months.

Erythromycin has a relatively poor evidence base for use in acne and also is high risk for bacterial resistance and therefore only recommended where other oral antibiotics are contraindicated. Trimethoprim has insufficient evidence to recommend
routine use and due to side-effects it should only be used in resistance cases of acne unresponsive to other antibiotics (unlicensed indication). Trimethoprim can cause a widespread maculopapular rash and rarely Stevens-Johnson syndrome. It also has the potential to cause bone marrow suppression.

Oral antibiotics can take up two months to produce significant effects, with full benefit occurring at four months. Continued treatment for eight months minimises the likelihood of relapse on discontinuation. A sensible approach is to continue topical therapy after antibiotic withdrawal, and reutilise the same effective antibiotic that previously worked if relapse occurs.

Hormonal treatments
Co-cyprindiol is currently licenced in the UK for the treatment of acne. One 2009 study comparing both co-cyprindiol (ethinylestradiol 35µg plus cyproterone acetate 2mg) and Qlaira (ethinylestradiol 30µg plus dienogest 2mg) against placebo found that they were similar in effectiveness for the treatment of mild to moderate acne. A Cochrane review published in 2012 compared combined oral contraceptives (COCs) for the treatment of acne, including those containing the progestogens levonorgestrel (Norgeston), norethisterone, norgestimate, drospirenone, dienogest and chlormadinone acetate. It concluded that of the six COCs evaluated there was no significant differences between them. There was also a lack of good trials comparing standard acne treatments to the COCs.

It is recommended that co-cyprindiol is stopped three to four months after the acne is controlled. It has an increased risk of deep vein thrombosis when compared with equivalent COCs and it is currently banned in France due to its side-effects. These risks need to be taken into consideration in combination with the data from the recent Cochrane review when deciding on a suitable COCs for acne treatment.

Isotretinoin
Isotretinoin is usually reserved for severe acne, i.e. nodular or conglobate acne with risk of permanent scarring, as well as acne that has been resistant to topical and oral therapies. It can also be considered in some cases of milder acne resistant to conventional therapies if there is significant psychological distress. The usual starting dose is 0.5mg per kg and can be increased up to 1.0mg per kg. A typical course can last six months; however, if a patient is on a low dose courses can be longer. It has a high success rate and clears 70–80 per cent after one course. Isotretinoin is more effective than topical treatments, antibiotics and hormonal treatments. There is some evidence that repeat courses of isotretinoin are relatively safe if required.

Some patients may be wary of isotretinoin due to media coverage of its side-effects, most notably mood changes and a possible increased suicidal tendency. However, the evidence for this is so far inconclusive and history of depression or suicidal behaviour in a patient does not contraindicate isotretinoin, especially if anxiety and depression are due to the acne itself. However, careful risk assessment, perhaps with psychiatric help, must be carried out on an individual basis. Other side-effects include dry mucous membranes, epistaxis, deranged liver function tests, elevated lipid levels, skin fragility, muscle and joint aches, and headaches. It is also a potent teratogen.

If referring a patient from primary care for consideration of isotretinoin it is helpful to check liver function tests and fasting lipids. If a woman is of child-bearing age and sexually active she should be advised to use appropriate hormonal contraception, COCs if possible. Double contraception must be used for a full cycle prior to commencement, during the course and for six weeks after the last isotretinoin dose.
Monotherapy
- benzoyl peroxide
- azelaic acid
- antibiotics: clindamycin, erythromycin
- retinoids: adapalene, tretinoin, isotretinoin
- nicotinamide

Combined topical treatments
- benzoyl peroxide + clindamycin (Duac)
- adapalene + benzoyl peroxide (Epiduo)
- erythromycin + zinc acetate (Zineryt)
- erythromycin + tretinoin (Aknemycin Plus)
- erythromycin + isotretinoin (Isotrexin)

Table 2. Topical acne treatments

- lymecycline 408mg once daily
- oxytetracycline 500mg twice daily
- tetracycline 500mg twice daily
- doxycycline 100mg once daily
- minocycline 50mg twice daily or 100mg once daily
- erythromycin 500mg twice daily
- trimethoprim 300mg twice daily (unlicensed indication)

Table 3. Systemic antibiotics available for the treatment for acne

When to refer
Referral to secondary care should be considered in those individuals whose acne has been unresponsive to topical therapies, oral antibiotics and hormonal treatments where appropriate. Early referral should also be considered for patients who have severe nodulocystic acne, especially if it is beginning to scar, acne fulminans (severe acne with arthralgias) and severe acne in pregnancy. Patients with darker skin types can develop disfiguring postinflammatory pigmentation and warrant earlier aggressive therapy. Referral should be considered in individuals whose acne is having a major psychological or social impact.

The after effects of acne
Treatments for acne scarring are beyond the scope of this article; however, it is important to mention that none of the aforementioned treatments can reverse acne scarring once it has taken place. Therefore to reduce the chances of scarring, early and appropriate treatment of acne is key.

Conclusion
In order to prescribe and treat acne effectively the clinician’s assessment is key. A stepwise approach for mild to moderate acne is appropriate. This can include topical treatments in isolation or in combination with oral antibiotics and hormonal treatments. Severe acne that is scarring, not responding to treatment or having significant psychological impact requires quicker escalation of treatment and an early referral to dermatology.

References

Declaration of interests
None to declare.

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Resources

Guidelines


Prescriber articles


Prescription review

In 2013, GPs in England wrote 1.77 million prescriptions for topical preparations for acne at a total cost of £22 million. Prescribing volume has changed little since 2009 but costs increased by 10 per cent over 2012, which was itself a 7 per cent increase over 2011.

Antibiotics continue to dominate this category, accounting for 72 per cent of volume and 74 per cent of costs. Of these, the combination of clindamycin and benzoyl peroxide is the most frequently prescribed and, after adapalene/benzoyl peroxide, has the highest cost per scrip. Most prescribing of clindamycin/benzoyl peroxide is of the higher strength gel (5 per cent benzoyl peroxide). Erythromycin is more popular than the cheaper clindamycin; this is primarily due to prescribing of erythromycin/zinc acetate lotion.

Prescribing of topical tretinoin has decreased by over 90 per cent since 2012 and it is now available only in little-prescribed combinations with antibiotics. By contrast, the use of isotretinoin increased by 73 per cent. Adapalene scripts were up by 17 per cent and adapalene/benzoyl peroxide prescribing increased by 57 per cent compared with 2012, with corresponding increases in cost.

Table 4. Number and cost of prescriptions for the treatment of acne, England, 2013

<table>
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<tr>
<th>Medication</th>
<th>No. scrips (000s)</th>
<th>NIC (£000s)</th>
<th>NIC per scrip (£)</th>
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<tr>
<td>adapalene</td>
<td>159</td>
<td>2370</td>
<td>14.94</td>
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<tr>
<td>adapalene/benzoyl peroxide</td>
<td>118</td>
<td>2292</td>
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<tr>
<td>azelaic acid</td>
<td>88</td>
<td>567</td>
<td>6.45</td>
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<tr>
<td>benzoyl peroxide</td>
<td>76</td>
<td>458</td>
<td>6.03</td>
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<tr>
<td>benzoyl peroxide/clindamycin</td>
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<td>9605</td>
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<td>9.27</td>
</tr>
</tbody>
</table>

For each section, one of the statements is false – which is it?

1. Acne:
   a. may have an adverse psychological and social impact
   b. may be due to an underlying endocrine disorder
   c. is a condition confined to patients aged under 20
   d. may cause scarring

c. there is no evidence that erythromycin/zinc acetate is associated with the emergence of bacterial resistance
d. the combination of clindamycin and benzoyl peroxide is more effective than either agent alone

2. Among the topical treatments for acne:
   a. treatment with benzoyl peroxide should be initiated at the highest concentration then titrated downwards
   b. benzoyl peroxide does not promote bacterial resistance
   c. azelaic acid may be valuable in patients with a darker skin type
   d. azelaic acid is effective for both inflamed and noninflamed acne lesions

4. When prescribing an oral antibiotic:
   a. lymecycline or oxytetracycline are both good first-line options
   b. tetracyclines must be avoided in patients under 12 years old
   c. the risk of bacterial resistance with oral erythromycin is high
   d. a combination of an oral and a topical antibiotic is preferred

5. In the management of acne:
   a. adapalene is less irritant than topical isotretinoin
   b. oral isotretinoin may be prescribed for a patient with a history of depression or suicidal behaviour
   c. treatment with co-cyprindiol should be stopped three to four weeks after acne is controlled
   d. there are no significant differences in efficacy between COCs in the treatment of acne