

DISEASES OF THE SKIN AND THEIR TREATMENT

(1) ACNEBy *Bill Cunliffe, FRCP*

This is the first of a series of three articles on diseases of the skin and their treatment. This week's article focuses on acne. The next two will look at rosacea and eczema

Acne is a common disease. Nearly all adolescents will suffer to a small degree from acne, which physicians call physiological acne. However, about 20 per cent of the population will at some time have problems with the disease that will merit advice from the pharmacist, general practitioner or, if severe enough, a dermatologist.

CLINICAL FEATURES

Acne predominantly starts in early puberty, although signs can be observed even before the teenage years. The first physical signs are those of greasiness (seborrhoea), and comedone (blackheads and whiteheads) formation (Figure 1). After a variable time, usually of the order of months, occasionally longer, inflammatory lesions develop (Figure 2). These consist of papules (small raised red spots, less than 5mm in diameter), and superficial pustules of similar size. Sometimes deeper lesions occur: these are referred to as either nodules or deep pustules and are larger than 5mm in diameter. Such lesions may be tender. However, itching is uncommon in acne.

As a consequence of inflammatory lesions, including even extensive papular/pustular lesions, acne can scar (Figure 3). The scars may be associated with a loss of collagen, producing either ice pick scars or atrophic macular scars. (Ice pick and macular scars both represent loss of fibrous tissue. Macular scars tend to be larger and shallower than ice pick scars, which are deeper and V-shaped.) Less commonly, there is increased fibrous reaction in the scarring process resulting in hypertrophic scars, ie, scars which are about the same size as the initial inflammatory lesion or larger scars, called keloids. Uncommonly, the deep lesions may fuse together resulting in what is called sinus tract disease, with inflammation tracking from one nodule to another (Figure 4). These lesions are a therapeutic nightmare and produce dreadful scarring.

Acne develops at the time when there is already a great deal of conflict and difficulty for the adolescent, and the presence of significant acne can make things worse. Thus, it is not unusual for acne to produce loss of personal esteem, difficulty in interaction with friends and relatives, problems with employment, anxiety and depression.

AETIOLOGY OF ACNE

The disease typically occurs on the face and the upper trunk, the sites of the pilosebaceous glands. Androgens are a prerequisite for acne. The early features of seborrhoea and comedone formation are due to androgen production from the adrenal glands. With the gradual development of gonadal activity, androgens are produced both from the testes and the ovaries resulting in a further increase in the seborrhoea and comedone formation.

The main androgen drive within the pilosebaceous unit to produce both the seborrhoea and comedone formation is dihydrotestosterone — the most active androgen metabolite in the pilosebaceous gland. Other factors responsible for comedone formation include an irritant effect of the lipid composition of sebum, local cytokine activity, in particular interleukin 1 alpha and possibly microbial colonisation. Microbial colonisation of the pilosebaceous duct with *Propionibacterium acnes* (*P. acnes*) is the next event and results in inflammation.

Acne is not infectious. The development of inflamed lesions



Figure 1: The first physical signs of acne are seborrhoea and comedone formation



Figure 2: After some months, inflammatory lesions develop



Figure 3: As a consequence of inflammatory lesions, acne may scar



Figure 4: Deep lesions can fuse together resulting in sinus tract disease

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relates to the microenvironment of the pilosebaceous duct. Pro-inflammatory factors are produced both by *P. acnes* and probably from the ductal keratinocytes/corneocytes. These extend into the dermis stimulating a T helper cell to produce a lymphocytic reaction (ie, to produce papules and nodules) as well as a polymorphonucleocyte reaction to produce pustules. Although rupture of the duct eventually occurs in many lesions, rupture of the duct is not essential for the onset of inflammation.

DRUG THERAPY

Table 1 summarises the mechanism of action of drugs used in acne. The only drugs that affect the seborrhoea are oral retinoids such as Isotretinoin (Roaccutane), or hormonal therapy such as Dianette (35µg of ethinylestradiol and cyproterone acetate) and spironolactone.

Topical retinoids are the mainstay in reducing comedones. There have been many studies confirming the benefit of such therapy but there are relatively few large studies to help the physician decide which is the optimum treatment. The following preparations are available in the UK:

- 1 Tretinoin in strength of 0.025% and 0.5% gels and creams
- 1 Isotretinoin gel
- 1 New formulations of all tretinoin, such as Acticin
- 1 Adapalene

These drugs also affect the microenvironment of the pilosebaceous duct and thereby also reduce inflamed lesions.

Topical antimicrobials are predominantly used in inflammatory acne and these include:

- 1 Benzoyl peroxide
- 1 Topical antibiotics, such as clindamycin, erythromycin and tetracycline
- 1 Combination products such as benzoyl peroxide with erythromycin, erythromycin with zinc
- 1 Azelaic acid (Skinoren) which has actions against both *P. acnes* and comedones

Nicotinamide in the form of Papulex Gel is a non-steroidal anti-inflammatory agent that can also reduce inflammatory lesions. Oral antibiotics (tetracycline, minocycline, erythromycin, trimethoprim) are all highly active against *P. acnes* and easily penetrate the pilosebaceous duct. Some of the antibiotics, particularly minocycline, also have a range of anti-inflammatory, non-microbiological actions and thus can reduce inflammation through this route.

Physical treatments can also be used in acne. These include aspiration of large "cysts" with a wide bore needle and the subsequent injection of triamcinolone acetonide. This can be particularly helpful, especially if the lesion is less than one week old. More established nodules, "cysts", may respond to cryotherapy by producing a low grade inflammatory response to the cold injury.

RECOMMENDED DOSES AND REGIMENS

Although there is a reasonable amount of evidence-based medicine to support the use of certain treatments in acne, there is still a lack of data to guide physicians, pharmacists and patients to which treatment is the appropriate choice.

Some topical therapies come in different doses and combinations. Most topical antimicrobials are recommended to be used twice daily, and topical retinoids daily, although they can be used twice daily if there is no irritation.

Table 2 indicates the doses of antibiotics commonly used in the average case of acne where that particular drug is indicated.

What really is lacking is information on the appropriate duration of treatment. Most physicians probably would prescribe topical therapies indefinitely provided the patient is responding. Indeed it is always wise to tell the patient that some form of topical therapy will probably be required for much of that patient's acne life. This could be anything from a few years up to 10 years or more. A small number of patients (up to 7 per cent) have acne persisting well up to the age of 40 years.

TABLE 1: MECHANISMS OF ACTION OF DRUGS PRESCRIBED IN ACNE

Action	Topical drug	Oral drug
Anti-comedonal	Retinoids Azelaic acid	Isotretinoin
Anti <i>P. acnes</i>	Benzoyl peroxide Azelaic acid Erythromycin Tetracycline Clindamycin	Tetracycline Erythromycin Minocycline Trimethoprim Isotretinoin
Anti-inflammatory	Tetracycline Erythromycin Clindamycin Nicotinamide	Tetracycline Minocycline Trimethoprim Isotretinoin
Anti-seborrhoeic	Spironolactone	Dianette Isotretinoin

Oral antibiotics will usually be prescribed for courses of six to eight months. Some physicians then stop the therapy without gradually reducing the dose. Other physicians gradually reduce the dose. There is no evidence to suggest which is the optimum approach. Dianette is used in females where period regulation and/or contraception may also be required. Indeed, Dianette therapy will often be dictated by the need for its other benefits and may be prescribed for several years. Oral isotretinoin is usually prescribed in doses of 0.5–1mg/kg/day for four to six months. Repeat courses of all treatments can be given if necessary. Clearly, if any treatment is not working well within two to three months or the acne is getting dramatically worse, alternative therapies need to be considered sooner rather than later.

TABLE 2: TYPICAL REGIMENS FOR ORAL ACNE THERAPY

Drug	Dose
Tetracycline	500mg <i>bd</i>
Oxytetracycline	500mg <i>bd</i>
Minocycline	100mg <i>od</i>
Erythromycin	500mg <i>bd</i>
Trimethoprim	200mg <i>bd</i>

CHOICE OF DRUG FOR EACH PATIENT

The choice of drug relates to the severity and type of the acne. The severity of the acne depends in part on how the acne appears visually in terms of comedones and inflammatory lesions. Many scoring systems are available. These are usually produced with a melamine backing to show different grades of acne for the face, back and chest. These are most useful in the clinic. The severity will also depend on how the disease affects the patient psychologically and socially. Several questionnaires are available to help better understand how the disease affects the patient's lifestyle. The presence of scarring will also contribute to acne severity; the failure of previous treatments will also influence how the patient feels about the disease, particularly if the response has not been good.

It is important for the physician and the pharmacist to assess whether the acne is predominantly inflammatory or non-inflammatory because this will dictate the choice of topical therapy (Table 1).

Figure 5 is an outline plan to guide the pharmacist and physician on the choice of drug in a particular situation. Patients with mild acne should be treated with topical therapies, using a retinoid where there are many comedones and an antimicrobial agent where there are lots of inflammatory lesions. Because of the increasing problems of *P. acnes* resistance, it is important to remember the beneficial effect of benzoyl peroxide which does not induce *P. acnes* resistance. Indeed, benzoyl peroxide can even reduce resistance. Similarly, combinations of benzoyl peroxide with topical antibiotics, such as Benzamycin and erythromycin with zinc, are associated with the development of less *P. acnes* resistance than is found with the antibiotic alone.

Moderate acne will usually be treated initially with oral tetracycline. Second-line drugs will include minocycline and trimethoprim. Topical therapy can also be co-prescribed with oral therapy but there is little evidence to show that co-prescribing really does help, although clinical dogma suggests this is the way forward. Some recent studies do support co-prescribing. It is important not to use different oral and topical antibiotics as this might increase the problems of resistance. A sexually active female, or a female who requires period regulation, may benefit from Dianette. Topical therapies should be co-prescribed with Dianette.

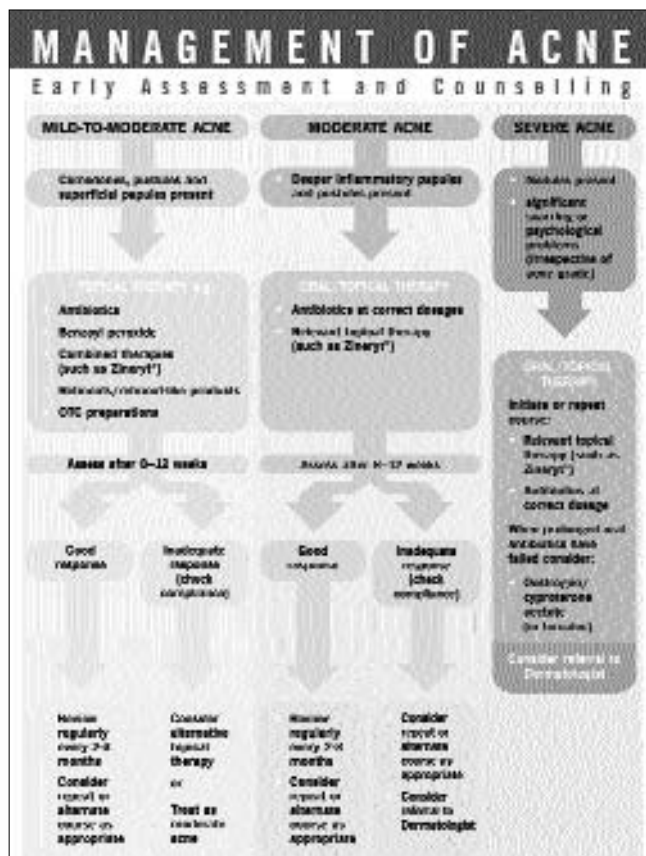


Figure 5: How to choose a treatment for a particular situation

Panel 1 summarises the National Institute of Clinical Excellence (NICE) guidelines for referral to a dermatologist. Pharmacists should recommend referral to the general practitioner if the acne is not responding to over-the-counter preparations, if the patient has got obvious scarring, or is psychologically and socially distressed by the disorder.

PATIENT RESPONSE

The pharmacist should stress that there will be little improvement in the first month. There should be 20 per cent improvement in two months, 40 per cent in four months and 80 per cent in eight months. If there is no improvement as identified in the NICE recommendations, or if the patient has severe acne (Figure 6), referral for isotretinoin is needed.

Isotretinoin is a hospital only drug. It is usually prescribed for four to six months in a dose of 0.5–1mg/kg/day. In nearly all patients, it produces 100 per cent clearance; in 60 per cent of patients it is associated with no recurrence. It is the only anti-acne drug which suppresses all the four aetiological factors of acne: increased sebum production, comedone formation, colonisation of the duct with *P. acnes* and inflammation. It does, however, have many side effects.

OTHER PHARMACIST ISSUES

The pharmacist has an important role in giving support to patients, stressing that acne is usually a treatable disease, particularly if the patient complies with treatment. The pharmacist can stress the need to comply especially given the fact that acne needs to be treated over many years, often in a somewhat vulnerable age group, many of whom are probably less compliant than the older patient with acne.

Some of the tetracyclines are less well absorbed if taken with food, milk or antacids. Iron and calcium also chelate tetracycline reducing absorption, so tetracycline and oxytetracycline are best taken half to one hour either side of a meal and not taken with milk. Minocycline, trimethoprim and erythromycin are much less affected by food.

Common questions that might be asked of the pharmacist are listed in Panel 2.



Figure 6: Severe acne might need treatment with isotretinoin

SIDE EFFECTS

The pharmacist can play a major role in monitoring side effects.

Topical therapies The pharmacist should tell the patient that virtually all topical therapies will produce a mild degree of primary irritant dermatitis. Indeed, the absence of an irritant dermatitis should make the pharmacist and the physician suspect the patient is not complying. If irritation is a significant problem, the frequency of application can be reduced and a moisturiser used once or twice a day; 1 per cent hydrocortisone cream can be used twice daily for a few days if there is a major irritant reaction. A true allergic dermatitis is rare.

Oral therapies Many oral antibiotics can produce a little abdominal colic and diarrhoea. Occasionally this may benefit from the use of loperamide or co-phenotrope, one tablet daily for a few days.

Vaginal candidiasis is common in women taking either Dianette or antibiotics. It is important to treat both the patient and the partner with anti-candida therapy.

Uncommon side effects may be a significant problem. Rarely with minocycline the patient may develop dose- and duration-dependent pigmentation (Figure 7). It is important not to give any patient who has a personal or family history of lupus erythematosus tetracyclines, in particular minocycline. Patients with drug induced lupus erythematosus may present with a fever, arthritis, liver problems, kidney problems and general malaise. Trimethoprim is associated in 5 per cent of patients with a drug rash.

Dianette Side effects of Dianette are the same as for other forms of contraceptive pill and it is important not to prescribe Dianette in women for whom the contraceptive pill would be contraindicated.

PANEL 1: A SUMMARY OF NICE GUIDELINES FOR REFERRAL OF ACNE PATIENTS

It is recommended that patients with acne should be referred to a specialist service if they:

- 1 Have a severe variant of acne such as acne fulminans or gram-negative folliculitis
- 1 Have severe or nodulocystic acne and could benefit from oral isotretinoin
- 1 Have severe social or psychological problems, including a morbid fear of deformity (dysmorphophobia)
- 1 Are at risk of, or are developing, scarring despite primary care therapies
- 1 Have moderate acne that has failed to respond to treatment which has included two courses of oral antibiotics, each lasting three months; failure is probably best based upon a subjective assessment by the patient
- 1 Are suspected of having an underlying endocrinological cause for the acne (such as polycystic ovary syndrome) that needs assessment
- 1 Have, or develop, features that makes the diagnosis uncertain

PANEL 2: COMMONLY ASKED QUESTIONS

Can I wear cosmetics? Yes, especially if they are non-comedogenic. It is best to avoid heavy make up. Recommend that the patient uses a cosmetic that feels comfortable and looks good, is non-antimicrobial and is reasonably priced.

Does diet influence acne? Probably not.

Does stress aggravate acne? Patients sometimes say that stress aggravates the acne. This possibility is not unreasonable because stress, through its effect on the pituitary-adrenal axis, may slightly increase the levels of circulating androgens.

Does acne flare before a period? A premenstrual flare occurs in about 60 per cent of females with acne.

Does sunshine help acne? Many patients report benefit from sunshine.



Figure 7: Dose- and duration-dependent pigmentation rarely results from minocycline treatment

Additionally, Dianette may produce more weight gain compared with other pills, no doubt due to its increased content of ethinylestradiol (35µg).

Isotretinoin Isotretinoin (Roaccutane), although the most effective treatment for acne and often associated with long-term remission, has many side effects. The systemic side effects of oral therapy are summarised in Table 3. The commonest side effects, however, are without doubt mucocutaneous, and include cheilitis, facial dermatitis, nasal crusting and conjunctivitis. These are usually controlled by the use of moisturisers and lip salve, even from the first or second day of starting such therapy. Secondary skin infection can be a problem with *Staphylococcus aureus*; this colonises dry skin which occurs as a consequence of treatment with oral isotretinoin. Anti-staphylococcal therapy for five days with flucloxacillin or erythromycin may be required.

The most important side effect is teratogenicity and it is important to carry out a pre-therapy pregnancy test on the second day of the period before starting therapy. The therapy must be started on the second or third day of the period and adequate contraception is essential before, during and for six weeks after stopping therapy. It must be stressed to the patient that she must not become pregnant otherwise an abortion will be required.

Myalgia and headaches rarely need treatment, but if necessary paracetamol and non-steroidal anti-inflammatory drugs are helpful. The data sheet provides data on many other uncommon side effects, the most important of which are mood changes and depression, which occur in a small number of patients taking Roaccutane.

Side effect	Risk/incidence
Teratogenicity	100%
Myalgia	10%
Arthralgia	10%
Arthritis	10%
Headaches	10%
Malaise	5%
Mood Swings	0.5–3%
Depression	0.5–3%

There are many other side effects listed in the Roaccutane data sheet

Depression is an uncommon and unpredictable event. Suicide has been infrequently reported. For the past five years, we have discussed adverse psychiatric events in detail with our patients and in that time have asked our patients to sign that this issue has been discussed. Likewise, we have asked all our female patients who are prescribed Roaccutane to sign a form indicating that we have discussed with them the need to avoid becoming pregnant.

We also give our patients, and have done since the drug first came on the market, a leaflet summarising the side effects perceived to be most important at that time, along with a telephone number so that patients can always be seen urgently. We always stress that our patients bring back any Roaccutane tablets they do not take although we ask them to complete the course of treatment which they have been prescribed. All these issues need to be reinforced by the pharmacist when dispensing Roaccutane.

In a small number of patients the acne flares badly while they are on therapy. There are several explanations, but should this happen an urgent visit to the dermatologist is required. Sometimes on seeing the active inflammation resolve while taking Roaccutane, the patient notices the presence and persistence of significant scarring. This observation may make the patient depressed. If in any doubt, the drug must be stopped and the patient immediately seen by the dermatologist for further advice on the management of any depression, whatever the cause.

SCARRING

There is little good treatment available for scarring so it is far better to treat the acne sooner rather than later to minimise the risk.

For keloid and hypertrophic scars the application of Silicon gel sheets from the pharmacist (over the counter), or the application of a potent steroid used for several weeks precisely to the scar may help as may intralesional triamcinolone.

Atrophic macular scars and ice pick scars may be helped by laser abrasion but NHS funding for this treatment is limited. The facility is available privately.

THE FUTURE

There is some ongoing research looking at the genetics of acne. There are many clinical subtypes of acne, possibly 22 different varieties, all of which clearly need to be categorised clinically so that the molecular geneticist can pinpoint what is most likely to be going wrong in terms of genetic control. It is quite likely that the inheritance is polygenic. It would also be advantageous to be able to pick out which youngsters in an acne prone family are likely to get acne so that the pharmacist or physician can perhaps treat the disease sooner rather than later.

Recently there has been an interest in the use of certain types of “light therapy” in acne. It has been known for many years that sunshine does help acne. Who has not come across a member of the family whose acne has usually been helped as a result of two weeks holiday in the sun?

High intensity blue light has also recently been shown by some American and Israeli colleagues to be of benefit in acne. This is an area which we and others are currently researching. A similar study showed that a combination of different light wavelengths (Dermalux) is also of benefit.¹

Topically applied aminolevulinic acid, when exposed to red light, increases the skin concentration of porphyrins, which are cytotoxic to the pilosebaceous gland and *P. acnes*. The result is a clearance of the acne for up to six months.

There has been little research done on “natural” acne resolution. This is somewhat surprising since such studies could perhaps give a handle on new pharmacological approaches. This is an area crying out to be investigated.

REFERENCE

1. Papageorgiou P, Katsambas A, Chu A. Phototherapy with blue (415nm) and red (660nm) light in the treatment of acne vulgaris. Br J Dermatol 2000;142:973–8.