COMPASS Therapeutic Notes on the Primary Care
Management of Acne in Primary Care

In this issue:	
	Page

Glossary of terms	
Acne conglobata	Very severe acne where inflammatory lesions predominate and coalesce, often accompanied by exudate or bleeding. This form of acne may cause extensive scarring. Systemic symptoms are absent.
Acne fulminans	A sudden severe inflammatory reaction that precipitates deep nodules and erosions, often with systemic effects (such as fever and arthralgia).
Cheilitis	Inflammation of the lips
Comedones	The basic acne lesion. An enlarged hair follicle plugged with oil and bacteria
Desquamation	The shedding of the outer layers of the skin
MHRA	Medicines and Healthcare products Regulatory Agency
Papulopustular acne	Presence of papules and pustules
Pilosebaceous unit	A unit consisting of one hair and an associated sebaceous gland
RCT	Randomised Controlled Trial
SmPC	Summary of Product Characteristics

Successful completion of the assessment questions at the end of this issue will provide you with **3 hours** towards your CPD/CME requirements. Further copies of this and any other edition in the COMPASS Therapeutic Notes series, including relevant CPD/CME assessment questions, can be found at:
www.medicinesni.com or
www.hscbusiness.hscni.net/services/2163.htm
GPs can complete the multiple choice questions on-line and print off their CPD/CME certificate at
www.medicinesni.com
Pharmacists should enter their MCQ answers at www.nicpld.org

Introduction, clinical features & complications of acne

Acne vulgaris (common acne) is a chronic inflammatory skin condition which is notable for open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules.[1]

A diagnosis of acne is often quite clear, and laboratory investigations are unnecessary, except where signs and symptoms suggest hyperandrogenism.[2,3] Acne is rarely misdiagnosed. However, other conditions can include some of the features of acne (**Table ONE**), but the presence of comedones confirms the diagnosis of acne.[4]

What are the clinical features of acne?

Acne presents with non-inflammatory or inflammatory lesions, or a mixture of the two.[5]

Non-inflammatory lesions are known as "comedones":[5]

- **blackheads** (open comedones) are follicles that have a wider than normal opening. They are filled with plugs of sebum and shed cells. This material has a typical black appearance due to melanin deposition and lipid oxidation.
- **whiteheads** (closed comedones) are follicles that are filled with the same material as blackheads but have a much smaller opening to the skin surface, and therefore appear white.

Inflammatory lesions mainly consist of:[5]

- superficial **papules** (red inflamed lesions, usually less than 5mm in diameter), and
- **pustules** (small, superficial lesions containing pus).

In more severe acne, **nodules** (deep papular lesions) and **cysts** (deep pustular lesions that carry a greater risk of scarring than more superficial lesions) may occur. In very severe acne, nodules may track together and form large, deep sinuses (acne conglobata).

Acne presents in a wide variety of clinical forms depending on the type, number and severity of the predominant lesion. In most patients, acne is a spectrum of disease. At one end lies the invisible microcomedone – the development of which is the first essential step in acne lesion formation – and at the other end is the deep scarring inflammatory nodule.[6] Acne principally affects the face (99% of sufferers), the back (60%), and the chest (15%).[5]

Who gets acne?

Acne affects almost everyone at some point in their life, up to 14% of people will consult their GP,[7] and about 0.3% will require referral to a dermatologist.[8] Peak incidence is seen in females aged 14-17 years and males aged 16-19 years.[5] Acne varies greatly in severity, and the person's perception of the problem will influence whether they seek medical help for it. Acne is the presenting problem in 3% of GP consultations in the 13-25 age group.[5]

Acne can also occur later in life. Approximately 5% of women and 1% of men aged 25-40 years either continue to get acne lesions or develop acne (late-onset acne) after adolescence.[5] Patients with persistent acne often have a family history of persistent acne.[7] This is a more demanding, articulate group of patients with high expectations for improvement. Without treatment, acne persists in most sufferers for an average of 8-12 years.[10] Currently, the understanding of acne has been refined toward a "chronic disease", overcoming the misconception of acne as a simple, self-limiting affliction of adolescents.[11]

Table ONE: Differential diagnosis [9]	
Rosacea	Most commonly seen in people over the age of 30 years and is associated with telangiectasia and flushing
Folliculitis and boils	Infection of hair follicles; diagnosis could be confirmed by taking swabs which usually reveal *Staph. aureus*
Sycosis barbae	Persistent folliculitis of the beard area
Milia	Small keratin cysts, most commonly around the eyes
Peri-oral dermatitis	Erythema and small papules around the mouth, nasolabial folds, and sometimes the lower eyelids
Acneiform eruption	Seen commonly during treatment with endothelial growth factor inhibitors such as cetuximab

Did you know…?
Recent evidence suggests that acne may be linked with smoking cigarettes, particularly in adult women smokers who were four times more likely to have acne than non-smoking controls.[12] In addition, studies have shown that severe acne increases with smoking.[13,14]

What causes acne?

There are 4 primary pathogenic factors, which interact in a complex manner to produce acne lesions:[7,15]

1. Androgen-induced sebum production by the sebaceous gland
2. Abnormal keratinisation resulting in the formation of comedones
3. Colonisation of the pilosebaceous duct with *Propionibacterium acnes*. *P. acnes* is an anaerobic bacterium that forms part of the normal cutaneous flora in adults. Colonisation by *P. acnes* leads to visible inflammation with swelling, redness, pain and release of inflammatory mediators into surrounding skin
4. Inflammation, resulting from an interaction between biological changes in the duct, *P. acnes* colonisation, and the production of pro-inflammatory cytokines in response

The formation of an acne lesion is thought to begin with the microscopic lesion known as the "microcomedo" or "microcomedone". This lesion, which is not yet clinically visible, forms when excess sebum collects in the follicle and abnormal epithelial desquamation occurs along with proliferation of *P. acnes*. The microcomedo is the precursor to all acne lesions.[15]

What are the complications of acne?

Although acne is a common, non-life threatening disease, untreated it can have serious, lifelong physical and psychological consequences[16 17] and health professionals should aim to treat it effectively.[18]

Physical complications

Acne can cause extensive and permanent **scarring**. Scarring is usually mild and only visible under bright lights. However, significant scarring (socially noticeable) is estimated to occur in 22% of people with acne[19] and has been implicated as a risk factor for suicide, particularly in men.[20] The development of post-acne scarring often represents the failure of adequate and timely medical therapy,[21] thus early and effective treatment of acne is the most appropriate way to prevent scarring.

Psychological complications

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.[22] The social, psychological, and emotional impairment that can result from acne has been reported to be similar to that associated with epilepsy, asthma, diabetes, and arthritis.[23] In particular, it is the psychosocial distress that acne produces that makes such a powerful argument for its timely and adequate treatment.

Even patients with mild to moderate acne have a higher prevalence of suicidal ideation, comparable to that among patients with far more chronic and disfiguring dermatological problems.[24] Other psychological consequences include lowered self-esteem and professional expectations, social inhibition, depression and anxiety.[25] Furthermore, severe acne has been associated with decreased employability in adult-hood.[26]

What are the goals of acne treatment?

The therapeutic goals in acne are to resolve existing lesions, prevent scarring and suppress the development of new lesions.[15] Successful management of acne involves choosing the right medications and helping the patient to use the medications as directed. The treatment of acne is often hampered by misunderstandings about the condition (See **Table TWO**) and unrealistic expectations of treatment. Patients often abandon treatment early because of slowness of response, skin irritation caused by treatment or inconvenient regimens. It is important to recognise that patients want treatment that produces rapid results with minimum inconvenience. Successful treatment depends not merely on the provision of efficacious products but also on support and encouragement to carry on with treatment for months rather than just days or weeks.

Myths and Frequently Asked Questions

Healthcare professionals have an important role in giving support to patients, stressing that acne is usually a treatable disease, particularly if the patient complies with treatment.[22] Some questions that are commonly asked are listed in **Table TWO**.

Are there any drugs that could cause or aggravate acne?

Topical and oral corticosteroids, anabolic steroids, androgens, iodides, bromides, ciclosporin, lithium, halothane, progestogens and vitamin B12 can all cause or aggravate acne.[7,33,34]

Counselling someone with acne:

► Reassure the person that acne is common, will not last forever, and effective treatment is available.
► Ask about previous treatments, including over-the-counter products.
► Patients should understand how to use their treatment and be aware of potential side-effects.
► The likely timescale for improvement and duration of treatment should be explained.
► Dispel common myths.
► Advise on good skin care. Skin should not be washed too frequently or vigorously; wash no more than twice a day using a mild soap or cleanser and lukewarm water. Do not use vigorous scrubbing. The use of abrasive soaps, cleansing granules, astringents, or exfoliating agents should be discouraged (advise use of a soft wash-cloth and fingers instead).[5]
► Advise patients to avoid picking spots, this leads to trauma, secondary infection, and scarring.

Table TWO: Myths about acne and commonly asked questions [22]

Patients will often carry beliefs about the cause(s) of their acne, [27-29] and will often blame themselves for the condition. Dispelling popular myths can have a positive impact on a person's motivation in coping with acne, improve adherence to treatment, and stop a person adopting unnecessary or potentially harmful behaviour.[18]

Is acne caused by poor hygiene?
Acne is not caused by poor hygiene and there is no evidence it is improved by cleaning.[30] In fact, excessive washing can aggravate acne. The black tip of a comedone is deposited melanin and oxidised sebum,[16] not dirt, and it cannot be removed by scrubbing. Vigorous washing or picking spots may actually make things worse.

Can I wear cosmetics?
Yes, especially if they are non-comedogenic but it is best to avoid heavy make-up.

Does diet influence acne?
Diet has little or no effect on acne. No studies have shown a link between acne and diet. In particular, no effect has been established between chocolate, dairy products, shellfish, or fatty foods.[31,32]

Does stress aggravate acne?
Patients sometimes report that stress aggravates 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 acne flare occurs in about 60% of females with acne.

Does sunshine help?
Many patients report benefit from sunshine, however, studies show sunlight probably has little benefit in acne.

Is acne infectious?
Acne is not infectious and cannot be passed on to other people. P. acnes is naturally present on skin but colonises follicles in acne.

How can compliance with acne treatments be improved?

Non-compliance is primarily the result of patient dissatisfaction due to treatment-related side-effects and the inability of some patients to follow what can be complex, multi-product regimens. There are several ways in which healthcare professionals can work with a patient to motivate him/her to comply with prescribed regimens, thereby improving response to treatment:

- treatment may be associated with short-term adverse effects. These may improve with continued use.
- at the start of treatment, acne may appear to initially worsen. It should be explained that this is because medications may be working on lesions that were not previously visible.
- explain why a specific treatment was chosen. This emphasises the individualised benefits and therefore encourages compliance
- suggesting how the recommended therapy can be incorporated into the patient's skin care regimen is important because tailoring treatment recommendations to fit within the patient's lifestyle will increase the likelihood of compliance.
- scheduling an initial follow-up visit between 4 and 8 weeks is important to assess response to treatment, as well as to give support to the patient.
- at each follow-up visit, ask about the patient's impression of treatment effectiveness and assess any adverse effects related to the current treatment.[35] Based on the observed response, the treatment plan is maintained, revised, or simplified according to the patient's specific needs.
- patients should be aware that long-term treatment is likely to be necessary to control their acne.

Assessing the severity of acne

When assessing the severity of acne, consider the distribution (face, back, chest, and upper arms), type and number of lesions (comedones, papules, pustules, nodules) and the presence or absence of scarring.[1,4] Physically, acne can be categorised as mild, moderate or severe (see **Table THREE**).

Table THREE: Grading of acne severity [1,36]

Mild acne	Moderate acne	Severe acne
Open and closed comedones (whiteheads and blackheads) a few papules and pustules	Comedones, more frequent papules and pustules, minimal scarring; can be subdivided into mainly comedonal or mainly inflammatory acne	Comedones, more pustules, and pustules plus nodular abscesses with more extensive scarring
Scarring often indicates previous episodes of severe acne (its presence may warrant more aggressive treatment to prevent further scarring).		

The psychological impact of acne

It is important to recognise that acne can have a substantial impact on a person's quality of life, affecting both self-esteem and psychosocial development.[37] Psychological morbidity is not a trivial problem, and it is compounded by multiple factors:[38]

- acne affects highly visible skin.
- popular culture and societal pressures dictate blemishless skin.
- acne can be dismissed by healthcare professionals as a trivial self-limiting condition.
- acne peaks in teenage years, a time crucial for building confidence and self-esteem.

Studies assessing the effect of acne on psychological health found a range of abnormalities including depression, suicidal ideation, anxiety, psychosomatic symptoms, shame, embarrassment, and social inhibition,[39] which improve with effective treatment.[40]

Many healthcare professionals and a significant proportion of the lay public dismiss acne as a natural part of growing up that has few real consequences. Yet considerable evidence shows that acne can be a psychologically damaging condition that lasts years.[26,33]

Acne severity and degree of psychological impairment do not necessarily correspond – mild disease in one person can cause high degrees of psychological disability, whereas another with more severe disease can seem less bothered by their acne.[41]

When is it appropriate to consider referring a person for specialist treatment?

Clinical Knowledge Summaries recommend the following referral advice for acne patients — see **Table FOUR**.

Table FOUR: Referral to specialist services for acne vulgaris [5]

Mild acne	• Refer to **psychiatry**, people who have severe psychosocial problems, including a morbid fear of deformity (body dysmorphic disorder). • Refer to **endocrinology or gynaecology**, women suspected of having an underlying endocrinological cause of acne (e.g. polycystic ovary syndrome).
Moderate acne	• Refer to **psychiatry**, people who have severe psychosocial problems, including a morbid fear of deformity. • Refer to **dermatology**: ○ People who are developing scarring, or are at risk of developing it, despite primary care interventions. ○ People who have moderate acne that has failed to respond adequately to treatment over a period of at least 6 months, and treatment failure should be judged on the person's perception of their condition. ○ People with features that make the diagnosis uncertain. • Refer routinely to **endocrinology or gynaecology**, women suspected of having an underlying endocrinological cause of acne.
Severe acne	• Refer urgently to a **dermatologist**, if the person has a severe variant of acne with systemic symptoms (such as acne fulminans). • Refer (soon) to a **dermatologist**, all other people with severe acne, including people with painful, deep, nodules or cysts (nodulocystic acne). • Refer to **psychiatry**, people who have severe psychosocial problems, including a morbid fear of deformity.

When should treatment of acne be started?

Acne medications should be started soon after the appearance of acne lesions to minimise the potential for physical and emotional scarring.[15,42] This is especially important because the clinical severity of acne does not correlate well with the impact on the patient; thus, the patient may feel significant embarrassment, anger, or other psychological disturbance even when disease is mild.[25]

How is it decided which treatment(s) should be used?

Treatment for acne is largely determined by factors such as severity, extent and duration of the disease; predisposition to scarring; post-inflammatory erythema and pigmentation; and patient preference and cost considerations. Response to previous treatment also needs to be considered, bearing in mind that many people will have bought topical preparations over-the-counter before consulting a healthcare professional. Patients should be advised of the importance of adherence to treatment to minimise the potential for scarring.[15]

The Global Alliance to Improve Outcomes in Acne[15] has produced useful guidance – this is summarised in **Table FIVE**.

Table FIVE: Global Alliance Acne Treatment Algorithm [15]					
	Mild acne		Moderate acne		Severe acne *
	Comedonal	Mixed and papular/pustular		Nodular	Nodular/conglobate
First choice	Topical retinoid	Topical retinoid + topical antibacterial	Oral antibacterial + topical retinoid +/- benzoyl peroxide	Oral antibacterial + topical retinoid + benzoyl peroxide	Oral isotretinoin
Alternatives	Different topical retinoid Or Azelaic acid Or Salicylic acid	Different topical retinoid + topical antibacterial Or Azelaic acid	Different oral antibacterial + different topical retinoid +/- benzoyl peroxide	Oral isotretinoin Or Different oral antibacterial + different topical retinoid +/- benzoyl peroxide	High dose oral antibacterial + topical retinoid + benzoyl peroxide
Alternatives (females only)			Oral anti-androgen + topical retinoid/azelaic acid +/- topical antibacterial	Oral anti-androgen + topical retinoid +/- oral antibacterial	High dose oral anti-androgen + topical retinoid +/- topical antibacterial
Maintenance therapy	Topical retinoid		Topical retinoid +/- benzoyl peroxide		
* Refer all people with severe acne for specialist assessment and treatment (for example with oral isotretinoin), and consider prescribing an oral antibiotic in combination with a topical drug whilst waiting for an appointment.					

Topical preparations for the management of acne

There are various topical treatment options for acne and no single agent has a beneficial effect on all the main factors in the disease pathogenesis.[43]

Formulation issues

The active ingredient of a topical preparation is a very important component of efficacy, but the vehicle also is an important component of drug tolerability. These factors, in turn affect whether the medication works – not just because of its efficacy but also because of any impact it may have on the use of and compliance with the medication regimen. Although no difference may exist between generic topical medications in the active ingredient, a difference in the vehicle means that the medication is different. As a result, a patient may have a different response (or lack of response) to the same medication in a different vehicle, and less-irritating products may be more likely to "work" because the patient is more compliant with therapy.[44]

The choice of formulation should be determined by skin type, acne distribution, and patient preference:[45]

- **gels**, **solutions** and **washes** are non-greasy and have a drying effect, which may be preferable for someone with oily skin.
- **creams** are moisturising, and may be preferable for someone with dry skin.
- **lotions** are useful for dry skin and for application to large areas of skin.
- **alcoholic bases** have a tendency to dry skin and may irritate sensitive skin.

How should topical agents be used?

The following advice should be given to all people using topical treatments:[5,33]

1. Wash the skin and leave to dry for about 20 minutes before applying treatment (to remove excess sebum).
2. Apply topical agents sparingly – more is not better. For example, a pea-sized amount of cream should be enough to treat the face.
3. Apply to all the affected areas, not just to the spots. Most topical drugs have a preventative action against new lesions forming, rather than treating lesions that have already formed, so areas that are clear of acne should also be treated until it is likely the disease is in full remission.
4. Avoid the eyes and mouth when applying a topical agent.
5. The person should be informed that topical treatments are effective and are worth persevering with, as improvements may not occur immediately, in fact there may be an initial deterioration in the condition.

Tolerability issues with topical preparations

Patients often report tolerability problems with topical acne treatments, for example, patients using benzoyl peroxide preparations may complain that the product causes skin dryness or irritation.[44] This is particularly problematic early in the course of treatment. To improve tolerability of topical agents, gradual dosing can be considered. For example, the use of a topical agent twice a week or every other day for the first few weeks of the regimen may be helpful; after this time, daily use can be instituted. Moisturisers can also be used to decrease irritation.[44]

For how long should topical treatments be used?

In general, topical treatment should be used for a period of **six weeks** before response is assessed.[46] Some improvement should become apparent during this time period, although maximal response may occur later. Once a satisfactory response has been achieved, it is uncertain how long treatment should be continued for. The decision should be made on a case by case basis. Factors to consider include the original severity of the acne, the psychological disability caused by the acne, and the adverse effects of treatment.

- **benzoyl peroxide** and **topical retinoids** can be used indefinitely as long as adverse effects do not occur. It may be possible to reduce application to alternate days or less during maintenance
- **topical antibacterials** should not usually be used long-term due to fears of resistance occurring (see later).
- **azelaic acid** should be used continuously over a period of several months. There is clinical experience for a continuous application time period of up to one year.

Most physicians probably prescribe topical therapies indefinitely provided the patient is responding.[22] Indeed it would be wise to tell the patient that some form of topical therapy will probably be required for much of the patient's acne-life. This could be anything from a few years up to 10 years or more.[22] A small number of patients (up to 7%) have acne persisting well up to the age of 40 years.[22]

Topical retinoids and related preparations

- Aknemycin® Plus (tretinoin + erythromycin)
- Differin® (adapalene)
- Epiduo® (adapalene + benzoyl peroxide)
- Isotrex® (isotretinoin)
- Isotrexin® (isotretinoin + erythromycin)
- Treclin® (tretinoin + clindamycin)

The topical retinoids available in the UK are **tretinoin**, **isotretinoin**, and **adapalene**. They are available in a variety of strengths and formulation. The effectiveness of topical retinoids in the treatment of acne is well documented,[48,49] although there is a lack of evidence from trials to show that any particular topical retinoid is superior to another, although higher -strength products, or products in an alcoholic vehicle, may irritate the skin more.[1]Topical retinoids should be a foundation in acne therapy for virtually all patients except those with the most severe disease.[15]

How do topical retinoids work?

Topical retinoids normalise follicular keratinisation, promote drainage of comedones, and inhibit new comedone formation.[50,51] They have been used historically mainly to treat comedones, but they are also effective at treating inflammatory lesions (if used in the longer term) by inhibiting microcomedone formation.[51] This is supported by good evidence from placebo-controlled trials.[10]

Topical retinoids decrease the number of comedones and inflammatory lesions by 40-70%.[4]

How should a topical retinoid be used?

Patients should apply a thin layer of the agent to any area affected by acne and continue until lesions clear. Without instruction many patients will apply only to inflamed spots. Application should be at bedtime because retinoids are inactivated by light.[52]

If irritation is particularly troublesome, consider advising the person to wash the product off their skin after a certain period (such as 20 minutes or more); most people can tolerate topical retinoids applied in this way.[5]

Several months of treatment with a topical retinoid may be needed to achieve an optimal response, and treatment should be continued until no new lesions develop.[8,42]

When are topical retinoids contra-indicated?

Topical retinoids should be avoided in:

- **pregnancy**.[42] Women of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered effective).[42]
- people with **very sensitive skin** (such as people with eczema).[5] Consider using adapalene in preference to tretinoin if sensitivity is a problem.[5]
- personal or familial history of **cutaneous epithelioma**.

What are the side-effects of using a topical retinoid?

The most common adverse effect associated with topical retinoid preparations is **local irritation**. Symptoms include erythema, scaling, dryness, itching, and burning. These effects often resolve after about 3 weeks usage,[53] but in the meantime, if symptoms are troublesome, consider the following measures:

- advise the person to persist with treatment, as irritation usually subsides over time.[16]
- apply the agent on alternate days to begin with, and increase to daily application once tolerance has developed,[5] or
- increase the product strength gradually as tolerance improves[45]
- switch to an alternative topical retinoid. More recently developed retinoids, such as adapalene, cause less irritation than tretinoin[5]
- advise the person to wash off the product after about 20 minutes; most people can tolerate topical retinoids applied in this way.
- consider changing the formulation of the drug (it may be the vehicle that is causing the irritation).

Topical retinoids increase the skin's **sensitivity to ultraviolet light**. This is especially important if they are also taking a tetracycline. Night usage of the product and the use of a sunscreen usually avoids this problem.[54]

Approximately 3 weeks after starting topical retinoid therapy, many patients report a **flare-up** of their acne.[55] There is then a further delay of 2 months before the retinoids exert their maximal effect.[54]

Maintenance treatment with topical retinoids

The nature of acne as a "chronic disease"[11] requires the definition of maintenance regimens to preserve the initial treatment success and prevent frequent relapses. Topical retinoids are suitable for maintenance treatment due to their multifactorial anti-acne efficacy without inducing bacterial resistance during long term treatment and their ability to prevent microcomedone formation. It has been shown that, after cessation of retinoid treatment, the number of microcomedones increases again,[56] which might explain the occurrence of frequent relapses when treatment is withdrawn following successful initial therapy.

Cautions with the use of topical retinoids

►Topical retinoids should be avoided in pregnancy

►Topical retinoids should be avoided in severe acne involving large areas.[42]

► Contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin should be avoided.[42]

► Use with caution in sensitive areas such as the neck, and accumulation in angles of the nose should be avoided.[42]

► Exposure to UV light (including sunlight, solariums) should be avoided; if sun exposure is unavoidable an appropriate sunscreen or protective clothing should be used.[42]

► Use of retinoids with abrasive cleansers, comedogenic or astringent cosmetics should also be avoided.[42]

► Allow peeling (e.g. resulting from the use of other irritant treatments) to subside before using a topical retinoid.[42]

Topical benzoyl peroxide

(Acnecide®, Brevoxyl®, PanOxyl®)

Benzoyl peroxide has been a widely used topical treatment for acne since the 1960s. Although a powerful oxidising agent, benzoyl peroxide is non-toxic to humans and is used in food processing to bleach flour and oils and in various industrial applications.[57] For the treatment of acne, benzoyl peroxide is available in a variety of strengths and formulations, both on prescription and over-the-counter from pharmacies. There is no evidence from trials that any one product is superior to another.

How does benzoyl peroxide act?

Topical benzoyl peroxide has numerous modes of activity. It has been shown to possess antimicrobial, anti-inflammatory,[58] keratolytic,[59] and wound-healing activity.[60,61]

It has been shown that *P. acnes* is capable of secreting protective biofilm polysaccharides,[62] which may explain some of the difficulty of delivering effective levels of antimicrobials within the skin. Benzoyl peroxide, with its oxidative properties, appears to have a role in destroying this biofilm. This model helps to illustrate the use of benzoyl peroxide in facilitating the delivery of topical antibacterials and other agents to the targeted bacteria.[62,63] It also explains why benzoyl peroxide has the ability to prevent or eliminate the development of *P. acnes* resistance.[64-68] In many years of use in acne management, bacterial resistance to benzoyl peroxide has not developed.

How should benzoyl peroxide products be applied?

Similar to other topical agents, benzoyl peroxide should be applied to the whole of the affected area, **not just the spots**.[69]

What are the adverse effects of benzoyl peroxide?

Benzoyl peroxide can cause **skin irritation**, **erythema**, **dryness**, and **skin peeling**. Although irritation tends to diminish as tolerance develops, it can be severe enough to limit use.[5] Minimise local adverse effects by considering the following:

- use a low strength of benzoyl peroxide. Evidence suggests that 2.5% preparations are as effective as 5% or 10% preparations,[45] and they are less likely to cause irritation. Thus, 2.5% is the concentration of choice
- wash off the application of benzoyl peroxide after 15 minutes initially, and increase exposure in increments of 15 minutes until the drug can be tolerated for 2 hours
- use water-based products instead of alcohol-based products[64]

Allergic contact dermatitis is a more serious adverse effect associated with benzoyl peroxide. It has been reported in approximately 1% to 3% of patients[70] and its occurrence necessitates discontinuing the treatment. It usually resolves when treatment is withdrawn.[45]

For how long should benzoyl peroxide be used?

The response to benzoyl peroxide is usually rapid, with improvement noted as early as five days after treatment has begun.[71,72] Most clinical improvement with benzoyl peroxide occurs within the first 6 weeks, although the maximal response may take up to 3 months. [5,46]

Once a satisfactory response has occurred, the decision to continue treatment should be made on an individual basis. Factors to consider include the original severity of the acne, the psychological disability caused by the acne, and adverse effects of treatment. Benzoyl peroxide may be used indefinitely (either alone or in combination with a topical retinoid) provided adverse effects do not occur. It may be possible to reduce application to alternate days or less frequently during maintenance.

Prescribing points – Benzoyl peroxide

► Avoid contact with eyes, mouth and mucus membranes [42]
► Benzoyl peroxide may cause bleaching of hair, clothing, towels, and bed-linen.[51]
► Avoid excessive exposure to sunlight.[42]
► Available as cream, gel, aquagel, and wash formulations.[42]
► For people with sensitive skin, weaker, aqueous products may be preferred.[5]
► Benzoyl peroxide inactivates topical retinoid when used concurrently. Therefore apply individual products 12 hours apart. A combined proprietary product (Epiduo®) is also available.[5,54,77]

Topical azelaic acid

(Finacea® and Skinoren®)

Azelaic acid is a naturally occurring decarboxylic acid that has been shown to be effective in reducing both inflammatory and non-inflammatory acne lesions.[69] Azelaic acid has moderate antibacterial and keratolytic activity as well as weak anti-inflammatory effects.[6] Clinical studies have shown it to be as effective as benzoyl peroxide or tretinoin in the treatment of mild to moderate acne and some patients prefer it because it is less likely to cause local irritation than benzoyl peroxide.[73-76] Because it is less irritant than other topical treatments, it can be a useful alternative if benzoyl peroxide or topical retinoids are not tolerated.[69]

What are the adverse effects of topical azelaic acid?

Mild transient **erythema** and **skin irritation** are the most frequently reported adverse events and these tend to subside after 3-4 weeks of continued use. No alteration in regimen is usually necessary.[51] Azelaic acid can **lighten the colour of the skin**, but this is rarely problematic in practice. Similarly, **photosensitivity** can occur but is rare and usually mild.[51]

Topical antibacterials

(Dalacin T®, Stiemycin®, Treclin®, Zindaclin® and Zineryt®)

Action

Topical antibacterials, such as clindamycin and erythromycin, are bacteriostatic for *P. acnes* and have also been demonstrated to have anti-inflammatory activities through inhibition of lipase production by *P. acnes* or inhibition of leukocyte chemotaxis.[71,78]

Efficacy

Topical antibacterials are generally well-tolerated and have been shown to reduce inflammatory lesions by 46-70% in several RCTs.[4]

Place in therapy

Topical preparations of erythromycin and clindamycin are used in the treatment of mild to moderate inflammatory acne[33,42,51] but appear to be no more effective than topical benzoyl peroxide or tretinoin.[42,79] Topical antibacterials are probably best reserved for patients who wish to avoid oral antibacterials or who cannot tolerate them.[42] Several topical antibacterial products are available and appear to be roughly equivalent in efficacy.[73]

Use

Where topical antibacterials are indicated (such as in papulopustular acne), they must be used in combination with a topical agent that has anti-resistance properties (such as benzoyl peroxide), not as monotherapy, and limited to short-term treatment (i.e. reviewed at 6-12 weeks).[43]

What are the adverse effects of topical antibacterials?

Mild skin **irritation** may occur with symptoms of erythema, peeling, dryness and burning, and may be due to the vehicle used.[71] Topical antibacterials rarely cause significant skin irritation unless there is a hypersensitivity reaction to the antibacterial used, in which case treatment should be stopped.

Although more commonly associated with *systemic* clindamycin, diarrhoea, abdominal pain, bloody diarrhoea, and colitis (including pseudomembranous colitis) have also been associated with topical clindamycin,[79] but this is likely to be very rare in practice.[71]

Is there a significant problem with resistance to topical antibacterials?

Resistance of *P. acnes* to topical antibacterials has become more prevalent and may result in loss of product efficacy.[70,80,81] In a large RCT in UK primary care, levels of resistance in *P. acnes* was found to be 47% with erythromycin and 41% with clindamycin.[46]

The problem of resistant *P. acnes* is most often seen with topical clindamycin and erythromycin, with some experts reporting neither of these agents useful unless combined with benzoyl peroxide.[18] Failure to respond to a topical antibacterial within 6 to 8 weeks should automatically prompt a change in treatment.[18]

Other topical preparations

Abrasive agents and vigorous scrubbing are not beneficial in acne and should be avoided,[42] as they can aggravate acne by promoting the development of inflammatory lesions.[16,97] **Peeling agents** such as sulphur-containing preparations and salicylic acid are generally considered inferior to the more modern topical treatments for acne. **Salicylic acid** is available in various preparations for sale direct to the public for the treatment of mild acne.[42] Salicylic acid may be an option for someone who cannot tolerate retinoids.[98] **Nicotinamide** (Nicam®) has potent anti-inflammatory activity *in vitro*, but there is little data to support its efficacy.[45]

Using combinations of topical agents

Given the multiple factors as well as the complex inter-relationship of these factors contributing to acne development, combination therapy targeted towards simultaneous processes has been increasingly favoured in practice. This can be done by alternating separate products or using proprietary combination products (see **Table SIX**). The choice should be made according to patient's preference bearing in mind that combined proprietary products:[5]

- do not allow for individual titration of component agents.
- are usually formulated with an alcoholic base, which may irritate sensitive skin.
- may be more convenient for people to use as they reduce the numbers of products and applications required and thus may increase compliance.
- are generally more expensive than single products. [43]

Prescribing point – topical antibacterials

Monotherapy with topical antibacterials should **not** be used routinely because *P. acnes* may become resistant within one month after daily treatment has begun.[82] Resistance can be avoided if a topical antibacterial is combined with benzoyl peroxide.[83]

Steps to combat bacterial resistance:

► Do not use topical antibacterials where other topical acne treatments can be expected to bring the same benefit.[42,71]
► Do not use a topical antibacterial alone;[71] rather use combined therapy with retinoids or benzoyl peroxide.[70]
► Stop topical antibacterials when there is no further improvement or the improvement is only slight.[71]
►6-8 weeks into treatment might be an appropriate time point at which to assess response to a topical antibacterial.[81]
► Where possible, treatment with topical antibiotic should be limited to 12 weeks duration.[5]
► Do not combine topical and systemic antibacterials.[71]
► Check the patient's compliance with treatment.

Table SIX: Practical considerations when combining topical treatments for acne			
Combination	**Proprietary combinations available**	**When combining separate products**	**Comments**
Benzoyl peroxide + topical antibacterial	Benzoyl peroxide + clindamycin (Duac® Once Daily) Benzoyl peroxide + potassium hydroxyquinoline sulphate (Quinoderm®)	Apply 12 hours apart (e.g. benzoyl peroxide at night and topical antibacterial in the morning). Avoid use of two products that have an alcoholic base, as this may increase skin irritation.	Concomitant use of benzoyl peroxide and topical clindamycin or erythromycin is more effective than either component alone [67,84-86] and decreases the risk of resistance. [68,83] Duac® gel needs to be refrigerated until it is dispensed. After dispensing, it then needs to be stored below 25°C. Shelf life after dispensing = 2 months.
Benzoyl peroxide + topical retinoid	Benzoyl peroxide + adapalene (Epiduo®)	Apply 12 hours apart (e.g. topical retinoid at night and benzoyl peroxide in the morning). Both products may irritate the skin; switch to an alternative combination if this is a problem.	The combination of a topical retinoid plus benzoyl peroxide is a logical formulation, because it targets 3 of 4 pathophysiologic factors and the antibacterial portion (benzoyl peroxide) is rapidly bactericidal without evidence of bacterial resistance. Benzoyl peroxide may oxidize a retinoid if they are applied as separate products.[77]
Topical retinoid + topical antibacterial	Tretinoin + erythromycin (Aknemycin® Plus) Isotretinoin + erythromycin (Isotrexin®) Tretinoin + clindamycin (Treclin®)	Apply 12 hours apart (e.g. topical retinoid at night and topical antibacterial in the morning).	A combination of topical retinoid and topical antibacterial is more effective than either agent used alone.[73,87-92] However, the agents should be applied at separate times, unless they are known to be compatible. Patients on combination therapy show faster signs of improvement.[92-95] This is believed to lead to greater patient adherence and reduce the risk of *P. acnes* resistance.
Notes:[58,96] ► Topical retinoids improve the penetration of other topical medications. ► Topical retinoids may help to improve the hyperpigmentation that is left in darker skin types after the resolution of inflammatory lesions.			

Oral preparations for the management of acne

Oral antibacterials

When topical agents are insufficient or not tolerated, or in cases of moderate to severe acne, especially when the chest, back and shoulders are involved, systemic antibacterials are often considered the next line of treatment.[99,100]

Oral antibacterials are usually reserved for:[33,70,101]

- moderate inflammatory acne
- patients who have not responded adequately to topical therapy or who cannot tolerate it
- those at greatest risk of scarring
- where lesions are predominantly on the chest, back, shoulders making topical therapy impractical,

Anti-comedonal treatment (e.g. with topical benzoyl peroxide) may also be required.[42]

Oral antibacterials reduce *P. acnes* within follicles, thereby inhibiting production of bacteria-induced inflammatory cytokines.[102] Compared to topical antibacterials, oral antibacterials are more effective and have a faster onset of action. Unfortunately, the risk of antibacterial resistance is significant.[103]

Which oral antibacterials are suitable for the treatment of acne?

Of the oral antibacterials, **oxytetracycline**, **tetracycline** and **lymecycline** are considered first-line (see **Table SEVEN** for doses). Alternatives to tetracyclines include **erythromycin**, and **doxycycline.** **Minocycline** is no longer considered suitable as a first-line acne treatment (see later).

Erythromycin should only be used as a *first-line* agent when tetracyclines are contraindicated.[66] There is a lack of evidence from placebo-controlled trials to verify the efficacy of erythromycin, although evidence from comparative trials indicates it is probably as effective as tetracyclines. However, there is evidence from observational and controlled studies that there are particular problems with the development of bacterial resistance to erythromycin. Erythromycin can be used as *second-line* choice following therapeutic failure of a tetracycline.

No oral antibacterial has been shown to be more effective than any other,[104] but clinical experience indicates that some people respond better to one antibacterial than another. There is no evidence that higher doses are more effective than lower doses or that controlled-release preparations are necessary.[105,106]

Northern Ireland Formulary choices

For local guidance on choice of antibacterials:

NI Formulary website http://niformulary.hscni.net
Or
MicroGuide http://cms.horizonsp.co.uk/viewer/nipha

An App is also available via App Store http://kaywa.me/7IeWs or Google Play http://kaywa.me/T1hzb

Table SEVEN: Oral antibacterial therapy for acne vulgaris [42,107]		
Antibacterial and dose	**Cost of 28 days treatment**	**Notes**
Doxycycline 100mg daily	£2.68	Contraindicated in pregnant women or in children under 12 years of age. Can be taken with food. Adverse reactions: GI upset, phototoxicity.
Erythromycin TABLETS 500mg twice daily	£6*	Safe in pregnant women and children. May cause GI upset. 42% of patients may show resistance.[108]
Lymecycline 408mg daily	£6.95	Contraindicated in pregnant women or in children under 12 years of age. Can be taken with food.
Oxytetracycline 500mg twice daily	£3.60	Contraindicated in pregnant women or in children under 12 years of age. Needs to be taken on an empty stomach.
Tetracycline 500mg twice daily	£7.92	Contraindicated in pregnant women or in children under 12 years of age. Needs to be taken on an empty stomach.
*Prescribe erythromycin as tablets; they cost considerably less than the capsules.[42]		

Why is minocycline not considered to be a first-line acne treatment?

Minocycline is NOT a first-line acne treatment based on the following:

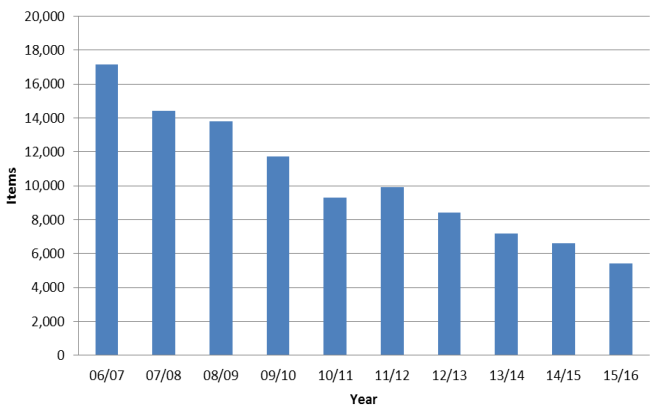
- evidence that minocycline might be more effective than other tetracyclines is, at best, weak, being limited to a few, poor quality trials with questionable results.[109,110]
- minocycline seems to be almost unique within tetracyclines in causing potentially irreversible slate-grey hyperpigmentation of the skin. Pigmentation of other tissues (e.g. the sclera, conjunctiva) has also been reported.[111,112]
- minocycline is associated with a higher risk of inducing lupus-like syndrome.[109] The overall hazard ratio for the association of minocycline to lupus erythematosus was 2.64 (95% confidence interval = 1.51 to 4.66).[113]
- minocycline has been associated with autoimmune hepatitis or other types of hepatotoxicity.

The SmPC for minocycline products recommends that if the drug is continued for over 6 months, patients should be monitored at least 3-monthly for features of hepatitis, systemic lupus erythematosus or unusual pigmentation.

Considering the non-superiority of its effects in acne, its specific adverse effects, its price and the alternatives, the benefits of minocycline are significantly lower than the potential risks.[114] Minocycline may be an effective treatment for *some* patients with acne but there is a lack of evidence that it is any better than other options.[104,115]

Consequently, the number of prescriptions for minocycline in NI has fallen steadily over the last ten years, as **Graph ONE** below shows.[189]

Graph ONE:



Actions for prescribers: Minocycline

The potential for serious adverse reactions with minocycline has led manufacturers to recommend "periodic" monitoring of blood, renal, and liver function. The BNF recommends monitoring for hepatotoxicity, pigmentation and systemic lupus erythematosus every 3 months, if the drug is taken for 6 months or more.[42]

After what time should efficacy of an oral antibacterial be assessed and for how long should treatment be continued?

Oral antibacterials usually cause a rapid and sustained improvement in acne; data from a large RCT indicated that 6-8 weeks is an appropriate time to assess response.[105] However, maximal improvement may only be apparent after 3-4 months, and it has been recommended that treatment should be continued for a minimum of 3 months before it is assumed to be ineffective.[16]

If an individual *does not respond* to oral antibacterials or stops responding, there is no evidence that increasing the frequency or dose is helpful. Such strategies increase the risk of resistance developing without increasing efficacy. The oral antibacterial should be stopped if no further improvement is evident;[38] a different oral antibacterial can be tried.[42,52]

If patients *respond well*, the oral antibacterial should be continued for 6-8 months in total and then the patient maintained on an appropriate topical regimen.[52] Oral antibacterials should NOT be routinely used for maintenance because alternatives exist with similar efficacy and preventative action.[66]

What happens when the course of oral antibacterial finishes?

An oral antibacterial can be very helpful in bringing moderate to severe acne under control. However, once adequate control is achieved, the oral antibacterial may be discontinued. Many patients do well with subsequent use of a topical regimen with a combination topical retinoid plus topical antibiotic or retinoid plus benzoyl peroxide combination. Maintenance therapy with topical retinoids or retinoid combinations may obviate the need for long-term systemic antibiotics.[116]

What are the adverse effects of the oral antibacterials used to treat acne?

The incidence of significant adverse effects with oral antibacterial use is low. However, adverse effect profiles may be helpful for each oral antibacterial used in the treatment of acne.

Tetracyclines

- Gastrointestinal disturbances are the most common adverse effects associated with use of tetracyclines orally. **Nausea**, **vomiting** and **diarrhoea** are the most common adverse effects. Tetracycline and oxytetracycline should be taken on an empty stomach, which may increase nausea. Doxycycline, lymecycline, and minocycline may be taken with food, which may help the person tolerate the drug.[51]
- **Vulvovaginal candidiasis** may occur as a result of the broad spectrum nature of tetracyclines.[45]
- Tetracyclines can cause severe **oesophagitis**, presenting as burning pain in the lower chest. To counteract this, it is recommended that tetracyclines are taken in an upright position with plenty of water, without chewing or breaking the tablets or capsules.[42]
- **Photosensitivity** may also occur with tetracycline use, especially doxycycline. As a precaution, people taking the drug should be advised to limit their exposure to sunlight (cover up with clothes and use sunblock), and avoid sun-lamps. Doxycycline has been reported to cause photosensitivity in 13 per 1 million prescriptions written.[117] Lymecycline is much less phototoxic than doxycycline.[118]
- **Benign intracranial hypertension** is a rare but important adverse effect of tetracycline-like drugs.[45] If a person taking a tetracycline develops headache and visual disturbances, the drug should be stopped immediately and advice sought.
- Tetracyclines as a class should not be used in pregnant women or in patients younger than 12 years to avoid the risks of **tooth discolouration** and **bone growth retardation** in the foetus or child.[51] When administered to children, all tetracyclines induce grey (63%), yellow (28%), or brown (10%) discoloration of teeth.[119] In adults, only minocycline induces tooth discolouration.

Minocycline

Minocycline shares most of the adverse effects that occur with other tetracyclines, but it is also associated with several adverse effects that are rarer but more severe:

- Drug-induced **hepatitis** is the most severe adverse effect associated with minocycline use, and this can be life-threatening. All tetracyclines have the potential to cause hepatic inflammation; however, it seems to be more common with minocycline.[109] This has led some physicians to suggest that minocycline should only be offered as a second-line treatment, after other antibacterials have failed to have a satisfactory effect.[120]
- Minocycline can cause **vestibular disturbances**. Typically, these present as headache, dizziness, ataxia, and drowsiness.[51] These adverse symptoms are usually reversible, and may be decreased by starting with a low dose of minocycline and increasing gradually.[45]
- **Skin discolouration** is a possible adverse reaction to minocycline, and presents as a grey-blue discolouration, particularly in areas that have been inflamed by acne.[45] This effect may be related to the cumulative dose of minocycline taken and may be irreversible.[109,111]

Erythromycin

Gastrointestinal adverse effects are common with prolonged erythromycin use, and these may be severe enough to limit its use.[45] However, erythromycin can be taken with food, which may help reduce nausea.

How significant a problem is resistance to oral antibacterials in the management of acne?

A major problem affecting oral antibacterial use in acne is bacterial resistance, which has been increasing.[80,121] Resistance has been seen with all antibacterials used to treat acne, but is most common with erythromycin.[1]

How can the chances of developing antibacterial resistance be lowered?

In an attempt to counteract the development of antibacterial resistance, consider the following:[16,122]

- stress the importance of adherence to treatment.
- prescribe adequate doses of an oral antibacterial.
- use antibacterials only when there is no other option.
- avoid concomitant use of oral and topical antibacterials.[42,71,82]
- use antibacterials for the minimum time possible.

If an oral antibacterial has failed and resistance is suspected, it is probably justified to try another antibacterial from a different class. However, avoid routinely switching or rotating antibacterials, as this practice promotes resistance.[122] If acne relapses after an antibacterial is stopped, restart the regimen if this was originally effective.

Hormonal treatment

Co-cyprindiol (2mg cyproterone acetate with 35micrograms ethinylestradiol)

Co-cyprindiol is licensed for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and /or hirsutism, in women of reproductive age. Co-cyprindiol should only be used after topical therapy or systemic antibiotic treatments have failed.[123] Co-cyprindiol is also an effective combined oral contraceptive (COC), but is *not licensed* for the sole purpose of oral contraception. Brands include Dianette®, Acnocin®, Cicafem®, Clairette®.

What are the adverse effects of co-cyprindiol?

Co-cyprindiol has been found to be associated with an increased risk of **venous thromboembolism** (VTE). The risk of VTE is considered to be 1.5 to 2 times higher compared with levonorgestrel-containing pills. Other adverse effects associated with co-cyprindiol are similar to those of other COCs and include **breast tenderness**, **mood changes**, and body **weight changes**.

For how long should co-cyprindiol be given?

A response to hormonal intervention may be seen after one menstrual cycle, but 3-6 months are usually needed to judge the full effect. [33,36]

Co-cyprindiol should be continued for only 3-4 menstrual cycles after the woman's acne has resolved, due to the risk of serious adverse effects such as VTE.[126] If contraceptive cover is still required after the course of co-cyprindiol is finished, the patient should change to another oral contraceptive. Note: other COCs can be effective in acne management (although unlicensed) and may be continued indefinitely.

If acne recurs after co-cyprindiol has been stopped can it be re-started?

If, on withdrawal of co-cyprindiol, the patient's acne relapses, then a repeat course of co-cyprindiol is indicated. No set interval between courses is suggested, but in order to maintain the menstrual cycle, it is suggested leaving a minimum of one month before restarting another course.[123]

Combined oral contraceptives

There is good evidence from placebo-controlled trials that COCs are effective in reducing lesion count, acne severity, and the woman's perception of the condition. [34,127-131] Clinical observation indicates that women with deep-seated nodules of the lower face and neck are a group in whom hormonal treatment may be especially useful.[82]

In general, after 6 to 9 months of use of a COC, there is a reduction in inflammatory lesions by 30-60%, an improvement of acne in 50-90% of patients, and non-inflammatory facial acne lesions are also reduced.[33,34] Of note, hormonal therapies seem to work best in women who report acne flare-up premenstrually.[132]

How do COCs work in the treatment of acne?

The beneficial effects of COCs on acne have been noted for many years.[97] COCs are useful in acne because oestrogen inhibits sebaceous gland activity and suppresses ovarian and adrenal androgen production. Androgens are one of the main factors in acne pathogenesis because they enhance follicular keratosis and influence sebum production.[133-135] There is no acne without sebum, which serves as a nutrient source for *P. acnes*, and androgens are the major sebotropic hormones. The increased sebum production in acne patients may be due to increased circulating androgens or a hyperresponsiveness of the target organ (the pilosebaceous unit) to androgens, or both.[1,82]

Prescribing points – Co-cyprindiol

► Brands include Acnocin®, Cicafem®, Clairette®, Dianette.®
► VTE occurs more frequently in women taking co-cyprindiol than those taking a low-dose COC. Prescribers are reminded that co-cyprindiol should not be used solely for contraception.[126]

Which COC?

There is a lack of good quality comparative trials to show any particular COC is superior to another.[5]
Note: **none of the COCs are licensed to treat acne**.

Progestogens have androgenic properties. Thus, progestogen-only contraceptives often worsen acne and should be avoided in acne patients.[33,34]

Oral retinoids

Oral isotretinoin is a synthetic form of vitamin A. Oral isotretinoin is indicated for severe acne such as nodulocystic and conglobate acne, but it is commonly used for severe acne that has failed to respond to adequate courses of standard oral and topical therapies.[139] It is also particularly useful in women who develop acne in the third or fourth decades of life, since late onset acne is frequently unresponsive to antibacterials.[42]

When the use of this agent is being considered, an assessment of the severity of disease should include the effect of the acne on the person, such as the potential for scarring.[33]

Isotretinoin is a toxic drug that should be prescribed **only by, or under the supervision of, a consultant dermatologist**. In Northern Ireland, oral isotretinoin is on the RED list for specialist medicines. This means that the responsibility for prescribing it remains with the consultant or specialist clinician. Supply of isotretinoin is via the relevant **hospital** pharmacy. (See www.ipnsm.hscni.net).

Prescribing and dispensing oral retinoids

GPs and other primary care prescribers should NOT prescribe oral retinoids, even on receipt of a request to do so from a private medical clinic/practice.

Community pharmacists should NOT dispense oral retinoids, even on receipt of a private prescription.

Private medical facilities have arrangements in place to prescribe and dispense oral retinoids themselves as patients must be enrolled in a pregnancy monitoring scheme.

How effective is oral isotretinoin in the treatment of acne?

Oral isotretinoin is the most effective drug available for the treatment of acne. However, despite its undeniable effectiveness, isotretinoin is not a curative drug.[140] After one course of oral isotretinoin:

- 40% of patients will be free of acne.
- 40% of patients will have recurrence of acne of low severity that responds to medications to which the acne had been previously resistant.
- 20% will need repeated treatment with oral isotretinoin at a future time;[72] factors linked with relapse are younger age, female gender, pre-pubertal acne or truncal acne and a high number of inflammatory lesions at the end of treatment.[141]

How does oral isotretinoin work in the treatment of acne?

Oral isotretinoin is thought to treat all the primary aetiologic factors of acne pathogenesis by: [36,142-151]

- decreasing sebum production (by 70%)
- normalising follicular keratinisation
- reducing follicular colonisation with *P. acnes*
- reducing inflammation

The combination of these actions explains the efficacy of oral isotretinoin.[82,152]

What are the side-effects of oral isotretinoin?

Isotretinoin has a significant pattern of adverse effects. The pattern is similar to that seen in hypervitaminosis A. Adverse effects associated with isotretinoin range from mild, temporary effects which resolve after the drug is discontinued, to rarer potentially fatal conditions.[153]

Milder side-effects
Most patients receiving isotretinoin experience variable dryness of skin and mucous membranes including nose, eyes and lips. These symptoms are dose-related, and may lead to active inflammation, e.g. cheilitis. This can usually be managed with the regular use of emollients, eye drops and lip balms. Because of these issues concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase.[139] Drying of the nasal mucosa may lead to colonisation with *Staphylococcus aureus*, the potential complications of which include abscesses, conjunctivitis, impetigo, cellulitis, and folliculitis.[154]

Rarer side-effects
Rarer side-effects include:[139,154-156]

- myositis and arthralgia
- intracranial hypertension
- hair loss
- drowsiness, dizziness and visual disturbances (patients should be warned that if they experience these effects, they should not drive, or operate machinery)
- erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (patients should be informed of the signs and symptoms of these serious skin eruptions and advised to stop treatment and contact their healthcare professional immediately if any of these arise)[157]
- elevated liver enzymes
- hypercholesterolaemia and elevation of serum triglycerides

Hypertriglyceridaemia, hypercholesterolaemia and elevated liver enzymes occur in 15-25% of patients but are rarely of clinical significance or severe enough to require dose reduction or discontinuation of treatment. Lipids rapidly drop to pretreatment levels after cessation of therapy. Monitoring of liver enzymes and lipids is now recommended before and 1 month after starting treatment and every 3 months thereafter.[139] In the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.[139]

Associations with use of isotretinoin and inflammatory bowel disease are controversial[158,159] as are associations with depression and suicide[160] (see later).

Teratogenicity
The most severe safety issue concerning oral isotretinoin is teratogenicity and the consequences of taking isotretinoin while pregnant are well described.[161] The main abnormalities found in isotretinoin embryopathy are craniofacial, central nervous system, cardiovascular and thymic. [162-166] In addition, foetal exposure to isotretinoin is associated with a high risk of adverse outcome with respect to mental functioning.[167] The UK National Teratology Information Service estimates that in foetal exposure to isotretinoin, 30% of infants with no gross malformations have mental retardation, and up to 60% have impaired neuropsychological function.[168]

The MHRA has issued formal prescribing guidance for isotretinoin that is designed to reduce the risk of pregnancy during treatment.[169] The regulations require that women are carefully counselled regarding the risks of pregnancy and should use effective contraception for one month before therapy, during therapy and for one month afterwards. Two simultaneous forms of contraception, including a barrier method, should preferably be used. Pregnancy tests are now required before treatment, every four weeks during treatment and five weeks afterwards.

MHRA guidance can be found at the following link: https://www.gov.uk/drug-safety-update/oral-retinoids-pregnancy-prevention-reminder-of-measures-to-minimise-teratogenic-risk

What about reports linking oral isotretinoin with depression or suicidal ideation?
Beginning in 1983, there were a number of case reports[170-172] as well as small case studies[173,174] suggesting that mood change, and particularly depression, can occur in association with treatment with oral isotretinoin. The clinical data supporting a relationship between isotretinoin and mood change are conflicting, with several small inconclusive studies, often with significant design faults. The current literature does not support nor disprove a causative link between isotretinoin and depression.[175,176] In particular it has not been possible to distinguish accurately between mood change due to the drug and to the acne itself (depression and suicidal ideation occur with severe acne in the absence of isotretinoin treatment[177-180]).

Healthcare professionals should be alert to the potential psychiatric side-effects which are not restricted to depression. When symptoms have been described, they have most commonly been fatigue, irritability, poor concentration, sadness, crying spells, loss of motivation and forgetfulness. It is estimated that a physician would need to start 2000 patients on oral isotretinoin in a year to see one additional suicide attempt.[177] The time course of onset of mood alteration is variable, but is often later in treatment, and in some cases depressive symptoms have occurred only in second or even third courses of therapy. Resolution of symptoms is usually rapid, within days to weeks of discontinuing the drug, although there are instances of prolonged illness requiring antidepressant therapy.[181]

Based on the available evidence, there is no need to discourage the use of isotretinoin in severe acne in patients who will benefit from treatment in terms of physical and psychological improvement. However, the following are recommended:[182,188]

1. A direct enquiry about previous psychiatric health should be made for all patients who are being considered for isotretinoin and the facts recorded in the notes
2. All patients, and their families, should be made aware of the possible potential for mood change
3. Direct enquiry about psychological symptoms should be made at each clinic visit.

What are the clinically significant drug interactions of oral isotretinoin?
Patients should not take **vitamin A** concurrently due to the risk of developing hypervitaminosis A.[139] Cases of benign intracranial hypertension have been reported with concomitant use of isotretinoin and **tetracyclines**. Therefore, concomitant treatment with tetracyclines should be avoided.[139] Concurrent administration of isotretinoin with **topical keratolytic** or **exfoliative** anti-acne agents should be avoided as local irritation may increase.[139] Oral isotretinoin can reduce the serum levels of **carbamazepine**, concurrent use requires close monitoring.[42]

Prescribing points – oral retinoids

Although not prescribed in primary care, healthcare professionals in primary care should note:

► Referral of patients who would benefit from isotretinoin is the responsibility of the GP. GPs are in a position not only to make suggestions or recommendations to patients regarding referral for consideration of isotretinoin treatment, but also to ensure patient decisions are based on realistic understanding of the benefits and risks of therapy.[183]

► Isotretinoin is an efficacious and widely-used therapy for severe acne[184,185] but it is recognised as having a wide range of side-effects.

► Doses of 0.5 to 1mg/kg per day are typical. It is given for at least 16 weeks; repeat courses are not normally required. Improvement may continue for up to 5 months after ending therapy.[51]

► GPs may find themselves in the middle of the debate surrounding depression trying to allay their patient's anxieties and doubts.[21] Although a causal link between isotretinoin use and psychiatric changes (including suicidal ideation) has **not** been established, the possibility should be considered before initiating treatment; if psychiatric changes occur during treatment, isotretinoin should be stopped, the prescriber informed, and specialist psychiatric advice should be sought.[42] A close partnership between dermatologist and GP is likely to be optimal in this situation.[183]

Websites:

British Association of Dermatologists:

(www.bad.org.uk) - Patient information leaflets, section for healthcare professional, specialist groups.

British Skin Foundation: (www.britishskinfoundation.org.uk) - A charity for skin disease research. Patient information leaflets, newsletters.

European Academy of Dermatology and Venereology: (www.eadv.org) - For healthcare professionals.

European Society for Dermatologic Research: (www.esdr.org) - For healthcare professionals, supports investigational dermatology.

Reference List

1. Strauss, J. S., Krowchuk, D. P., Leyden, J. J., et al. Guidelines of care for acne vulgaris management. J.Am.Acad.Dermatol. 2007; 56: 651-663.
2. Jabbour, S. A. Cutaneous manifestations of endocrine disorders: a guide for dermatologists. Am.J.Clin.Dermatol. 2003; 4: 315-331.
3. Tourniaire, J. and Pugeat, M. Strategic approach of hyperandrogenism in women. Horm.Res. 1983; 18: 125-134.
4. Haider, A. and Shaw, J. C. Treatment of acne vulgaris. JAMA 2004; 292: 726-735.
5. Acne vulgaris. Clinical Knowledge Summaries 2014;
6. Gollnick, H. Current concepts of the pathogenesis of acne: implications for drug treatment. Drugs 2003; 63: 1579-1596.
7. Acne vulgaris. Primary Care Dermatology Society 2010;
8. Purdy, S. and de, Berker D. Acne. BMJ 2006; 333: 949-953.
9. Clark, C. Acne: causes and clinical features. Clinical Pharmacist 2009; 1: 163-167.
10. Purdy, S. Acne vulgaris. Clin.Evid. 2006; 2183-2201.
11. Gollnick, H. P., Finlay, A. Y. and Shear, N. Can we define acne as a chronic disease? If so, how and when? Am.J.Clin.Dermatol. 2008; 9: 279-284.
12. Capitanio, B., Sinagra, J. L., Ottaviani, M., et al. Acne and smoking. Dermatoendocrinol. 2009; 1: 129-135.
13. Schafer, T., Nienhaus, A., Vieluf, D., et al. Epidemiology of acne in the general population: the risk of smoking. Br.J.Dermatol. 2001; 145: 100-104.
14. Klaz, I., Kochba, I., Shohat, T., et al. Severe acne vulgaris and tobacco smoking in young men. J.Invest Dermatol. 2006; 126: 1749-1752.
15. Thiboutot, D., Gollnick, H., Bettoli, V., et al. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. J.Am.Acad.Dermatol. 2009; 60: S1-50.
16. MeReC. The treatment of acne vulgaris: an update. MeReC Bulletin 1999; 10: 29-32.
17. Gupta, M. A., Johnson, A. M. and Gupta, A. K. The development of an Acne Quality of Life scale: reliability, validity, and relation to subjective acne severity in mild to moderate acne vulgaris. Acta Derm.Venereol. 1998; 78: 451-456.
18. Webster, G. F. Acne vulgaris. BMJ 2002; 325: 475-479.
19. Healy, E. and Simpson, N. Acne vulgaris. BMJ 1994; 308: 831-833.
20. Cotterill, J. A. and Cunliffe, W. J. Suicide in dermatological patients. Br.J.Dermatol. 1997; 137: 246-250.
21. Goodman, G. Acne and acne scarring - the case for active and early intervention. Aust.Fam.Physician 2006; 35: 503-504.
22. Cunliffe, W. Acne. Pharmaceutical Journal 2001; 267: 749-752.
23. Mallon, E., Newton, J. N., Klassen, A., et al. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. Br.J.Dermatol. 1999; 140: 672-676.
24. Gupta, M. A. and Gupta, A. K. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. Br.J.Dermatol. 1998; 139: 846-850.
25. Lasek, R. J. and Chren, M. M. Acne vulgaris and the quality of life of adult dermatology patients. Arch Dermatol. 1998; 134: 454-458.
26. Cunliffe, W. J. Acne and unemployment. Br.J.Dermatol. 1986; 115: 386.
27. Rasmussen, J. E. and Smith, S. B. Patient concepts and misconceptions about acne. Arch.Dermatol. 1983; 119: 570-572.
28. Brajac, I., Bilic-Zulle, L., Tkalcic, M., et al. Acne vulgaris: myths and misconceptions among patients and family physicians. Patient.Educ.Couns. 2004; 54: 21-25.
29. Tan, J. K., Vasey, K. and Fung, K. Y. Beliefs and perceptions of patients with acne. J.Am.Acad.Dermatol. 2001; 44: 439-445.
30. Magin, P., Pond, D., Smith, W., et al. A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight. Fam.Pract. 2005; 22: 62-70.
31. Adebamowo, C. A., Spiegelman, D., Danby, F. W., et al. High school dietary dairy intake and teenage acne. J.Am.Acad.Dermatol. 2005; 52: 207-214.
32. Fulton, J. E., Jr., Plewig, G. and Kligman, A. M. Effect of chocolate on acne vulgaris. JAMA 1969; 210: 2071-2074.
33. James, W. D. Clinical practice. Acne. N.Engl.J.Med. 2005; 352: 1463-1472.
34. Arowojolu, A. O., Gallo, M. F., Lopez, L. M., et al. Combined oral contraceptive pills for treatment of acne. Cochrane.Database.Syst.Rev. 2009; CD004425.
35. Del Rosso, J. Q. and Tanghetti, E. The clinical impact of vehicle technology using a patented formulation of benzoyl peroxide 5%/clindamycin 1% gel: comparative assessments of skin tolerability and evaluation of combination use with a topical retinoid. J.Drugs Dermatol. 2006; 5: 160-164.
36. Kraft, J. and Freiman, A. Management of acne. CMAJ. 2011; 183: E430-E435.
37. Magin, P., Adams, J., Heading, G., et al. Psychological sequelae of acne vulgaris: results of a qualitative study. Can.Fam.Physician 2006; 52: 978-979.
38. Williams, H. C., Dellavalle, R. P. and Garner, S. Acne vulgaris. Lancet 2011;
39. Kubota, Y., Shirahige, Y., Nakai, K., et al. Community-based epidemiological study of psychosocial effects of acne in Japanese adolescents. J.Dermatol. 2010; 37: 617-622.
40. Hahm, B. J., Min, S. U., Yoon, M. Y., et al. Changes of psychiatric parameters and their relationships by oral isotretinoin in acne patients. J.Dermatol. 2009; 36: 255-261.
41. Law, M. P., Chuh, A. A., Lee, A., et al. Acne prevalence and beyond: acne disability and its predictive factors among Chinese late adolescents in Hong Kong. Clin.Exp.Dermatol. 2010; 35: 16-21.
42. RPSGB / BMA. British National Formulary. BNF June 2016 ;
43. What role for topical antibacterials in acne? Drug Ther.Bull. 2010; 48: 141-144.
44. Eichenfield, L. F., Fowler, J. F., Jr., Fried, R. G., et al. Perspectives on therapeutic options for acne: an update. Semin.Cutan.Med.Surg. 2010; 29: 13-16.
45. Brown, S. K. and Shalita, A. R. Acne vulgaris. Lancet 1998; 351: 1871-1876.
46. Ozolins, M., Eady, E. A., Avery, A., et al. Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne. Health Technol.Assess. 2005; 9: iii -212.
47. Bayer. Skinoren Cream. Summary of Product Characteristics 2016;
48. Shalita, A., Weiss, J. S., Chalker, D. K., et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. J.Am.Acad.Dermatol. 1996; 34: 482-485.
49. Grosshans, E., Marks, R., Mascaro, J. M., et al. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. Br.J.Dermatol. 1998; 139 Suppl 52: 26-33.
50. Bergfeld, W. F. The evaluation and management of acne: economic considerations. J.Am.Acad.Dermatol. 1995; 32: S52-S56.
51. Thiboutot, D. New treatments and therapeutic strategies for acne. Arch Fam.Med. 2000; 9: 179-187.
52. Seaton, E. Pathogenesis and recommended management of acne. Prescriber 2011; November: 46-57.
53. Thiboutot, D. M. An overview of acne and its treatment. Cutis 1996; 57: 8-12.
54. Goodman, G. Managing acne vulgaris effectively. Aust.Fam.Physician 2006; 35: 705-709.
55. Gibson, J. R. Rationale for the development of new topical treatments for acne vulgaris. Cutis 1996; 57: 13-19.
56. Thielitz, A., Helmdach, M., Ropke, E. M., et al. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. Br.J.Dermatol. 2001; 145: 19-27.
57. Cotterill, J. A. Benzoyl peroxide. Acta Derm.Venereol.Suppl (Stockh) 1980; Suppl 89: 57-63.
58. Gollnick, H. and Schramm, M. Topical drug treatment in acne. Dermatology 1998; 196: 119-125.
59. Waller, J. M., Dreher, F., Behnam, S., et al. 'Keratolytic' properties of benzoyl peroxide and retinoic acid resemble salicylic acid in man. Skin Pharmacol.Physiol 2006; 19: 283-289.
60. Fanta, D., Bardach, H. and Poitscheck, C. Investigations on the bacteriostatic effect of benzoyl peroxide. Arch.Dermatol.Res. 1979; 264: 369-371.
61. Alvarez, O. M., Mertz, P. M. and Eaglstein, W. H. Benzoyl peroxide and epidermal wound healing. Arch.Dermatol. 1983; 119: 222-225.
62. Burkhart, C. N. and Burkhart, C. G. Genome sequence of Propionibacterium acnes reveals immunogenic and surface-associated genes confirming existence of the acne biofilm. Int.J.Dermatol. 2006; 45: 872.
63. Burkhart, C. N. and Burkhart, C. G. Microbiology's principle of biofilms as a major factor in the pathogenesis of acne vulgaris. Int.J.Dermatol. 2003; 42: 925-927.
64. Fyrand, O. and Jakobsen, H. B. Water-based versus alcohol-based benzoyl peroxide preparations in the treatment of acne vulgaris. Dermatologica 1986; 172: 263-267.
65. Del Rosso, J. Q. and Leyden, J. J. Status report on antibiotic resistance: implications for the dermatologist. Dermatol.Clin. 2007; 25: 127-32, v.
66. Dreno, B., Bettoli, V., Ochsendorf, F., et al. European recommendations on the use of oral antibiotics for acne. Eur.J.Dermatol. 2004; 14: 391-399.
67. Eady, E. A., Farmery, M. R., Ross, J. I., et al. Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. Br.J.Dermatol. 1994; 131: 331-336.
68. Eady, E. A., Bojar, R. A., Jones, C. E., et al. The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. Br.J.Dermatol. 1996; 134: 107-113.
69. Clark, C. Acne treatment. Clinical Pharmacist 2009; 1: 168-175.
70. Sykes, N. L., Jr. and Webster, G. F. Acne. A review of optimum treatment. Drugs 1994; 48: 59-70.
71. Dreno, B. Topical antibacterial therapy for acne vulgaris. Drugs 2004; 64: 2389-2397.
72. White, G. M. Acne therapy. Adv.Dermatol. 1999; 14: 29-58.
73. Martindale. The complete drug reference. 34th edition. 2005.
74. Cunliffe, W. J. and Holland, K. T. Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. Acta Derm.Venereol.Suppl (Stockh) 1989; 143: 31-34.
75. Katsambas, A., Graupe, K. and Stratigos, J. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. Acta Derm.Venereol.Suppl (Stockh) 1989; 143: 35-39.
76. Hjorth, N. and Graupe, K. Azelaic acid for the treatment of acne. A clinical comparison with oral tetracycline. Acta Derm.Venereol.Suppl (Stockh) 1989; 143: 45-48.
77. Handojo, I. The combined use of topical benzoyl peroxide and tretinoin in the treatment of acne vulgaris. Int.J.Dermatol. 1979; 18: 489-496.
78. Del Rosso, J. Q. Journal of Drugs in Dermatology: New methods and Techniques. Managing acne with adapalene 0.1% and 0.3% gels. Introduction. J.Drugs Dermatol. 2008; 7: s2.
79. Siegle, R. J., Fekety, R., Sarbone, P. D., et al. Effects of topical clindamycin on intestinal microflora in patients with acne. J.Am.Acad.Dermatol. 1986; 15: 180-185.
80. Eady, E. A., Cove, J. H., Holland, K. T., et al. Erythromycin resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. Br.J.Dermatol. 1989; 121: 51-57.
81. Eady, E. A., Jones, C. E., Tipper, J. L., et al. Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. BMJ 1993; 306: 555-556.
82. Gollnick, H., Cunliffe, W., Berson, D., et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. J.Am.Acad.Dermatol. 2003; 49: S1-37.
83. Cunliffe, W. J., Holland, K. T., Bojar, R., et al. A randomized, double-blind comparison of a clindamycin phosphate/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. Clin.Ther. 2002; 24: 1117-1133.

84. Bikowski, J. B. Clinical experience results with clindamycin 1% benzoyl peroxide 5% gel (Duac) as monotherapy and in combination. J.Drugs Dermatol. 2005; 4: 164-171.
85. Thiboutot, D., Zaenglein, A., Weiss, J., et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. J.Am.Acad.Dermatol. 2008; 59: 792-800.
86. Leyden, J., Kaidbey, K. and Levy, S. F. The combination formulation of clindamycin 1% plus benzoyl peroxide 5% versus 3 different formulations of topical clindamycin alone in the reduction of Propionibacterium acnes. An in vivo comparative study. Am.J.Clin.Dermatol. 2001; 2: 263-266.
87. Zouboulis, C. C., Derumeaux, L., Decroix, J., et al. A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin gel formulation (Velac) applied once daily and a clindamycin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. Br.J.Dermatol. 2000; 143: 498-505.
88. Leyden, J. J., Krochmal, L. and Yaroshinsky, A. Two randomized, double-blind, controlled trials of 2219 subjects to compare the combination clindamycin/tretinoin hydrogel with each agent alone and vehicle for the treatment of acne vulgaris. J.Am.Acad.Dermatol. 2006; 54: 73-81.
89. Mills, O. H., Jr. and Kligman, A. M. Treatment of acne vulgaris with topically applied erythromycin and tretinoin. Acta Derm.Venereol. 1978; 58: 555-557.
90. Tanghetti, E., Abramovits, W., Solomon, B., et al. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: a multicenter, double-blind, randomized parallel-group trial. J.Drugs Dermatol. 2006; 5: 256-261.
91. Eichenfield, L. F. and Wortzman, M. A novel gel formulation of 0.25% tretinoin and 1.2% clindamycin phosphate: efficacy in acne vulgaris patients aged 12 to 18 years. Pediatr.Dermatol. 2009; 26: 257-261.
92. Weiss, J. S. and Shavin, J. S. Topical retinoid and antibiotic combination therapy for acne management. J.Drugs Dermatol. 2004; 3: 146-154.
93. Thiboutot, D. M., Weiss, J., Bucko, A., et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. J.Am.Acad.Dermatol. 2007; 57: 791-799.
94. Gold, L. S., Tan, J., Cruz-Santana, A., et al. A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. Cutis 2009; 84: 110-116.
95. Wolf, J. E., Jr., Kaplan, D., Kraus, S. J., et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. J.Am.Acad.Dermatol. 2003; 49: S211-S217.
96. Jacyk, W. K. and Mpofu, P. Adapalene gel 0.1% for topical treatment of acne vulgaris in African patients. Cutis 2001; 68: 48-54.
97. Leyden, J. J. Therapy for acne vulgaris. N.Engl.J.Med. 1997; 336: 1156-1162.
98. Shalita, A. R. Treatment of mild and moderate acne vulgaris with salicylic acid in an alcohol-detergent vehicle. Cutis 1981; 28: 556-8, 561.
99. Oprica, C. and Nord, C. E. European surveillance study on the antibiotic susceptibility of Propionibacterium acnes. Clin.Microbiol.Infect. 2005; 11: 204-213.
100. Masters, P. A., O'Bryan, T. A., Zurlo, J., et al. Trimethoprim-sulfamethoxazole revisited. Arch.Intern.Med. 2003; 163: 402-410.
101. Webster, G. F. Acne and rosacea. Med.Clin.North Am. 1998; 82: 1145-54, vi.
102. Vowels, B. R., Yang, S. and Leyden, J. J. Induction of proinflammatory cytokines by a soluble factor of Propionibacterium acnes: implications for chronic inflammatory acne. Infect.Immun. 1995; 63: 3158-3165.
103. Coates, P., Vyakrnam, S., Eady, E. A., et al. Prevalence of antibiotic-resistant propionibacteria on the skin of acne patients: 10-year surveillance data and snapshot distribution study. Br.J.Dermatol. 2002; 146: 840-848.
104. Garner, S. E., Eady, E. A., Popescu, C., et al. Minocycline for acne vulgaris: efficacy and safety. Cochrane.Database.Syst.Rev. 2003; CD002086.
105. Ozolins, M., Eady, E. A., Avery, A. J., et al. Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. Lancet 2004; 364: 2188-2195.
106. Simonart, T., Dramaix, M. and De, Maertelaer, V. Efficacy of tetracyclines in the treatment of acne vulgaris: a review. Br.J.Dermatol. 2008; 158: 208-216.
107. Northern Ireland Drug Tariff. July 2016 http://www.hscbusiness.hscni.net/services/2034.htm
Ref Type: Internet Communication
108. Burkhart, C. G. and Burkhart, C. N. Treatment of acne vulgaris without antibiotics: tertiary amine-benzoyl peroxide combination vs. benzoyl peroxide alone (Proactiv Solution). Int.J.Dermatol. 2007; 46: 89-93.
109. Garner, S. E., Eady, E. A., Popescu, C., et al. Minocycline for acne vulgaris: efficacy and safety. Cochrane.Database.Syst.Rev. 2003; CD002086.
110. Pierard-Franchimont, C., Goffin, V., Arrese, J. E., et al. Lymecycline and minocycline in inflammatory acne: a randomized, double-blind intent-to-treat study on clinical and in vivo antibacterial efficacy. Skin Pharmacol.Appl.Skin Physiol 2002; 15: 112-119.
111. Mouton, R. W., Jordaan, H. F. and Schneider, J. W. A new type of minocycline-induced cutaneous hyperpigmentation. Clin.Exp.Dermatol. 2004; 29: 8-14.
112. McAllum, P. and Slomovic, A. Scleral and conjunctival pigmentation following minocycline therapy. Can.J.Ophthalmol. 2007; 42: 626-627.
113. Margolis, D. J., Hoffstad, O. and Bilker, W. Association or lack of association between tetracycline class antibiotics used for acne vulgaris and lupus erythematosus. Br.J.Dermatol. 2007; 157: 540-546.
114. Ochsendorf, F. Minocycline in acne vulgaris: benefits and risks. Am.J.Clin.Dermatol. 2010; 11: 327-341.
115. McManus, P. and Iheanacho, I. Don't use minocycline as first line oral antibiotic in acne. BMJ 2007; 334: 154.
116. Leyden, J., Thiboutot, D. M., Shalita, A. R., et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: a multicenter, double-blind, randomized, parallel-group study. Arch.Dermatol. 2006; 142: 605-612.
117. Smith, K. and Leyden, J. J. Safety of doxycycline and minocycline: a systematic review. Clin.Ther. 2005; 27: 1329-1342.
118. Bjellerup, M. and Ljunggren, B. Differences in phototoxic potency should be considered when tetracyclines are prescribed during summer-time. A study on doxycycline and lymecycline in human volunteers, using an objective method for recording erythema. Br.J.Dermatol. 1994; 130: 356-360.
119. Bernier, C. and Dreno, B. [Minocycline]. Ann.Dermatol.Venereol. 2001; 128: 627-637.
120. Ferner, R. E. and Moss, C. Minocycline for acne. BMJ 1996; 312: 138.
121. Miller, Y. W., Eady, E. A., Lacey, R. W., et al. Sequential antibiotic therapy for acne promotes the carriage of resistant staphylococci on the skin of contacts. J.Antimicrob.Chemother. 1996; 38: 829-837.
122. Cooper, A. J. Systematic review of Propionibacterium acnes resistance to systemic antibiotics. Med.J.Aust. 1998; 169: 259-261.
123. Bayer. Dianette. Summary of Product Characteristics 2016;
124. Vasilakis-Scaramozza, C. and Jick, H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives. Lancet 2001; 358: 1427-1429.
125. Seaman, H. E., de Vries, C. S. and Farmer, R. D. The risk of venous thromboembolism in women prescribed cyproterone acetate in combination with ethinyl estradiol: a nested cohort analysis and case-control study. Hum.Reprod. 2003; 18: 522-526.
126. MHRA. Cyproterone acetate with ethinylestradiol (co-cyprindiol): recommended duration of use. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084884 . 2008.
Ref Type: Internet Communication
127. Leyden, J., Shalita, A., Hordinsky, M., et al. Efficacy of a low-dose oral contraceptive containing 20 microg of ethinyl estradiol and 100 microg of levonorgestrel for the treatment of moderate acne: A randomized, placebo-controlled trial. J.Am.Acad.Dermatol. 2002; 47: 399-409.
128. Lucky, A. W., Henderson, T. A., Olson, W. H., et al. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. J.Am.Acad.Dermatol. 1997; 37: 746-754.
129. Redmond, G. P., Olson, W. H., Lippman, J. S., et al. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. Obstet.Gynecol. 1997; 89: 615-622.
130. Thiboutot, D., Archer, D. F., Lemay, A., et al. A randomized, controlled trial of a low-dose contraceptive containing 20 microg of ethinyl estradiol and 100 microg of levonorgestrel for acne treatment. Fertil.Steril. 2001; 76: 461-468.
131. Koltun, W., Lucky, A. W., Thiboutot, D., et al. Efficacy and safety of 3 mg drospirenone/20 mcg ethinylestradiol oral contraceptive administered in 24/4 regimen in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled trial. Contraception 2008; 77: 249-256.
132. Thiboutot, D. M. Endocrinological evaluation and hormonal therapy for women with difficult acne. J.Eur.Acad.Dermatol.Venereol. 2001; 15 Suppl 3: 57-61.
133. Pochi, P. E. and Strauss, J. S. Endocrinologic control of the development and activity of the human sebaceous gland. J.Invest Dermatol. 1974; 62: 191-201.
134. Ebling, F. J. Hormonal control and methods of measuring sebaceous gland activity. J.Invest Dermatol. 1974; 62: 161-171.
135. Thiboutot, D. M., Knaggs, H., Gilliland, K., et al. Activity of type 1 5 alpha-reductase is greater in the follicular infrainfundibulum compared with the epidermis. Br.J.Dermatol. 1997; 136: 166-171.
136. van Vloten, W. A. and Sigurdsson, V. Selecting an oral contraceptive agent for the treatment of acne in women. Am.J.Clin.Dermatol. 2004; 5: 435-441.
137. Zouboulis, C. C. [Treatment of acne with antiandrogens--an evidence-based review]. J.Dtsch.Dermatol.Ges. 2003; 1: 535-546.
138. van Vloten, W. A., van Haselen, C. W., van Zuuren, E. J., et al. The effect of 2 combined oral Contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. Cutis 2002; 69: 2-15.
139. Roche Products Ltd. Roaccutane Capsules. Summary of Product Characteristics 2015; www.medicines.org.uk:
140. Alestas, T., Ganceviciene, R., Fimmel, S., et al. Enzymes involved in the biosynthesis of leukotriene B4 and prostaglandin E2 are active in sebaceous glands. J.Mol.Med.(Berl) 2006; 84: 75-87.
141. Quereux, G., Volteau, C., N'Guyen, J. M., et al. Prospective study of risk factors of relapse after treatment of acne with oral isotretinoin. Dermatology 2006; 212: 168-176.
142. Stewart, M. E., Benoit, A. M., Stranieri, A. M., et al. Effect of oral 13-cis-retinoic acid at three dose levels on sustainable rates of sebum secretion and on acne. J.Am.Acad.Dermatol. 1983; 8: 532-538.
143. King, K., Jones, D. H., Daltrey, D. C., et al. A double-blind study of the effects of 13-cis-retinoic acid on acne, sebum excretion rate and microbial population. Br.J.Dermatol. 1982; 107: 583-590.
144. Farrell, L. N., Strauss, J. S. and Stranieri, A. M. The treatment of severe cystic acne with 13-cis-retinoic acid. Evaluation of sebum production and the clinical response in a multiple-dose trial. J.Am.Acad.Dermatol. 1980; 3: 602-611.
145. Harper, J. C. and Thiboutot, D. M. Pathogenesis of acne: recent research advances. Adv.Dermatol. 2003; 19: 1-10.
146. Coates, P., Adams, C. A., Cunliffe, W. J., et al. Does oral isotretinoin prevent Propionibacterium acnes resistance? Dermatology 1997; 195 Suppl 1: 4-9.
147. Coates, P., Vyakrnam, S., Ravenscroft, J. C., et al. Efficacy of oral isotretinoin in the control of skin and nasal colonization by antibiotic-resistant propionibacteria in patients with acne. Br.J.Dermatol. 2005; 153: 1126-1136.
148. Cooper, A. J. Treatment of acne with isotretinoin: recommendations based on Australian experience. Australas.J.Dermatol. 2003; 44: 97-105.
149. Papakonstantinou, E., Aletras, A. J., Glass, E., et al. Matrix metalloproteinases of epithelial origin in facial sebum of patients with acne and their regulation by isotretinoin. J.Invest Dermatol. 2005; 125: 673-684.
150. Wozel, G., Chang, A., Zultak, M., et al. The effect of topical retinoids on the leukotriene-B4-induced migration of polymorphonuclear leukocytes into human skin. Arch.Dermatol.Res. 1991; 283: 158-161

151. Ganceviciene, R., Graziene, V., Bohm, M., et al. Increased in situ expression of melanocortin-1 receptor in sebaceous glands of lesional skin of patients with acne vulgaris. Exp.Dermatol. 2007; 16: 547-552.
152. Peck, G. L., Olsen, T. G., Butkus, D., et al. Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. J.Am.Acad.Dermatol. 1982; 6: 735-745.
153. McLane, J. Analysis of common side effects of isotretinoin. J.Am.Acad.Dermatol. 2001; 45: S188-S194.
154. Leyden, J. J. and James, W. D. Staphylococcus aureus infection as a complication of isotretinoin therapy. Arch.Dermatol. 1987; 123: 606-608.
155. Zane, L. T., Leyden, W. A., Marqueling, A. L., et al. A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. Arch Dermatol. 2006; 142: 1016-1022.
156. DiGiovanna, J. J. Systemic retinoid therapy. Dermatol.Clin. 2001; 19: 161-167.
157. MHRA. Isotretinoin: risk of serious skin reactions. Drug Safety Update 2010; 4: A2.
158. Bernstein, C. N., Nugent, Z., Longobardi, T., et al. Isotretinoin is not associated with inflammatory bowel disease: a population-based case-control study. Am.J.Gastroenterol. 2009; 104: 2774-2778.
159. Crockett, S. D., Porter, C. Q., Martin, C. F., et al. Isotretinoin use and the risk of inflammatory bowel disease: a case-control study. Am.J.Gastroenterol. 2010; 105: 1986-1993.
160. Wysowski, D. K., Pitts, M. and Beitz, J. An analysis of reports of depression and suicide in patients treated with isotretinoin. J.Am.Acad.Dermatol. 2001; 45: 515-519.
161. Strauss, J. S., Cunningham, W. J., Leyden, J. J., et al. Isotretinoin and teratogenicity. J.Am.Acad.Dermatol. 1988; 19: 353-354.
162. Sladden, M. J. and Harman, K. E. What is the chance of a normal pregnancy in a woman whose fetus has been exposed to isotretinoin? Arch.Dermatol. 2007; 143: 1187-1188.
163. Dai, W. S., LaBraico, J. M. and Stern, R. S. Epidemiology of isotretinoin exposure during pregnancy. J.Am.Acad.Dermatol. 1992; 26: 599-606.
164. Lammer, E. J., Chen, D. T., Hoar, R. M., et al. Retinoic acid embryopathy. N.Engl.J.Med. 1985; 313: 837-841.
165. Lynberg, M. C., Khoury, M. J., Lammer, E. J., et al. Sensitivity, specificity, and positive predictive value of multiple malformations in isotretinoin embryopathy surveillance. Teratology 1990; 42: 513-519.
166. Stern, R. S., Rosa, F. and Baum, C. Isotretinoin and pregnancy. J.Am.Acad.Dermatol. 1984; 10: 851-854.
167. Adams, J. and Lammer, E. J. Neurobehavioral teratology of isotretinoin. Reprod.Toxicol. 1993; 7: 175-177.
168. UK Teratology Information Service. Use of isotretinoin in pregnancy. www.uktis.org 2013;
169. MHRA. Isotretinoin for severe acne. http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-G-L/Isotretinoinforsevereacne/index.htm#4 . 2011.
Ref Type: Internet Communication
170. Byrne, A. and Hnatko, G. Depression associated with isotretinoin therapy. Can.J.Psychiatry 1995; 40: 567.
171. Gatti, S. and Serri, F. Acute depression from isotretinoin. J.Am.Acad.Dermatol. 1991; 25: 132.
172. Hazen, P. G., Carney, J. F., Walker, A. E., et al. Depression--a side effect of 13-cis-retinoic acid therapy. J.Am.Acad.Dermatol. 1983; 9: 278-279.
173. Scheinman, P. L., Peck, G. L., Rubinow, D. R., et al. Acute depression from isotretinoin. J.Am.Acad.Dermatol. 1990; 22: 1112-1114.
174. Bruno, N. P., Beacham, B. E. and Burnett, J. W. Adverse effects of isotretinoin therapy. Cutis 1984; 33: 484-6, 489.
175. Marqueling, A. L. and Zane, L. T. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. Semin.Cutan.Med.Surg. 2007; 26: 210-220.
176. Strahan, J. E. and Raimer, S. Isotretinoin and the controversy of psychiatric adverse effects. Int.J.Dermatol. 2006; 45: 789-799.
177. Sundstrom, A., Alfredsson, L., Sjolin-Forsberg, G., et al. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. BMJ 2010; 341: c5812.
178. Halvorsen, J. A., Stern, R. S., Dalgard, F., et al. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. J.Invest Dermatol. 2011; 131: 363-370.
179. Kellett, S. C. and Gawkrodger, D. J. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. Br.J.Dermatol. 1999; 140: 273-282.
180. Rubinow, D. R., Peck, G. L., Squillace, K. M., et al. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. J.Am.Acad.Dermatol. 1987; 17: 25-32.
181. Ferguson, S. A., Cisneros, F. J., Gough, B., et al. Chronic oral treatment with 13-cis-retinoic acid (isotretinoin) or all-trans-retinoic acid does not alter depression-like behaviors in rats. Toxicol.Sci. 2005; 87: 451-459.
182. Goodfield, M. J., Cox, N. H., Bowser, A., et al. Advice on the safe introduction and continued use of isotretinoin in acne in the U.K. 2010. Br.J.Dermatol. 2010; 162: 1172-1179.
183. Magin, P., Pond, D. and Smith, W. Isotretinoin, depression and suicide: a review of the evidence. Br.J.Gen Pract. 2005; 55: 134-138.
184. Brecher, A. R. and Orlow, S. J. Oral retinoid therapy for dermatologic conditions in children and adolescents. J.Am.Acad.Dermatol. 2003; 49: 171-182.
185. Ellis, C. N. and Krach, K. J. Uses and complications of isotretinoin therapy. J.Am.Acad.Dermatol. 2001; 45: S150-S157.
186. MHRA. Cyproterone acetate with ethinylestradiol (co-cyprindiol): balance of benefits and risks remains positive. Drug Safety Update, June 2013.
187. MHRA. Oral retinoids: pregnancy prevention—reminder of measures to minimise teratogenic risk. Drug Safety Update, June 2013.
188. MHRA. Isotretinoin (Roaccutane): reminder of possible risk of psychiatric disorders. Drug Safety Update, 2014.
189. HSCB/BSO. Prescribing data, 2016.

This material was prepared on behalf of the Northern Ireland Health and Social Care Board by:

Lynn Keenan BSc (Hons) MSc MPS
(2016 Review by Michelle O'Prey)
Medicines Management Information Pharmacist

COMPASS Unit
Pharmaceutical Department
NI Health and Social Care Board
2 Franklin Street, Belfast
BT2 8DQ.

Any queries on re-use should be directed to Michelle O'Prey
(e-mail michelle.o'prey@hscni.net, telephone 028 9536 3925)

With thanks to the following for kindly reviewing this document:

- **Dr P O'Hare.** General Practitioner/Associate Specialist in Dermatology, Altnagelvin Hospital, WHSCT
- **Dr D O'Kane.** Consultant Dermatologist, Royal Victoria Hospital and Royal Belfast Hospital for Sick Children, BHSCT

The editorial panel for this edition of COMPASS Therapeutic Notes:

- Dr Bryan Burke (General Practitioner)
- Miss Veranne Lynch (NICE Medicine and Prescribing Centre Associate / Pharmacy Advisor HSCB)
- Dr Ursula Mason (General Practitioner)
- Mrs Stephanie Sloan (Community Pharmacist)
- Dr Thérèse Rafferty (Medicines Management Information Analyst, HSCBSO)

Health and Social Care Board

COMPASS THERAPEUTIC NOTES ASSESSMENT
Management of Acne in Primary Care

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 250 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.
Each issue of the Therapeutic Notes is accompanied by a set of assessment questions. These can contribute 2 hours towards your CPD/CME requirements. Submit your completed MCQs to the appropriate address (shown below) or complete online (see below). Assessment forms for each topic can be submitted in **any order** and at **any time**.

If you would like extra copies of Therapeutic Notes and MCQ forms for this and any other topic you can:
Visit the COMPASS Web site**:** **www.medicinesni.com** or **www.hscbusiness.hscni.net/services/2163.htm**
or
Email your requests to: **compass.team@hscni.net**
or
Phone the COMPASS Team on: 028 9053 5661

You can now complete your COMPASS multiple choice assessment questions and print off your completion certificate online:

- **Doctors and nurses should submit their answers at: www.medicinesni.com**
- **Pharmacists should submit their answers at: www.nicpld.org**

Are you a

Pharmacist? ☐ Community ☐ Hospital ☐ Other (please specify) _____

GP? ☐ Enter your cipher number: _____

Nurse? ☐ Enter your PIN number: _____

Title: Mr/Mrs/Miss/Ms/Dr

Surname: _____ First name: _____

Address: _____

_____

Postcode: _____

GPs and Nurses:
Complete the form overleaf and return to:
COMPASS Unit
Pharmaceutical Department
HSC Business Services Organisation
2 Franklin Street
Belfast
BT2 8DQ

Pharmacists:
Complete the form overleaf and return to:
Northern Ireland Centre for Pharmacy Learning & Development
FREEPOST NICPLD
Belfast BT9 7BL

Health and Social Care Board

COMPASS THERAPEUTIC NOTES ASSESSMENT
Management of Acne in Primary Care

For copies of the Therapeutic Notes and assessment forms for this and any other topic please visit: **www.medicinesni.com** or **www.hscbusiness.hscni.net/services/2163.htm**

Successful completion of these assessment questions equates with **2 hours** Continuing Professional Development time. Circle your answer TRUE (T) or FALSE (F) for each question. When completed please post this form to the relevant address shown overleaf. Alternatively, you can submit your answers online:

- **Doctors and nurses** should submit their answers at: **www.medicinesni.com**
- **Pharmacists** should submit their answers at: **www.nicpld.org**

1	**Topical retinoids:**			
	a	Should be a foundation in acne therapy for virtually all patients except those with the most severe disease.	T	F
	b	May cause a flare-up of acne about 3 weeks after initiation.	T	F
	c	Are contraindicated in pregnancy.	T	F
	d	Are not associated with skin irritation.	T	F
2	**Topical benzoyl peroxide:**			
	a	Is unaffected by bacterial resistance.	T	F
	b	Commonly causes skin irritation.	T	F
	c	Can bleach hair, clothing, towels and bed-linen.	T	F
	d	Should only be used for around 3 months.	T	F
3	**Topical antibacterials:**			
	a	Are more effective than benzoyl peroxide or topical tretinoin.	T	F
	b	Commonly cause significant skin irritation.	T	F
	c	Are best used as monotherapy.	T	F
	d	Can be used indefinitely.	T	F
4	**Oral antibacterials:**			
	a	Show marked differences in efficacy in acne management.	T	F
	b	Minocycline is an appropriate first-line oral antibacterial for acne management.	T	F
	c	Should be used for a minimum of 3 months before being assumed to be ineffective.	T	F
	d	Should be combined from the start of treatment with a topical retinoid or benzoyl peroxide.	T	F
5	**Hormonal treatment of acne:**			
	a	The progestogen-only pill will produce beneficial effects in acne.	T	F
	b	Co-cyprindiol (e.g. Dianette®) is licensed as a contraceptive.	T	F
	c	The full effectiveness of co-cyprindiol or other hormonal treatment for acne can be judged after 3-6 months use.	T	F
	d	Venous thromboembolism occurs more frequently in women taking co-cyprindiol than those taking a low dose combined oral contraceptive.	T	F