CLINICAL GUIDELINE

# Acne Guideline 2005 Update

**Compiled by Werner Sinclair and H Francois Jordaan and largely based on a consensus document of the Global Alliance to Improve Outcomes in Acne**

*Objective.* The guidelines on the management of acne vulgaris have been developed in an attempt to improve the outcomes of acne treatment in South Africa. This extremely common condition has a major impact on the quality of life of South African young people and it is expected that if implemented, these guidelines will play a role in improving this situation.

*Recommendations.* All health care workers involved in the management of acne should take note of these guidelines and endeavour to implement them in clinical practice. All treatment methods and procedures not substantiated by evidence from the literature should be discontinued and avoided to decrease the financial burden of acne treatment.

*Validation.* These guidelines were developed through general consensus by a group of about 40 internationally recognised experts in the field of acne treatment (the Global Alliance to Improve Outcomes in Acne, see details below) and further refined for South African circumstances by the majority of South African dermatologists who attended a series of six discussions held in the major centres of South Africa during 2004.

*Guideline sponsor.* The meetings of the Global Alliance to Improve Outcomes in Acne as well as the South African discussion meetings were sponsored by Galderma.

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## 1. Introduction

Acne vulgaris is an extremely prevalent skin condition,[1] affecting the majority of teenagers to a certain degree at some point. The impact on the quality of life of young people is highly significant.[2] It has a greater negative effect on the emotions and social functioning of teenagers than diseases like asthma and epilepsy.[3] It is often associated with anxiety, depression and unemployment.[4] The impact of the condition is often difficult to determine clinically,[5] but one can assume that almost all acne patients will experience this impact to some degree.

Medical treatment can make a very big difference,[6] often clearing the condition completely, or bringing about significant improvement in those who do not experience complete clearance.

The 'Global Alliance to Improve Outcomes in Acne' was formed in 2001 as a world-wide effort to bring together a group of recognised experts in the field of acne treatment. The aim was to review the current state of knowledge in this field, to work through all the relevant literature available systematically, to have meetings to discuss the evidence thus collected, and to draw up a set of recommendations for acne management to be distributed to all participating countries where the general implementation of these guidelines would be encouraged.

Two main groups were formed, in America and Europe. Meetings were held separately but information was shared and there was unification of the ultimate guidelines. Africa, Australia and South America were included with the European group and the South African delegates attended most of the meetings in Europe.

Four meetings were held in Europe. Brussels hosted these in November 2002 and January 2003, Seville in April 2003 and Barcelona in October 2003.

The information and recommendations originating from these meetings were published in the *Journal of the American Academy of Dermatology* (2003; **49:** S1-38) and were brought back to South Africa and discussed with South African dermatologists in a series of meetings held during March and April 2004 at six main centres in the country. About 80% of local dermatologists attended these meetings, commented on the recommendations, and gave input on special circumstances applicable to South Africa. All the information gathered from these meetings was then incorporated into the guidelines as set out in the rest of this document. The recommendations are therefore highly representative of the current global approach to the treatment of acne, and at the same time reflect the thinking of the majority of local dermatologists. The guidelines should carry the necessary weight and authority to ensure general acceptability among all South African health care workers who manage acne cases and should therefore be applied by dermatologists, general medical practitioners, gynaecologists, pharmacists, nurses and also beauticians.

This review discusses use of the major classes of anti-acne therapy and the way it should be used, with recommendations in each instance, and management of the different grades of acne vulgaris.

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### Consensus of the Global Alliance

**Acne has very significant impact on patients**

- Negative effect on emotions and social functioning
- Associated with anxiety, depression, unemployment
- Impact not always easy to assess clinically

### Recommendations of the Global Alliance

**Quality of life**

- Effective treatment dramatically improves a patient's quality of life (QOL)
- Use of a simple QOL assessment tool can help clinicians optimise therapy

## 2. Why Guidelines?

Guidelines for the treatment of acne vulgaris are necessary because a huge variation exists in the approach of different dermatologists and other health care workers involved in acne management. Some of the methods used are not supported by any evidence in the literature and some methods are clearly detrimental to the patient, the community or the patient's finances. A significant proportion of dermatologists also deviate from the accepted regimens. In our present climate of managed health care, health care funders are increasingly relying on evidence-based decisions when deciding on reimbursement of treatments. Similar trends are followed in the public medicine sector.

One should also remember that non-dermatologists treat more acne than dermatologists, hence it is particularly important for the former to have a set of practical guidelines to facilitate the best possible outcomes in acne treatment.

A further consideration is that new evidence is constantly emerging and new drugs are being developed on a regular basis. These factors should be taken into account when guidelines are drawn up. Guidelines can never be static, and constant revision is the norm. Guidelines were published in this *Journal* in 1999; while many of these principles are still applicable, they have been largely revised here.

## 3. Pathophysiology of acne vulgaris

It is very important to be knowledgeable about the pathophysiology of this condition. The pathogenetic factors represent specific targets for treatment and it has been proved that combinations of treatment directed at different pathogenetic factors will achieve better results than different treatment methods aimed at the same factors.[7]

The main pathogenetic factors involved in acne are the following: (*i*) production of androgens in the body; (*ii*) excessive sebum production; (*iii*) abnormal desquamation of the follicular epithelium in the duct of the sebaceous gland; (*iv*) proliferation of *Propionibacterium acnes*; and (*v*) inflammatory and immunological responses.

It is important to realise that acne is androgen-dependent. The main hormone responsible for increasing sebum production is dihydrotestosterone, converted from testosterone in the sebaceous glands by the enzyme 5-alpha-reductase.[8-10]

The primary lesion in acne is the microcomedo. It is not visible to the naked eye but histological analysis shows hyperkeratosis of the intrafollicular sebaceous ducts and dilatation of the sebaceous glands. In the acne-prone patient, about 30% of facial follicles will be in this state at any given time. An additional concept is that of the inflammatory microcomedo, still not visible to the naked eye, but which shows inflammation on histological examination.[11] This lesion forms an important target in the treatment of acne, especially as far as maintenance treatment is concerned.

It has also become evident that interleukin-1-alpha, an inflammatory cytokine, plays a major role in inducing inflammation in the microcomedo, with resultant activation of the entire acne process.

*P. acnes* is a Gram-positive, pleomorphic, anaerobic rod; its important role in acne has been well proven.[12] There is a very strong correlation between the number of these bacteria and the level of sebum production[16] and it has been shown that only living propionibacteria are able to induce inflammation in acne cysts.[13-16] Humoral and cellular immune responses induced by this bacterium, namely the generation of extracellular enzymes,[17] the production of interleukin-1-alpha,[18] the generation of heat-shock proteins and a mitogenic effect on T-cells, correlate with acne severity. A positive chemotactic effect on neutrophils is an important consequence of the breakdown of sebum into free fatty acids by bacterial lipase.[19,20] These bacteria are not involved in comedogenesis but they are very prominent in inducing inflammation through immunological mechanisms.[21]

At present there is no evidence to suggest that coagulase-negative *Staphylococcus aureus*, *S. epidermidis* or *Pityrosporum ovale* play any significant role in the pathogenesis of acne vulgaris.

### Consensus of the Global Alliance

**Knowledge of pathophysiology should influence treatment**

- Primary pathophysiological factors in acne:
  - Androgen production
  - Excessive sebum production
  - Abnormal desquamation of the follicular epithelium
  - *P. acnes* proliferation
  - Inflammation and immune response
- Treatment should target as many factors as possible

## 4. Clinical diagnosis of acne vulgaris

Acne vulgaris can present with a variety of skin lesions, namely comedones, both open and closed, inflammatory papules, pustules, nodules, cysts, conglobate lesions, sinuses, scars and even ulcers. However, several other skin diseases present with very similar-looking skin lesions and a diagnosis is not always as straightforward as it would seem. It is always important to ascertain whether comedones are present because comedones are virtually diagnostic of acne vulgaris and it is very difficult to make this diagnosis in their absence.

While acne involves mostly the face it often extends onto the trunk, most often the back, and can also involve the upper arms, thighs and even the buttocks. The scalp is very rarely involved even though it is richly supplied with sebaceous glands.

## 5. Grading of acne vulgaris

It is necessary to grade acne vulgaris according to severity; this is very important in decision making when treatment is planned. Grading can, however, be very problematic and highly subjective, especially when clinicians also use the number of different skin lesions to determine severity.

The simplest way of grading acne is based on the predominant type of lesion present on the skin, regardless of number. This makes therapeutic sense if one assumes that, for example, one comedo present on the face will respond as well to treatment as a thousand comedones. The acne is therefore graded according to the type of lesions present and the latter will dictate the form of therapy implemented. Grading is always done according to the most severe lesions present.

One can therefore grade acne as follows:

- Grade 1: Comedones only
- Grade 2: Inflammatory papules present in addition to the comedones
- Grade 3: Pustules present in addition to any of the above
- Grade 4: Nodules, cysts, conglobate lesions or ulcers present in addition to any of the above

More complicated grading systems rely heavily on the use of photographs or diagrams. In such systems the clinical appearance of the patient is compared with a standard set of photographs and severity is decided on according to correspondence with a particular photograph. This system is often difficult to reproduce, highly subjective, and does not always reflect the exact pathology present and therefore is not reliable in indicating the exact treatment required for the particular case.

In addition to the actual grade of the acne, one should take into account the extent of involvement because this will certainly influence the decision on the treatment method. The presence of scarring should also be noted. A patient with scarring would immediately be placed in a more severe category than one without scarring.

## 6. Use of antibiotics in treatment of acne vulgaris

Antibiotics are the most frequently used type of drug in the treatment of acne. They can be used both topically and systemically, the latter being far more effective. It is generally accepted that antibiotics, especially in topical form, are largely abused in the management of acne and many of the problems experienced with the use of antibiotics are due to the inappropriate use of topical preparations.

It is not the purpose of this review to discuss the pharmacology of these drugs in detail, but certain aspects of the mechanisms of action and the most important side-effects will be addressed.

Different classes of antibiotics are used in acne management. Most frequently used are the tetracyclines, especially doxycycline, lymecycline, minocycline and the older first-generation tetracyclines. Erythromycin is also frequently used, both topically and systemically, and the same applies to clindamycin. Co-trimoxazole is also commonly used,[22,23] as it is inexpensive and often highly effective. As a rule the penicillins are ineffective in this context.

### 6.1 Mechanism of action of oral antibiotics

The cyclines are the most widely studied group of drugs in this regard. They exert both antibacterial and non-antibacterial action in combating acne. Among the non-antibacterial activities, inhibition of bacterial lipases, anti-inflammatory activity and immunosuppression are among the most important. For the cyclines as a group, 11 different anti-inflammatory effects have been discovered, which include among others, inhibition of neutrophil leucotaxis,[24] reduction in cytokine secretion, decrease in metalloproteinase activity and direct inhibition of lymphocyte mitosis.[25-28] These activities are used in a variety of other diseases, but in acne the antibacterial effects are probably the most important.

### 6.2 *Propionibacterium* resistance to antibiotics used for acne

Successful treatment reduces the population of *P. acnes* but does not eradicate it. Acne is not cured, there is merely a temporary reduction in the number of bacteria. Widespread use of antibiotics has led to the emergence of resistance and therapeutic failure.[29,30] Therapeutic failure can also be caused by poor compliance, incorrect use of the drug, inadequate potency prescribed and folliculitis caused by other bacteria.

Antibiotic resistance among these bacteria has increased dramatically over the past 25 years, with a figure of 62% quoted for the UK at the moment. Resistance is now an

international problem, induced by the use of antibiotics. Resistant bacteria can also be transferred to close contacts and to and from physicians, with dermatologists being particularly at risk. Several factors are at play in causing resistance. The most important of these is the prescription of prolonged courses of antibiotics, multiple courses of antibiotics and the use of topical preparations. The edge of a topically treated area will always have a zone where the concentration of antibiotic will be suboptimal, encouraging the growth of resistant bacteria.

### 6.3 How to prevent resistance

One should avoid the needless use of antibiotics; they are only indicated for moderate to severe acne (grades 2 - 4). They should be used in combination treatment and never as monotherapy. Minimum duration of treatment should be 6 weeks and maximum duration 12 weeks. Strict compliance by the patient is necessary, and if topical antibiotics are used they should be combined with topical non-antibiotic antimicrobials like benzoyl peroxide.

Antiresistance agents that can be used include benzoyl peroxide, zinc acetate and oral isotretinoin.

### 6.4 Which oral cyclines are used in acne treatment?

Minocycline, doxycycline and lymecycline have similar efficacy.[31] As far as side-effects are concerned, doxycycline is prone to cause phototoxicity and gastrointestinal disturbance and minocycline can cause hyperpigmentation, hypersensitivity syndromes, serum sickness-like illness and drug-induced lupus.[32,33] These side-effects are fortunately rare, but nevertheless serious.[34] It is recommended that if minocycline is to be used for more than 3 months, liver functions and ANA determination need to be done 3-monthly.[35] Lymecycline appears to be free of these side-effects.[36]

Pharmacoeconomically, there is very little difference between these 3 drugs, with doxycycline being slightly less expensive than the other 2 in South Africa.

On the whole there is at the moment very little use for first-generation tetracyclines like oxytetracycline in the treatment of acne vulgaris. Their effectiveness cannot compare with that of the more modern drugs and they are not significantly cheaper any more, giving them poor cost-effectiveness ratios.

## Recommendations of the Global Alliance

### Oral antibiotics for acne

- Oral cyclines should be considered as a first choice when treating acne
- Lymecycline should be considered as a first-choice antibiotic when treating moderate to severe inflammatory acne
- Doxycycline or minocycline can be prescribed as second choice
- First-generation tetracyclines should be considered a third choice
- Erythromycin can be used in children under 12 years old or during pregnancy
- Co-trimoxazole can be considered in selected cases

### 6.5 Optimal dosing of oral cyclines in acne treatment

As mentioned above, the correct dosing is essential to prevent bacterial resistance, and even though low doses have been shown to be effective this will increase bacterial resistance. It is therefore encouraged that high doses be used for the full duration of treatment to increase efficiency and to reduce the emergence of resistance.

## Recommendations of the Global Alliance

### Optimal dosage for antibiotics in acne

- 300 - 600 mg per day for lymecycline
- 100 - 200 mg per day for doxycycline and minocycline
- One gram per day for oxytetracycline
- Topical antibiotics should never be used as monotherapy

### 6.6 Optimal duration of oral antibiotic treatment

It has been shown that oral antibiotics will induce improvement during the first 3 or 4 months of treatment, with little improvement thereafter, while antibiotic resistance will become more apparent after 4 months of treatment. It is therefore felt that courses of antibiotics for acne should be limited to a maximum of 4 months.

## Recommendations of the Global Alliance

### Duration of antibiotic treatment

- Oral antibiotics should be prescribed for 3 months
- An additional month can be considered if a steady improvement has been seen over the previous 3 months, but total clearance has not been achieved
- Compliance should be checked in patients who do not respond well

## 7. Use of topical retinoids in acne treatment

Topical retinoids target the microcomedo, which forms the earliest precursor of visible acne lesions. These preparations also have very significant anti-inflammatory effects through inhibition of toll-like receptors, which is not only useful in treating inflammatory acne, but also plays a major role in treating the inflammatory microcomedo, as mentioned in the discussion on the pathophysiology. They can therefore be used with great success in established inflammatory acne, right from the start of treatment,[37] and they are also extremely useful in maintenance therapy where long-term use can prevent the formation of new lesions and suppress the further development of inflammatory microcomedones.

The different topical retinoids available, namely tretinoin, adapalene, isotretinoin and tazarotene, have similar efficacy[38] but share a common side-effect in the form of initial irritation on application.[39] Of the four preparations, adapalene seems to be the one least prone to cause significant irritation.[40] This irritation effect is more pronounced on the Highveld of South Africa with its drier climate than on the coast. It is therefore important to use the cream formulations on the Highveld, while the gel formulations can be freely used at the coast.

It is also very important to realise that topical retinoids should be applied to the whole affected area and not only on visible lesions. This is because in addition to their therapeutic effect on visible lesions, their main action is preventive, working on skin without apparent lesions.

### Consensus of the Global Alliance

**Topical retinoids have multiple anti-acne actions**

- Inhibits/reduces number of microcomedones
- Reduces mature comedones
- Reduces inflammatory lesions
- Promotes normal desquamation of follicular epithelium
- Anti-inflammatory
- Enhances penetration of other drugs
- Maintains remission by inhibiting microcomedones

### Recommendations of the Global Alliance

**Topical retinoids in acne treatment**

- Should be the primary form of treatment for most forms of acne vulgaris
- Use early for best results
- Add antimicrobial therapy for inflammatory lesions when present
- Should be applied to the entire affected area
- Essential part of maintenance therapy

## 8. Use of topical benzoyl peroxide in acne treatment

Benzoyl peroxide is an extremely useful preparation in the management of acne. It has a mild but significant keratolytic effect, therefore acting in a comedolytic fashion, but is also a broad-spectrum antimicrobial, acting in a non-antibiotic fashion. It can therefore be used alone in cases of mild acne,[41] in combination with topical retinoids in severe comedonal and early inflammatory acne, and as an antiresistance agent in combination with systemic antibiotics when prolonged or repeated courses of the latter are necessary.

Benzoyl peroxide is available in different strengths, usually 5% or 10% gels and creams, and in the form of facial washes.

### Consensus of the Global Alliance

**Benzoyl peroxide is a useful adjunctive treatment**

- Potent antimicrobial effects
- Slower-acting than systemic antibiotics
- No resistance reported to date
- Useful in patients with mild to moderate acne

### Recommendations of the Global Alliance

**Benzoyl peroxide**

- Use in patients with mild to moderate acne
- Apply once or twice daily to entire affected area
- Use lower strengths in persons with:
  - Sensitive skin
  - Very young or anxious patients
- Higher concentrations and washes for:
  - Chest, shoulders, back

## 9. Combination therapy for acne vulgaris

Oral antibiotics and topical retinoids have been shown to have synergistic mechanisms through independent processes. Clearing of both inflammatory lesions and comedones is faster[42] and more complete with a combination of these 2 preparations than with antibiotics alone.[43,44] The simultaneous use of topical retinoids limits the duration of antimicrobial therapy, enhances the penetration of antibiotics into the skin and increases the follicular cell turnover allowing more antibiotics to be transported into the sebaceous unit.[41]

Benzoyl peroxide can be added to topical retinoids and systemic antibiotics in order to decrease resistance[44] or it can be used in combination with topical retinoids either on alternate

days or on a daily basis, one being applied in the morning and the other at night.

### Consensus of the Global Alliance

**Combination therapy is now standard of care for mild to moderate acne**

- Antimicrobial therapy plus topical retinoids is significantly better than antimicrobials alone
- Clearance of both inflammatory lesions and comedones is faster
- Combination therapy allows targeting of different pathophysiological factors
- Topical retinoids are likely to enhance penetration of antimicrobials, and to speed up action of antibiotics
- Topical retinoids added early, at start of treatment, give fastest results
- Antibiotic can be discontinued when inflammatory lesions resolve (3 - 4 months)
- If this is not possible, benzoyl peroxide or benzoyl peroxide/antibiotic combination can be used
- Success can be maintained with topical retinoids

### Recommendations of the Global Alliance

**Combination therapy**

- Oral antibiotics should not be used alone
- Oral antibiotics should not be combined with topical antibiotics (increases the risk of bacterial resistance and provides no additive action)
- Oral antibiotics should always be combined with a topical retinoid from the start (3 pathogenic factors addressed)
- Benzoyl peroxide can be added to topical retinoids and oral antibiotics in order to lower the incidence of bacterial resistance
- Benzoyl peroxide should be added when longer courses of antibiotics are used
- Topical retinoids and benzoyl peroxide can be used in combination, either on alternate days or one in the morning and the other at night

## 10. Importance of maintenance therapy in acne

With the exception of a full course of systemic isotretinoin, other acne therapies will merely suppress the process and not cure the condition. This is especially applicable when systemic antibiotics are used. It is therefore imperative that maintenance therapy be instituted in all instances.[45] Topical retinoids are the treatment of choice for maintenance, as explained above, for a minimum period of 12 months after completion of the initial systemic treatment. Benzoyl peroxide can be added to the retinoids at this stage, especially if inflammatory lesions still appear. Topical retinoids can also be used as maintenance treatment after completion of a course of systemic isotretinoin to prevent relapse.

Other preparations that can be used for long-term maintenance are azelaic acid[46] and salicylic acid, but these represent the second and third choices. In females the use of oral contraception, even without anti-androgen effect, also represents excellent maintenance therapy, with or without added topical retinoids.

### Consensus of the Global Alliance

**Maintenance therapy**

- The microcomedo is the precursor of all acne lesions
- The process of microcomedo formation is permanent and persists after acne is cleared
- Avoiding microcomedo formation has a preventive effect in acne
- Microcomedones are the main target of topical retinoids

### Recommendations of the Global Alliance

**Maintenance therapy**

- After the acute phase of acne treatment (> 90% improvement), maintenance therapy should always be considered to limit relapse
- Topical retinoids are the treatment of choice for maintenance therapy
- Suggested duration of maintenance therapy is 6 - 12 months
- Benzoyl peroxide can be added to topical retinoids to lower bacterial resistance after antibiotic treatment
- Second choices for maintenance therapy are azelaic acid and salicylic acid

## 11. Hormonal treatment of acne vulgaris

Acne is an androgen-dependent condition and in females the androgens can be effectively blocked or reduced, often leading to significant improvement in or clearing of the condition. It represents an excellent choice for women who need oral contraception and should be used early for patients with moderate to severe acne who also have signs of androgen over-

activity (**S**eborrhoea, **A**cne, **H**irsutism, **A**ndrogenic alopecia (SAHA)). It is useful in combination treatment, in women with late-onset acne and in patients with prominent premenstrual acne flares.

Ordinary combination oral contraceptives are often effective in mild forms of acne,[47] but for more severe forms antiandrogens must be used. The most effective available is cyproterone acetate, either in a dosage of 2 mg added to ethinylestradiol, or in a dosage of 10 mg taken for 15 days per cycle, added to a contraceptive[48] for more severe cases. It is very important to remember that cyproterone represents an effective progestogen, therefore acting as effective contraception in combination with ethinylestradiol and additional contraception is not necessary when this preparation is prescribed.

Some authorities feel that the routine use of a topical retinoid in combination with hormonal therapy brings about a much quicker response than hormonal treatment alone and should be regarded as an acceptable treatment option.

## Consensus of the Global Alliance

### Hormonal therapy is useful in androgen-driven acne

- Excellent choice for women who need oral contraception for gynaecological reasons
- Should be used early for patients with moderate or severe acne or with SAHA signs
- Useful in combination treatment
- Useful in women with late-onset acne

## Recommendations of the Global Alliance

### Hormonal therapy

- Use early in female patients with clinical signs of hyperandrogenism (endocrine evaluation – dehydroepiandrosterone (DHEAS), testosterone, luteinising hormone/follicle-stimulating hormone (LH/FSH) ratio)[49,50]
- Consider in women with normal serum androgens:
  - Persistent inflammatory papules, nodules on lower face
  - Prominent acne flare at menstruation
- Mainstay of hormonal therapy: oral contraceptives, cyproterone acetate, drospirenone, spironolactone[51]

## 12. Systemic isotretinoin as treatment for acne vulgaris

Very few authorities question the fact that this preparation represents by far the most effective anti-acne treatment.[52,53] Used in the correct dose, it very seldom fails to clear acne completely and it effects a permanent cure in a high percentage of cases, with cure rates varying from 38% to 66%, depending on the definition of a cure.[54]

Isotretinoin addresses all the pathophysiological factors involved in acne and usually achieves dramatic results even in more severe cases. There is no doubt that it is the drug of choice for severe acne, with benefits far outweighing the risks involved. It has, however, become fashionable to use the drug for less severe cases where other more conservative treatments may have been successful, often prescribed under pressure from patients. Physicians should nevertheless adhere to the prescribed indications for use of this drug to prevent medicolegal consequences.

This drug causes numerous side-effects, some of which are serious, but most of which are not. Most patients experience the period on this drug as very unpleasant, but they endure the nuisance side-effects because they see the benefits very soon after starting treatment. The most serious side-effect is of course the teratogenic effect of the medication. This side-effect is entirely preventable[55] if the patient adheres to strict contraception for a month before the start of treatment, undergoes a negative pregnancy test thereafter and starts medication on the third day of her next menstrual period. Effective contraception has to continue for 1 month after taking the last tablet in the course. Monthly negative pregnancy tests are recommended in South Africa but are compulsory in the USA. The patient should be fully aware of the risks, and should sign written consent for use of the drug and indicating her understanding that a therapeutic abortion would be compulsory should she fall pregnant during treatment.

Consensus has not been reached on the issue of depression and suicide resulting from the use of isotretinoin. Statistically speaking, there is a lower incidence of suicide in patients who are on treatment with this drug, compared with a similar population not exposed to it. General consensus has not been reached on whether a small subset of patients will react with a depressive response in an idiosyncratic, unpredictable way. Caution is advised in patients with a history of depression; mood swings should be reported by the patient and the drug should be discontinued should any symptoms of depression occur on treatment.[56-58]

The other side-effects of isotretinoin are of a less serious nature[59] but the patient should be aware of the dry skin and mucosae that will be experienced, the initial temporary worsening of the acne, the photosensitivity that occurs in 5% of cases, the possibility of joint and muscle pain, the severe night blindness that can hamper driving at night, the possibility of mild hair loss that may occur and the fact that liver enzymes and triglyceride levels may become raised during treatment. Blood tests to determine baseline liver enzyme levels and triglycerides need to be done before treatment starts and should be repeated after 1 month of treatment. Should the

baseline and 1-month values both be normal, further blood testing is unnecessary.

The effect of isotretinoin on bone metabolism has been under discussion for decades.[60,61] Treatment with high dosages over prolonged periods for diseases of cornification has been associated with skeletal abnormalities including hyperostosis, calcification of spinal ligaments and osteoporosis. It has recently been shown that the normal 4 - 5-month course of isotretinoin does not cause any skeletal abnormalities, but there are no data available on patients who were exposed to long-term, low-dosage use of this drug. This uncertainty, together with the teratogenic effect, are the main reasons why long-term low-dosage treatment should be strongly discouraged at this stage.

At each visit the patient should be questioned about headaches; nightly or early-morning headaches could indicate raised intracranial pressure which is an uncommon side-effect of this drug but which can be precipitated by the concomitant use of tetracyclines or systemic corticosteroids. These last 2 drugs should be used with circumspection in these patients.

The correct indications for isotretinoin in acne are indicated in the 'Recommendations of the Global Alliance' on this page.

The dosage used for a full course of treatment is very important.[62-64] This should not be below 0.5 mg/kg per day and should not exceed 1 mg/kg per day, in order to limit side-effects. The duration of treatment is determined by the body weight of the patient and the daily dose taken. One should aim for a minimum target of 120 mg per kg as a total cumulative dose but this can be increased to 150 mg per kg if a satisfactory result has not been achieved once 120 mg/kg has been reached. The chances for a permanent cure are dramatically reduced if treatment is discontinued before the threshold of 120 mg/kg has been reached, even if the acne has cleared completely before then.

There may be an indication for the so-called pulse-dosage regimen, where 0.5 mg/kg is taken daily on the first 7 days of each month. This is usually free from side-effects, except for the teratogenic effect, and has proved to be highly effective for patients who relapsed after a previous full course of this drug, as well as for older patients with chronic, indolent, resistant acne. South African dermatologists felt that this regimen should be included in the accepted guidelines for this country.

A special set of circumstances in which low-dosage continuous isotretinoin may be used, involves young teenagers with very severe comedonal acne. These patients respond very poorly to topical comedolytic agents initially, and a 4 - 6-month course of 10 - 20 mg of isotretinoin per day can lead to prompt clearance of these lesions, whereafter maintenance with topical retinoids should be highly effective.

High-dosage vitamin A used to be a popular treatment for acne in the past, but evidence for its effectiveness is lacking and because of the severe potential toxicity of this medication, its use in acne should be discouraged.

### Consensus of the Global Alliance

**Oral isotretinoin is standard of care for severe acne**

- Targets all the pathophysiological factors
- May achieve dramatic results even in severe disease
- May be used more frequently in moderate and unresponsive disease
- Side-effects common but manageable
- Variable rate of recurrence; retreatment may be needed

### Recommendations of the Global Alliance

**Oral isotretinoin**

- Indications:
  - Severe nodulocystic acne and its variants
  - Inflammatory acne with scarring
  - Moderate to severe acne unresponsive to treatment with:
    - Three months of combination treatment including systemic cyclines
    - Four cycles of anti-androgen containing hormonal treatment
  - Acne with severe psychological distress (dysmorphophobic patients)
  - Gram-negative folliculitis
  - Frequently relapsing acne where repeated or prolonged courses of systemic antibiotics are needed
- Patient counselling is critical (side-effects, teratogenicity, monitoring)
- Typical dosage: 0.5 - 1 mg/kg/day, cumulative dosage 120 - 150 mg/kg
- Pulse-dosing permitted for relapse cases or older patients with chronic, indolent acne
- Recurrence is common; a topical retinoid should be used as maintenance treatment after isotretinoin treatment

## 13. Other drugs that may be used in acne treatment

Many patients, especially among the poor, may not have access to expensive modern treatments for very severe inflammatory acne. In these cases a combination of co-trimoxazole and low-dosage prednisone for a few weeks may give excellent results. Another useful drug in this scenario is dapsone, which at a dosage of 50 - 150 mg per day can bring about complete clearance of nodular inflammatory acne. The condition can be controlled with long-term maintenance treatment, with low-dosage dapsone being relatively safe, provided that the patient has a normal glucose-6-phosphate dehydrogenase (G6PD) level and that full blood counts are initially done regularly to detect any resulting anaemia.

## 14. Adjunctive therapies

The most important aspect of adjunctive therapy is the patient's understanding of the treatment. This will reduce lapses in compliance, improve outcomes and prevent problems like drug resistance.

Skin care regimens are generally of very little use and never cost-effective. The face should be cleansed twice daily with water and soft soap and the use of moisturising creams should be limited, except in patients taking systemic isotretinoin.

Office procedures such as comedo extraction, chemical peels and intralesional corticosteroids may be useful in selected cases but cannot replace medical treatment.

## Consensus of the Global Alliance

### General acne management strategies form useful part of therapy

- Patient understanding of therapy (use, expected results, the risk of worsening acne)
- Skin care regimens
- Office procedures: comedo extraction, chemical peels, and intralesional corticosteroids

## Recommendations of the Global Alliance

### General management principles

- Take careful patient history
- Teach patients about gentle skin cleansing
- Show appropriate application techniques for topical therapies
- Help patients to have realistic expectations of therapy
- Show empathy for patient's distress due to acne

## 15. Management of the different grades of acne vulgaris

**Grade 1.** This degree of acne should be managed topically. A topical retinoid will suffice in most cases, but the addition of benzoyl peroxide or azelaic acid may be necessary in resistant cases.

**Grade 2.** In milder cases with superficial inflammatory papules, one can follow the same treatment as above. However, where the papules are more deeply situated, a systemic antibiotic is indicated.

**Grade 3.** In these cases there is always a severe, deep inflammatory process present with a marked influx of neutrophils, necessitating systemic antibiotics. These should always be used in combination with a topical retinoid and, if the systemic treatment needs to go on for longer than 3 months, a topical antiresistance agent should be added.

Hormonal treatment can be used with good success at this stage in female patients who desire contraception or who have other gynaecological indications for this treatment.

**Grade 4.** Systemic isotretinoin represents the drug of choice in these patients. In females, an oral contraceptive combined with anti-androgens can sometimes be effective. Systemic antibiotics can bring about excellent improvement in these cases, but the improvement is of short duration and these drugs do not represent a long-term solution for this type of acne; unacceptably long courses of antibiotics are usually necessary.

## 16. Summary of Guideline principles

- Most acne cases should receive a retinoid, either systemically or topically.
- Inflammatory acne responds very well to retinoids, and there is consequently no need to delay their introduction into the treatment regimen.
- The anti-inflammatory effect of retinoids starts in the invisible microcomedo.
- Retinoids should be used in combination treatment from the inception and as maintenance.
- The main purpose of the retinoids is to minimise the use of antibiotics.
- Lymecycline appears to be the tetracycline of choice for acne at the moment, based on its cost-effectiveness and side-effect profile.
- Bacterial resistance involving *P. acnes* and other organisms is a problem; if antibiotics are needed for more than 4 months, one should always add benzoyl peroxide or another antiresistance agent.
- Systemic retinoids represent the treatment of choice for severe forms of acne.
- Systemic retinoids should not be given routinely for acne, even in men.
- The use of topical retinoid maintenance after systemic isotretinoin depends on the response to the systemic drug.
- Hormonal treatment can be used early and as monotherapy in females who desire contraception and as maintenance.

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