A clinically practical approach to acne

Part 2: treatment

Familiarity with the growing range of effective acne therapies will help in treatment suggestions for acne. Quick reduction of the severity of the inflammatory process in this condition helps reduce the risk of permanent scarring.

JOHN SULLIVAN
MB BS, FACD
VERONICA PREDA
BSc, MB BS

Dr Sullivan is Medical Director, Department of Dermatology, Liverpool Hospital, Sydney South West Area Health Service (SSWAHS); Conjoint Senior Lecturer, Faculty of Medicine, University of New South Wales; Consultant Dermatologist at Southderm, Kogarah, and at Central Sydney Dermatology, Sydney; and Chairperson of All About Acne (www.allaboutacne.com.au)
Dr Preda is a Research Assistant in the Department of Dermatology, Liverpool Hospital, SSWAHS; and Conjoint Associate Lecturer, Faculty of Medicine, University of New South Wales, Sydney, NSW.

Acne is more than just a normal part of growing up, and poorly controlled acne can have a lasting legacy in terms of physical and psychological scars.[1,2] This article, the second of two on acne by these authors, discusses the topical and systemic treatment of acne. The pathogenesis of acne, the various types of acne lesions and general advice on lifelong skin care practices in people prone to acne, including the use of medicated cleansers and realistic sun protection, were discussed in the first article, which was published in the January 2008 issue of *Medicine Today*.

Types of treatment

Acne therapy involves strategies to quickly control the more visible and inflammatory acne lesions. For patients with severe acne, therapies that quickly reduce the severity of the inflammatory process also help decrease the risk of permanent scarring. Acne may be treated using either topical or systemic therapies, or combinations of these.

The clinical relevance of the multiple actions of most acne therapies has been consistently demonstrated in a growing number of blinded studies. Patients with mild acne can often be effectively managed using an appropriately chosen monotherapy. Anti-inflammatory acne therapies, despite being devoid of the direct comedolytic activity conferred by antimicrobial agents such as antibiotics, are associated with a clinically significant reduction in comedone counts over

IN SUMMARY

- Acne may be treated using either topical or systemic therapies, or combinations of these.
- For mild to moderate acne, many topical treatments are at least as effective as monotherapy with oral antibiotics.
- For more severe or widespread acne, using a topical therapy with another topical therapy or a systemic therapy achieves more rapid and greater control.
- Agents with proven efficacy as topical acne therapies include benzoyl peroxide, salicylic acid microgel complex, topical antibiotics and topical retinoids.
- Agents with proven efficacy as systemic acne therapies include systemic antibiotics and retinoids, certain combined oral contraceptives, spironolactone and metformin.
- Retinoids, tetracyclines and spironolactone are not safe to use during pregnancy.
- Poor adherence is a common reason for 'treatment failure', and is often due to side effects (such as irritation), incorrect product use and/or inconvenient regimens.

Figure 1. Severe acne in a man in his early 20s. Combination therapies, including systemic treatments, are required to treat this patient's severely inflamed lesions and reduce the risk of further scarring. Such treatment will also provide the basis for long-term control.

time. This feature highlights the importance of follicular inflammation in promoting comedone formation. Retinoids, benzoyl peroxide and the salicylic acid microgel complex all reduce inflammatory lesions and open and closed comedones. Patients with severe acne usually require combination therapies with anti-inflammatory and antimicrobial actions as well as comedolytic properties to treat the existing lesions and provide the basis for better long-term control (Figure 1).

For mild to moderate inflammatory facial acne, many topical treatments have proven to be at least as effective as mono-therapy with oral antibiotics. For more severe or widespread acne, topical therapy can be used in conjunction with another topical therapy or with a systemic therapy to help achieve more rapid and greater control, both in the short and long term.

A simple treatment regimen

Females are generally more likely than males to adhere to regimens that involve applying two or more medicated therapies each day. Males generally prefer pills to topical preparations but if they must use a topical therapy, once a day use will increase compliance. Many teenagers are prepared to sacrifice some control of their acne for the convenience and simplicity of the therapy regimen. As a patient's acne improves, the motivation to continue to follow complex treatment regimens often quickly declines until the acne returns.

Therapeutic agents

The various acne treatments have different modes of action and speeds of clinical benefits, and also different effects on comedonal and inflammatory acne lesions. The different therapeutic groups of acne treatments are compared in Table 1. This table helps explain why certain therapy combinations result in greater patient benefits. For example, combining topical retinoid therapy with either a topical or systemic antibiotic during the first six- to 12 weeks of treatment results in more rapid acne control than would be obtained using a topical retinoid only; the improved disease control after this six- to 12-week period is maintained using the topical retinoid alone.[3,4] Combination therapies are discussed in the box page 40.[4,5]

Topical acne therapies

The agents used in topical acne therapies are benzoyl peroxide, salicylic acid microgel complex, topical antibiotics and topical retinoids, either alone or in combinations. Most topical acne therapies are delivered using leave-on gels or creams. Medicated cleansers contain the same range of active ingredients as topical therapies but as they are used as washes and then rinsed off their active ingredients are only briefly in contact with the skin.

Topical therapies appropriate for use in mild to moderate acne are listed in Table 2.

The numerous over-the-counter cosmetic treatments for acne contain a variety of other ingredients, such as the hydrophobic broad spectrum antibacterial/antiseptic agents triclosan, sulfur, bentonite, witch hazel and many others. Discussion of these is beyond the scope of this article. Suffice to say, triclosan can have a role in cosmetics but is not in the medical literature as having a large role, and sulfur masks have been used for many years in the treatment of acne but evidence from peer review is lacking.

Azelaic acid has been shown to be effective in clinical trials, with comedolytic and antibacterial properties, but has limited efficacy compared with other agents.[5] Peer review literature supporting its efficacy is lacking. However, it is safe to use in pregnancy.

Salicylic acid has been used for many years for the treatment of acne, but it is less potent than topical retinoids. Salicylic acid is often used in mild acne, particularly in patients who cannot tolerate topical retinoids. Various salicylic acid preparations are available, ranging from cleansers to moisturisers to leave-on gels. Some of these contain salicylic acid as a microgel complex, which has enhanced delivery properties and has been proven to be effective in acne.[6-8]

Applying topical therapies

Topical acne therapies should be applied 10 to 15 minutes after the skin has dried

Table 1. Therapeutic groups of acne treatments*

Group	Examples	Beneficial actions	Comedonal acne	Inflammatory acne	Onset and time to maximum clinical benefits
Cleansers	Surfactants (e.g. sodium lauryl sulfate)	Remove oils (solubilise sebum), debris, bacteria	✓	✓	1 to 2 weeks
	Antibacterials and antiseptics (e.g. Montaline C40)	Reduce bacterial numbers	✓	✓	1 to 6 weeks
	Salicylic acid	Solubilises sebum Comedolytic	+/-	+/-	Days to weeks
Antibiotics and antibacterials	Benzoyl peroxide	Comedolytic and prevents comedone formation Anti-inflammatory	✓	✓	Hours to days to 6 weeks
	Salicylic acid microgel complex	Solubilises sebum Comedolytic and prevents comedone formation Antimicrobial Anti-inflammatory	✓✓	✓	Hours to days to 6 weeks
	Topical: clindamycin, erythromycin Systemic: tetracyclines, macrolides, sulfonamides	Anti-inflammatory Antimicrobial Reduce comedone formation	✓	✓✓	1 to 6 weeks
Retinoids	Topical: adapalene, isotretinoin, tazarotene, tretinoin	Comedolytic and prevent comedone formation Anti-inflammatory Even out pigment changes and reduce scarring	✓✓	✓	4 to 12 weeks
	Systemic: isotretinoin	As for topical retinoids, and markedly reduces sebum production and, indirectly, *Propionibacterium acnes* Can induce prolonged remissions	✓✓✓	✓✓	4 to 16 weeks
Hormones	Some combined oral contraceptives	Reduce and alter sebum production, reduce keratin plug formation and, indirectly, *P. acnes* numbers	✓✓	✓✓	12 to 36 weeks
	Spironolactone		✓	✓	54 to 12 weeks

* Over-the-counter antiacne products contain a range of 'active' ingredients not mentioned in this table. Peer reviewed literature supporting the efficacy of these ingredients is generally lacking and their discussion is beyond the scope of this article.

following cleansing. Application to moist skin increases the likelihood of skin irritation. Patients derive greatest benefits with direct application of topical acne creams, gels or lotions to the entire affected area as these preparations do not just treat isolated active lesions but also help prevent new lesions from forming.

Duration of therapy

Topical antibiotics, benzoyl peroxide and combination products all work relatively quickly to improve flares (beginning

Combination therapies for acne

Topical acne treatments alone can be surprisingly effective for controlling localised facial acne. However, combination therapy (a topical therapy with another topical, or a topical therapy with a systemic therapy) is a consideration in certain patients. These patients are those who have more severe, deep, widespread and inflammatory acne and those who fail to respond to or tolerate topical therapy. The combinations increase the treatment benefits and also help reduce the side effects of each agent.

Examples of combination therapies

- For rapid control of an inflammatory acne facial flare consider combination therapy of a topical or systemic antibiotic with topical benzoyl peroxide, retinoid and/or salicylic microgel complex.
- Benzoyl peroxide has been shown to increase the effectiveness of erythromycin and clindamycin and can even restore the antibiotic sensitivity of the bacterium concerned.[5] Separate benzoyl peroxide and antibiotic creams or gels or the combination product Duac Once Daily Gel (5% benzoyl peroxide, 1% clindamycin) can be used. The simplicity of use and the better tolerability of the combination product, which has been formulated to protect against benzoyl peroxide irritation in all but the most sensitive skin, have been associated with greater adherence, higher patient preference and successful nightly application in most patients.[4]
- Several trials support the practice of combining a topical retinoid (particularly adapalene and tazarotene) with a topical antibiotic when initiating treatment for inflammatory facial acne. This combination produces clinically significant benefits over either product alone, including faster onset of benefits, a greater reduction in acne lesion count and a lower incidence of irritation. The lower irritancy of the combination allows most patients to tolerate nightly retinoid use from day one.[4]

within hours to days). For mild to moderate acne, they are usually recommended for six- to 12-week courses, tailored to response and tolerance (see Table 2). For infrequent flares, intermittent courses of therapy can be considered. If flares are more frequent or have a significant impact, regular long-term maintenance therapy with either benzoyl peroxide or a topical retinoid should be considered.

The relapsing–remitting nature of acne necessitates counselling the patient not to give up on a new treatment regimen until he or she has given it a fair go. Therefore, although benefits in trials often start within days to weeks, a therapeutic trial should normally be for a minimum of six weeks for products containing antibiotics and/or benzoyl peroxide, and three months for those containing retinoids. The implications of the development of antibiotic resistance in patients infected with *Propionibacterium acnes* are discussed later in the article (under 'Systemic antibiotics').

Preventing treatment-related problems

Although benzoyl peroxide and salicylic acid microgel complex work quickly, skin irritation (red, dry and/or peeling skin) and increased skin sensitivity to sunlight may be a problem with benzoyl peroxide, and also with the slower acting topical retinoids (Figure 2). The use of benzoyl peroxide and salicylic acid microgel complex as acne treatments is discussed in the box on page 42.[6,7] Many patients interpret skin irritation from a topical treatment as failure of the treatment to improve their acne and/or the treatment making the acne worse.

Figure 2. Skin irritation, cheilitis and desquamation in a patient taking systemic isotretinoin. This reaction occurs in 15 to 20% of patients prescribed topical retinoids and/or benzoyl peroxide but can be minimised or prevented by introducing these therapies gradually, together with gentle skin care measures and/or a topical or systemic antibiotic. Sun protection and avoidance measures are also important as these therapies increase skin sensitivity to sunlight.

To reduce the risk of irritation, topical retinoids and benzoyl peroxide should be applied at night and used sparingly, avoiding sensitive areas such as the periorbital, perinasal and perioral skin. When initiating therapy, particularly in patients with sensitive skin, start second-nightly for the first three to four weeks and then increase to nightly use, changing back to every other night if it is not well tolerated. Although benzoyl peroxide can be used up to twice daily, such use often results in clinically significant irritant skin reactions that usually settle on changing back to nightly use. Benzoyl peroxide can bleach hair, sheets, towels and clothing. For this reason it should be applied at least 30 minutes before going to bed, and an old or white pillowslip should be used on pillows.

If retinoid or benzoyl peroxide irritation occurs, advise the patient to wait at least 30 minutes after washing before applying these medicated therapies. Use of a smaller amount and/or use only every

Benzoyl peroxide versus salicylic acid microgel complex as acne treatments

Before a recent series of industry-sponsored trials comparing benzoyl peroxide and salicylic acid microgel complex, acne treatment studies classically only reassessed acne severity after a week of therapy. This recent series is one of the first to answer a very important question for patients: how quickly do the different acne treatments result in visible improvements in inflammatory acne lesions?[6,7]

Both benzoyl peroxide and salicylic acid microgel complex work quickly. When used twice a day they resulted in over 50% of subjects reporting an improvement in their inflammatory acne lesions within eight hours of starting treatment. By eight hours, clinically significant improvement was observed in over 75% of treated lesions (clinician assessed). Improvement over placebo continued to the seventh day, and regular use maintained this reduction in inflammatory papules and pustules. The salicylic acid microgel complex was slightly better in improving the less inflammatory acne lesions, including open comedones and dilated plugged pores.[6,7]

Skin irritation

These sponsored trials also emphasised the importance of implementing strategies that help avoid skin irritation side effects when starting topical benzoyl peroxide therapy. Many patients interpret skin irritation due to a topical treatment as failure of the treatment to improve their acne and/or the treatment making their acne worse.

Table 2. Topical medicated therapies for mild to moderate facial acne

Minimal or mild acne

- Benzoyl peroxide 2.5 to 5% cream or gel nightly (Benzac, Brevoxyl, Oxy, PanOxyl Preparations)
- Salicylic acid microgel complex (gel or leave-on wipes) twice daily (e.g. Neutrogena Rapid Clear range)
- Azelaic acid (Acnederm Medicated Lotion, Finacea) – not routinely used

Mild to moderate acne or inadequate response to above after six weeks

- Retinoid cream or gel second-nightly for three weeks then nightly:
  - adapalene 0.1% cream or gel (Differin Topical Cream/Gel)
  - isotretinoin 0.05% gel (Isotrex Gel)
  - tazarotene 0.05% (increasing to 0.1% if inadequate) cream (Zorac Cream)
  - tretinoin 0.05% (increasing to 0.1% if still inadequate) cream or gel (Retin-A, ReTrieve Cream, Stieva-A)
- Benzoyl peroxide 5% plus clindamycin 1% combination gel (Duac Once Daily Gel) nightly*
- Benzoyl peroxide 4 or 5% cream or gel nightly in combination with an antibiotic, either erythromycin 2% gel (Eryacne) or clindamycin 1% lotion (ClindaTech, Dalacin T Topical Lotion, Zindaclin, Clindabenz Acne Treatment Kit [benzoyl peroxide and clindamycin combination pack]), each morning*
- Benzoyl peroxide 4 or 5% cream or gel twice daily – for patients with oily nonsensitive skin

Rapid control of inflammatory acne

Consider an initial combination with a topical antibiotic:

- Retinoid nightly and erythromycin 2% gel or clindamycin 1% lotion each morning or twice daily*
- Benzoyl peroxide 5% plus clindamycin 1% combination gel nightly*
- Benzoyl peroxide 4 or 5% nightly and erythromycin 2% gel or clindamycin 1% lotion each morning or twice daily*
- Salicylic acid microgel complex twice daily and erythromycin 2% gel or clindamycin 1% lotion each morning or twice daily*

* Once good control has been achieved (usually after six to 12 or more weeks of treatment), consider stopping the antibiotic and relying on retinoid or benzoyl peroxide monotherapy for maintaining control. Subsequent flares can then be managed by reinitiating the same antibiotic combination (again usually for six to 12 weeks) until good control is re-established. Topical antibiotics can be used once or twice daily in combination with benzoyl peroxide and retinoids. The combination product Duac is more effective and better tolerated than its separate products.

other day until the irritation clears can help, as may immediate application of a light noncomedogenic moisturiser over the topical acne therapy.

The topical retinoids available in Australia vary greatly in their tendency to cause skin irritation. Variation is mainly due to differences in the product base or formulation, and to a lesser extent to actual differences in the retinoids. Industry-sponsored studies comparing the relative tolerability and efficacy of the different topical retinoids (adapalene, isotretinoin, tretinoin and tazarotene) used generic comparators. Given the enormous variation that can be measured between the generics available on the Australian market in regard to skin irritancy,[4] these industry-designed, sponsored and run studies have potential for bias and should not be used for making clinical decisions.

Changing therapy

If on review a topical acne treatment

has not proved beneficial, always probe deeper before entirely changing therapy. Poor adherence is a common reason for 'treatment failure', and is often due to side effects such as irritation, incorrect product use and/or difficulty fitting treatment recommendations with a patient's routine.

Systemic acne therapies

The agents used in the systemic treatment of acne are antibiotics, retinoids, certain combined oral contraceptives (COCs), spironolactone and metformin. Systemic acne therapies are often used in conjunction with topical acne therapies for more severe or widespread acne.

Antibiotics are the first line systemic therapy in males, who generally prefer taking tablets to applying creams or gels. Women, however, have the possible issues of premenstrual acne and pregnancy, and the risks of becoming pregnant while taking tetracyclines and retinoids must be considered. Also, the systemic side effects of vaginal candidiasis may complicate the use of oral antibiotics.

Systemic antibiotics

Oral antibiotics are usually prescribed as six-week, three-month or six-month courses that can be repeated as required. If insufficient response is seen with one antibiotic, including a trial at the higher recommended dose, a different antibiotic may be tried (doxycycline is first-line therapy). Table 3 lists antibiotics suitable for systemic use in the treatment of acne. In females, the addition of hormonal therapy should be considered. Antibiotics (both systemic and topical) often work well in combination with benzoyl peroxide or a topical retinoid to better control facial acne.

Resistance of *P. acnes* to oral erythromycin develops more frequently than resistance to other systemic antibiotics. Oral erythromycin is, however, a useful option for managing acne flares during pregnancy and/or those at risk of pregnancy.[9]

Fixed drug eruptions can occur with doxycycline therapy, usually within hours of taking doxycyline and most commonly on the face or groin area (Figure 3). They settle within weeks of stopping therapy but can sometimes cause hyperpigmentation that can take months to fade. If on the face, fading can be hastened by acne treatments, including topical tretinoin.

Minocycline and sulfonamide antimicrobial agents should not be used as first line therapy because of the relatively higher frequency of serious hypersensitivity reactions with these agents (Figure 4). These reactions include the drug hypersensitivity syndrome and, additionally for the sulfonamides, Stevens-Johnson syndrome and toxic epidermal necrolysis. Minocycline also causes delayed reactions (starting months or years into therapy), including blue–grey pigmentation of acne and other scars, and drug-induced lupus (which can show overlapping features with polyarteritis nodosa). Minocycline also appears to carry the greatest risk of causing benign intracranial hypertension. Because of the risk of adverse reactions, recommended antibiotic doses, particularly of minocycline, should not be exceeded.[10]

Antibiotic resistance

Antibiotics have been, and remain, an important part of acne management. Their benefits in acne are due to both their anti-inflammatory and antimicrobial

Table 3. Systemic antibiotic acne therapies

Moderate facial acne failing topical therapy and/or widespread mild to moderate acne

- First-line therapy: Doxycycline 50 to 100 mg nightly

If above not tolerated or contraindicated consider:

- Second-line therapy: Erythromycin (E-Mycin, EES, Eryc Capsules) 250 mg twice daily or roxithromycin 150 mg nightly
- Third-line therapy: Minocycline (Akamin, Minomycin) 50 to 100 mg nightly

Moderate to severe facial acne and/or widespread acne failing to respond sufficiently to a six-week trial of above

- First-line therapy: Doxycycline 150 to 200 mg daily (in larger males)

If above not tolerated or contraindicated consider:

- Second-line therapy: Erythromycin 500 mg twice daily or roxithromycin 300 mg nightly
- Third-line therapy: Minocycline 100 mg nightly or trimethoprim 160 mg plus sulfamethoxazole 800 mg (Bactrim DS, Resprim Forte, Septrin Forte) twice daily

Significant facial acne and/or insufficient facial response to above

Combine systemic antibiotic and a topical therapy:

- Retinoid – adapalene 0.1% cream or gel (Differin Topical Cream/Gel), isotretinoin 0.05% gel (Isotrex Gel), tazarotene 0.1% cream (Zorac Cream), tretinoin 0.05% or 0.1% cream or gel (Retin-A, ReTrieve Cream, Stieva-A) nightly*
- Benzoyl peroxide 4 to 5% cream or gel (Benzac, Brevoxyl, Oxy, PanOxyl Preparations) nightly*
- Salicylic acid microgel complex twice daily (e.g. Neutrogena Rapid Clear range)*

* Once good control has been achieved (after usually six to 12 or more weeks of treatment), consider stopping the antibiotic and relying on retinoid or benzoyl peroxide monotherapy for maintaining control. Subsequent flares can then be managed by reinitiating the same antibiotic combination (again usually for six to 12 weeks) until good control is re-established. Topical antibiotics can be used once or twice daily in combination with benzoyl peroxide and retinoids. The combination product Duac is more effective and better tolerated than its separate products.

Acne treatment: adverse drug reactions

Figure 3 (left). A fixed drug eruption due to doxycycline therapy in a 17-year-old male. The red, irritable, round or oval raised plaques usually become evident and/or noticeably worsen within hours of taking doxycyline. They most commonly occur on the face or groin area, and can occasionally develop a central blister. The eruption settles within weeks of stopping therapy but can sometimes cause hyperpigmentation that can take months to fade. Fading of hyperpigmentation on the face can be quickened by acne treatments such as topical tretinoin.

Figures 4a to c (below). Minocycline hypersensitivity syndrome in a 16-year-old male after 10 weeks of minocycline therapy. Features included a fever, sore throat, cervical lymphadenopathy, malaise, shortness of breath, a puffy swollen head and neck with erythema, pustules and erosion on the face (a, left), a skin eruption including diffuse truncal erythema and scale (b, centre), along with prominent hand and foot involvement with tender erythematous swelling that resolved with significant peeling and desquamation (c, right). There was associated hepatitis and pneumonitis. Complete resolution of symptoms took 12 weeks.

properties. This heavy reliance on antibiotics has seen an increase in the prevalence of *P. acnes* resistance to commonly used agents. For this reason antibiotic therapy should be reviewed (i.e. given in courses).

Benzoyl peroxide has been shown to restore microbiological antibiotic sensitivity and thereby reduce the development of antibiotic resistance.[9] Therefore, when tolerated, benzoyl peroxide should be included in the regimen as a means of minimising antibiotic resistance. If it is not tolerated, consider combining antibiotic therapy and salicylic acid microgel complex. This combination may have a similar beneficial effect to the antibiotic and benzoyl peroxide combination but requires further study.

Other strategies for suspected antibiotic resistance are hormonal therapy for long-term control of mild to moderate acne in females, and systemic isotretinoin for more severe forms of acne in males and females and for long-term control of mild to moderate acne in males.

Systemic retinoids

Oral isotretinoin (Isohexal, Oratane, Roaccutane) carries an extremely high risk of causing birth defects and requires dermatologist prescription. Commencement of the combined oral contraceptive (COC) pill should be considered in female patients being referred to a dermatologist for oral isotretinoin.

Over 25 years of clinical use of oral isotretinoin has shown that it is extremely useful in the treatment of severe acne. It is also useful in the management of less severe acne when there is treatment resistance and for the management of acne that is producing physical or psychological scarring when other treatments have failed.[10]

Should a patient taking oral isotretinoin suspect that she has become pregnant, the retinoid should be stopped immediately and pregnancy testing undertaken. The prescribing dermatologist should be contacted, and the patient should have a consultation with a medical professional expert in pregnancy counselling, including the issues surrounding abortion.

Table 4. Combined oral contraceptive pills useful in acne

Progestogen	Oestrogen	COC generation	Trade names
Cyproterone acetate 2 mg*	Ethinyloestradiol 35 µg	4th	Brenda-35 ED, Diane-35 ED, Estelle-35 ED, Juliet-35 ED
Levonorgestrel 100 µg*	Ethinyloestradiol 20 µg	2nd	Loette, Microgynon 20 ED, Microlevlen ED
Dienogest 2 mg	Ethinyloestradiol 30 µg	3rd	Valette
Drospirenone 3 mg	Ethinyloestradiol 30 µg	Spironolactone analogue	Yasmin
Desogestrel 150 µg	Ethinyloestradiol 30 µg	3rd	Marvelon 28
Gestodene 75 µg	Ethinyloestradiol 30 µg	3rd	Femoden ED, Minulet

* Reasonably good quality controlled trials have shown that cyproterone and low dose levonorgestrel-containing products have benefits in acne over comparator third-generation COCs. The benefits are greatest for cyproterone. Placebo-controlled trials have shown benefits in acne for all third-generation progestogens and the 'spironolactone analogue' drospirenone. Only the four cyproterone acetate-containing COCs and the low dose levonorgestrel-containing COC Loette are registered for an acne indication by the TGA in Australia.

Combined oral contraceptives

The COC pills that are likely to improve acne are those containing cyproterone acetate, desogestrel, dienogest, drospirenone, gestodene or low-dose (100 µg) levonorgestrel as the progestogen (Table 4). Progestogen-only oral contraceptive pills and implantable contraceptives generally worsen acne.

Hormonal therapies can be effective in the long-term control of acne and should be considered in girls and women troubled with mild to severe persistent and/or recurrent acne. Clinically significant benefits can, however, be frustratingly slow to appear, with visible benefits often taking three or more months and maximal improvement some six to nine months.

Combining COC therapy and a topical acne therapy for the first few months of COC use may give more rapid and better long-term control of facial acne than COC therapy alone. Similarly, combination with a systemic antibiotic for the first three to six months generally gives more rapid control of acne. COC and systemic antibiotic combinations have not been shown to increase risk of contraceptive failure, but COC product information warns of theoretical COC failure when taken with antibiotics. It is wise to inform patients of this possible risk and their need to use a second method of contraception during this period.[11]

For women with more severe acne, cyproterone-containing COCs (the anti-androgenic, fourth-generation COCs) have the greatest benefits, including in those with polycystic ovarian disease, but they do possibly have a higher thromboembolic risk. For more mild disease, consider the second-generation COCs that contain low doses of both levonorgestrel and oestrogen (thereby giving the best risk profile). Third-generation and spironolactone derivative COCs are beneficial for women requiring a higher oestrogen dose. Uncontrolled studies suggest potentially greater benefits with dienogest and drospirenone over other third-generation COCs, including those containing desogestrel.[12]

Spironolactone

Spironolactone (Aldactone, Spiractin), a synthetic steroid and weak diuretic, can improve acne control. It is usually prescribed in conjunction with a COC in cases of acne associated with seborrhoea and/or hypertrichosis. The usual dose is 50 to 100 mg daily for a six- to nine-month course that can be repeated.[5] Use with the COC protects against irregular and heavy periods, which can limit its tolerance. Seborrhoea usually improves after the first cycle and acne over the next two cycles.

Patients should be warned about the symptoms of hypotension. Although uncommon at the spironolactone doses used for acne in otherwise young healthy individuals, dose modification should be considered in those slight of build (decrease to 25 to 50 mg daily).

Metformin and weight loss

Hormonal therapies for acne are more successful in obese patients when the issues of insulin resistance and weight loss are addressed. Polycystic ovarian syndrome and insulin resistance are often associated in both obese and lean females, and this association should be investigated. These patients frequently have acne as well.

Studies have shown a similar acne improvement at six months with weight loss and/or metformin therapy as with use of cyproterone-containing COCs.[13] Metformin dosing used in studies was 500 mg twice daily for three months, then 1000 mg twice daily. As well as improving acne, metformin and weight loss reduce insulin resistance and reduce the risk of diseases associated with obesity.[14]

Metformin may be used in combination with topical acne therapies and also systemic antibiotics for acne. Further research into combination treatments of hormonal and metformin therapy for acne are required.

Pregnancy and acne

Patients with acne and polycystic ovarian syndrome who want to become pregnant can benefit twofold from taking metformin as it both improves acne and increases fertility. Most other treatments used to assist conception, either traditionally or by *in vitro* fertilisation, may temporarily worsen acne.

Patients who have hormonal acne will generally experience acne flares during the first trimester but their acne usually rapidly improves and clears by the last trimester, and breastfeeding appears to slow its return. Many women with persistent acne observe their acne to be progressively less severe or disappear with subsequent pregnancies.

Acne treatments with proven safety in pregnancy include:

- benzoyl peroxide
- erythromycin (topical and oral)
- clindamycin
- erythromycin and clindamycin combination gel
- azelaic acid.

The following agents should be avoided in all women able to conceive:

- oral isotretinoin
- tetracycline antibiotics (doxycycline and minocycline)
- spironolactone
- retinoid creams and gels.

The systemic retinoid isotretinoin is the only acne medication with proven teratogenicity and carries an extremely high risk of causing birth defects. As mentioned earlier, if a patient taking oral isotretinoin suspects that she has become pregnant, the retinoid should be immediately stopped, pregnancy testing undertaken, the prescribing dermatologist contacted, and the patient counselled about the pregnancy, including abortion.

While those women who become pregnant while taking spironolactone should stop the drug immediately, reassuringly there is no evidence of any risk of harm if spironolactone is inadvertently taken during the first few months of pregnancy. Spironolactone has not been associated with teratogenic defects but if taken during the last few months of pregnancy it could interfere with the normal development of a male child. Tetracycline antibiotics also carry proven risks later in pregnancy when the teeth and bones are being deposited.

The risk associated with systemic

retinoids has led to the recommendation that no woman planning to become pregnant or who is pregnant should use creams or gels containing retinoids. If a woman using a topical retinoid finds out that she is pregnant she should immediately stop using the preparation. Data from a large number of pregnancies exposed to topical retinoids, along with that from large studies looking into the absorption of tretinoin after topical cream use on the face, are reassuring regarding pregnancy risk, and suggest that no significant elevation in systemic retinoid levels occurs with limited skin application of tretinoin.[11]

Future acne therapies

Future directions in acne management include light therapy and photodynamic therapy.

Blue light therapy

Blue light therapy (wavelength, 420 nm) has been clinically demonstrated to be effective in the treatment of acne. It is thought to work by the photodynamic eradication of *P. acnes*, via destruction of porphyrins in the bacterial cells, a key factor in the pathogenesis of acne vulgaris.[15]

Photodynamic therapy

Photodynamic therapy (PDT) involves the use of photochemical reactions mediated through the interaction of photo - sensitising agents, light and oxygen for the treatment of malignant or benign diseases. The therapy has been shown to have the potential for the long-term improvement of acne vulgaris.

PDT is a two-step procedure. A photosensitiser administered by topical, oral or intravenous routes is taken up by the target cells. The photosensitiser is then activated in the presence of oxygen by a specific wavelength of light. By the photosensitiser being preferentially absorbed by hyperproliferative tissue and the light source being directly targeted on the lesional tissue, PDT achieves dual selectivity, minimising damage to adjacent healthy structures. Aminolevulinic acid (ALA) is the topical sensitiser used in acne treatment, although recently methyl aminolevulinate (MAL) has also been shown to be safe and effective in the treatment of acne vulgaris.[15]

Significant clinical improvement and a decrease in sebum production and sebaceous gland size have been shown after PDT. Histological analysis showed destruction of sebaceous glands, which suggests that this therapy has the potential for long-term improvement of acne.

Additional small studies using various light sources, including the Blu-U and intense pulse light, have also been published and suggest that ALA PDT has efficacy for the treatment of acne.[16] However, PDT is not a mainstay treatment in acne as the exact number of treatments required is unknown and it has not been around long enough to assess its role.

Conclusion

Medical professionals have access to a growing range of effective acne therapies. However, therapies that work in some patients may not be tolerated in others. Poor compliance and incorrect use or inappropriate choice of topical acne therapies and other skin care products are major reasons why patients return dissatisfied with treatment suggestions. It is thus worthwhile being familiar with the many acne therapies and the range of skin care products suitable for use on acne prone skin.

Further information on the treatment of acne is available on the All about acne website, www.allaboutacne.com.au. MT

A list of references is available on request to the editorial office.

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A clinically practical approach to acne

Part 2: Treatment

JOHN SULLIVAN MB BS, FACD **VERONICA PREDA** BSc, MB BS

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