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Real Word Acne Therapy in Primary Care

Neel Malhotra¹, Timothy E. Pyra² and Jaggi Rao²

¹Faculty of Medicine and Dentistry, Department of Medicine, University of Alberta, Edmonton, AB, Canada. ²Division of Dermatology and Cutaneous Sciences, Department of Medicine, University of Alberta, Edmonton, AB, Canada. Corresponding author email: jrao@ualberta.ca

Abstract: Acne vulgaris is a common presenting complaint to the family physician. With its multitude of treatment options and varying degrees of presentation severity, the management of acne vulgaris in the primary health care setting can be overwhelming. This review provides a framework for primary care physicians for the management of acne vulgaris. It presents information regarding the basic mechanism of action, pharmacokinetic profile, safety, efficacy, patient preference and role in therapy for the major modalities of acne treatment relevant to primary care.

Keywords: acne vulgaris, therapy, review

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Introduction

Acne vulgaris is a common skin disease resulting from inflammation of the pilosebaceous unit. Estimates of lifetime prevalence range from 73.3% to nearly 100%.^{1,2} Although acne most frequently occurs in adolescence, 42.5% of men and 50.9% of women experience acne in their 20s, and a significant percentage of patients continue to be affected well into adulthood.¹

Pathogenetically, the four key factors leading to the development of acne are: (1) follicular hyperproliferation and plugging, (2) increased sebum production, (3) follicular colonization by and activity of *Propionibacterium acnes* (*P. acnes*), and (4) inflammation.^{2,3} The effects of androgens on sebocytes and infundibular keratinocytes, action of *P. acnes* on Toll-like receptor-2 (TLR-2) receptors, secretion of cytokines, altered sebum lipids, and a host immunological reactions have all been implicated in the multifactorial pathway leading to follicular hyperkeratosis and subsequent acne lesions.⁴

Hyperproliferation of ductal keratinocytes leads to the development of microcomedones, the subclinical precursor to all other acne lesions.⁵ Hormonal influences initiate this process of comedogenesis.^{5,6} Accumulation of lipids, bacteria, and cell fragments within the follicle leads to visible lesions, and inflammation occurs through the action of *P. acnes* and generation of inflammatory mediators.⁶ Clinically apparent acne lesions consist of closed and open comedones (whiteheads and blackheads, respectively) and a spectrum of inflammatory lesions including papules, pustules, nodules, and cysts. Acne predominantly occurs on the face, chest, shoulders, and back—areas with the greatest numbers of pilosebaceous units.

Though it is not a life-threatening condition, the effects of acne on the patient cannot be understated. Detrimental physical effects include discomfort, post-inflammatory hyperpigmentation, and scarring.⁷ Acne can also have several psychosocial sequelae including depression, anxiety, anger, low self-esteem, social withdrawal, difficulties in interpersonal relationships, and impaired school or occupational performance.⁷⁻⁹ Worldwide, the market for prescription medications to treat acne was \$2.0 billion US in 2001. The over-the-counter market was 2 to 4 times this amount.¹⁰

The current armamentarium available to clinicians in primary care consists mainly of topical retinoids, topical antimicrobials, systemic antibiotics, oral contraceptives, and oral isotretinoin. Other treatments are available including several procedural, laser, or light therapies, however these are not typically offered in a primary care setting. Each of these therapies target one or more of the factors that are implicated in the development of acne.² Therapy should be tailored to each individual patient, selecting both for skin characteristics and acne type. Adherence to treatment depends on safety and efficacy profiles, so these will be discussed for each medication.

Topical retinoids

Derivatives of vitamin A, topical retinoids are a mainstay of acne therapy, either alone or in combination with other agents. The three topical retinoids most commonly used in clinical practice are tretinoin, adapalene, and tazarotene. Tretinoin is available as a cream (0.025%, 0.05%, 0.1%), gel (0.01% and 0.025%) and a liquid (0.05%). Adapalene is available as a cream, gel, or solution (0.1% or 0.3%). Tazarotene is available as a gel or cream (0.05% or 0.1%).

Mechanism of action, metabolism and pharmacokinetic profile

The primary mechanism of action of topical retinoids involves preventing the formation of comedones (that is, they are anticomedogenic) and treating existing comedones (that is, they are comedolytic).^{6,11-13} Retinoic acids activate nuclear retinoic acid receptors, which increases follicular epithelial cell turnover and reverses abnormal desquamation, ultimately reducing comedogenesis and promoting the resolution of existing comedones.^{11,13-15} Numerous studies have also demonstrated that topical retinoids have direct anti-inflammatory effects related to the modulation of non-specific immunity including a reduction in TLR2 receptors, inflammatory mediators, and altering inflammatory cell activity.^{3,11,16}

The percutaneous absorption of tretinoin, adapalene, and tazarotene is low and they do not alter the natural levels of systemic, endogenous retinoids.¹⁷ Systemic tretinoin is metabolized by the liver and cleared by the kidneys. Consequently, it is possible that systemically absorbed tretinoin could interact with medications affecting the cytochrome P450 enzymes.¹⁷



Safety

The most common adverse effect of topical retinoids is local irritation including erythema, dryness, burning, peeling, and itching.^{6,18} Topical tretinoin and adapalene have not been linked to systemic toxicity, but are nonetheless Food and Drug Administration (FDA) Pregnancy Category C drugs (benefits must outweigh the risks) and are also not recommended during lactation.¹⁷ Similarly, topical tazarotene has not been linked to systemic toxicity, but is a Category X drug (prohibited in pregnancy) and should also be avoided during lactation.¹⁷

Efficacy

Topical tretinoin, adapalene, and tazarotene have all been shown to have therapeutic efficacy compared to placebo or their vehicle.^{19–22} Tretinoin is the oldest of the three, and was found to be effective in both non-inflammatory (comedonal) and inflammatory acne.¹⁸ In a large meta-analysis, adapalene was found to have equal efficacy when compared to tretinoin, and to work more quickly.²³ When 0.3% and 0.1% adapalene gels were compared, the higher concentration demonstrated a greater improvement in acne lesions.²⁴ Comparative trials have shown that tazarotene is also more effective than tretinoin.^{25,26}

Topical retinoids are effective in maintenance therapy because of their anti-comedogenic effects, which prevent the formation of new lesions.⁶ Indeed, clinical studies have provided evidence for the ability of adapalene to prevent the formation of acne precursor lesions and thus provide successful maintenance following initial treatment.^{12,24}

Patient preference

Multiple studies demonstrate that tretinoin, adapalene, and tazarotene have all been well-tolerated with no major adverse events.^{19–26} Cutaneous irritation is frequently experienced with topical retinoid therapy with approximately 50% of patients in one study applying tazarotene once or twice daily reporting some degree of irritation.²⁷ It is important to note, however, that these effects tend to be mild and transient and that none of the patients in that study discontinued therapy.²⁷ Cutaneous irritation can be minimized through the application of moisturizers and by avoiding sunlight and extreme weather conditions.¹⁷

Adapalene has been found to have superior tolerability compared to tretinoin and tazarotene.^{22,26,28} Although new tretinoin microsphere preparations have been found to cause less irritation compared to older tretinoin formulations, adapalene is still the least irritating topical retinoid.^{20,29} Another advantage of adapalene is its more rapid onset of action compared to tretinoin therapy.²³

Place in therapy

Many recent review articles on the treatment of acne have suggested that topical retinoids should be a primary treatment for most forms of acne, alone or in combination with other agents.^{6,11,18} Despite this recommendation, a recent study demonstrated a trend towards decreased use of topical retinoids by non-dermatologist physicians.³⁰ Consensus guidelines recommend monotherapy with topical retinoids as first line for mild, comedonal acne.^{3,6} For mild inflammatory acne, topical retinoids should be combined with a topical antimicrobial, whereas for moderate or severe inflammatory acne, they should be combined with an oral antibiotic or possibly a hormonal agent in females.^{3,6,18} Additionally, topical retinoids on their own or in combination with benzoyl peroxide are currently recommended for maintenance therapy following courses of systemic treatment.³

Topical antibiotics

Topical antibiotics have many advantages over oral therapy in the treatment of acne vulgaris: decreased risk of systemic adverse effects, higher local concentration of the medication, and lower overall doses.³¹ The topical antibiotics commonly encountered in clinical practice are clindamycin and erythromycin. These macrolides are each available as a gel, lotion, or solution with strengths of 1% for clindamycin and 2% or 4% for erythromycin.

Mechanism of action, metabolism and pharmacokinetic profile

The mechanism of action of topical antibiotics in the treatment of acne is both antibacterial and anti-inflammatory. Clindamycin and erythromycin are bacteriostatic for *P. acnes* and work by irreversibly binding to the 50S ribosomal subunit.^{32,33} It is important to note, however, that acne is not an infection, but rather that *P. acnes* induces inflammation.³³ It does



this by producing pro-inflammatory mediators and the activation of toll-like receptors on keratinocytes.^{6,34} In addition to decreasing the number of *P. acnes*, antibiotics inhibit its ability to produce lipase (which hydrolyzes triglycerides into glycerol and pro-inflammatory free fatty acids), and suppress leukocyte chemotaxis.^{32,34}

Systemic absorption of both clindamycin and erythromycin applied topically is low. Clindamycin is metabolized by the liver, cleared by the kidneys and excreted by the biliary system and in the feces.¹⁷

Safety

Topical antibiotics are generally very well-tolerated and any side effects are typically minor.^{6,34,35} The most common problems reported by patients are local erythema, dryness, itching, burning, and peeling.³⁴ Topical clindamycin can infrequently cause diarrhea. Rarely, pseudomembranous colitis has also been reported.^{17,36} It is an FDA Pregnancy Category B drug and there are no reports of adverse effects due to breastfeeding while using topical clindamycin.¹⁷ No systemic adverse effects have been reported with the use of topical erythromycin, and it is also a Pregnancy Category B drug.¹⁷ Erythromycin is not recommended during lactation as it is unknown whether it is excreted during lactation.¹⁷

Studies have found that treatment with topical macrolides leads to increased rates of resistance to these antibiotics.³⁷ This occurs either through the selection of pre-existing resistant strains or the development of a new resistant phenotype during treatment, and longer duration of therapy increases the likelihood of resistance.³⁴ Not only is antibiotic resistance problematic because it reduces the effectiveness of topical antibiotics in the treatment of acne, but it can also lead to an increase in resistance during treatment of other, more pathogenic bacteria (eg, *Staphylococcus Aureus*).⁶ In a study comparing clindamycin/benzoyl peroxide (BPO) combination therapy with clindamycin monotherapy, resistant *P. acnes* counts increased to >1600% after 16 weeks of treatment compared to no increase with the combination group.²⁸

Efficacy

The efficacy of topical clindamycin and erythromycin in treating acne has been well-established through several high quality clinical studies.^{38–40} A review

by Toyoda and Morohashi⁴¹ concluded that topical clindamycin and erythromycin are effective in the treatment of acne vulgaris, with greater effect for inflammatory as opposed to non-inflammatory types. When compared to oral antibiotic therapy, however, topical antibiotic therapy is less effective and slower acting.⁶

More recently there is increased concern that bacterial resistance to macrolides has led to decreased efficacy of topical antibiotic therapy in acne. A systematic review by Simonart and Dramaix⁴² of 50 controlled trials found that the effect of topical erythromycin on inflammatory and noninflammatory lesion counts has decreased significantly over time, which is likely related to the development of resistance in *P. acnes*. This review did not find any temporally associated decrease in the effectiveness of topical clindamycin, however *P. acnes* resistance to clindamycin has been demonstrated in the literature.⁴³

Patient preference

Topical antibiotics are typically very well-tolerated with local irritation being the most common side effect.^{32,34} Patients may prefer topical combination products due to their increased efficacy and quick onset.⁶

Place in therapy

Due to the potential for antibiotic resistance, the use of topical antibiotics as monotherapy should be limited.^{3,6,34} Several steps can be taken to limit exposure to antibiotics. Topical antibiotics in combination with topical retinoids or BPO should be used in mild to moderate inflammatory acne.^{6,15} These combinations have been shown to be more efficacious and better tolerated. There is also evidence suggesting that they prevent bacterial resistance.⁶ Additionally, topical antibiotic therapy should be stopped once inflammatory lesions begin to resolve, or after 6–8 weeks if no improvement has been observed.^{3,34} If the latter occurs, another treatment option should be selected. Once topical antibiotic treatment has been discontinued, topical retinoids alone or in combination with BPO can be used as an appropriate maintenance therapy. Topical antibiotics should not be used in combination with oral antibiotics, as this combination may further increase the risk of resistance.³



Benzoyl peroxide

BPO is a non-antibiotic antibacterial used in the treatment of acne vulgaris.⁴⁴ It can be applied once or twice daily, and is available as cream, lotion, gel, foam, wipes, solutions, or pads at strengths of 1%, 2.5%, 4%, 5%, and 10%. In addition to monotherapy, combination therapies involving BPO are common and highly effective.

Mechanism of action, metabolism and pharmacokinetic profile

BPO's primary mechanism of action is antibacterial—reactive oxygen species are generated that kill bacteria by oxidizing constituents of their cell membranes.⁴⁵ In addition to its antimicrobial activity, studies have also shown that BPO has keratolytic and anti-inflammatory properties, which are likely contribute to its clinical effectiveness.^{46,47} Being lipophilic, BPO penetrates the stratum corneum and is broken down into benzoic acid and hydrogen peroxide. Any systemically absorbed benzoic acid undergoes rapid renal clearance.⁴⁸

Safety

BPO has been used for many years in acne therapy, and its safety has been thoroughly established. Cutaneous irritation (dryness, stinging, burning, erythema, or peeling) is the most common adverse effect, with irritant dermatitis occurring in a very small number of patients.^{44,48} These effects typically resolve within several days of treatment.^{6,44} A study comparing 2.5%, 5%, and 10% BPO found no difference in efficacy, but the 2.5% and 5% strengths were better tolerated than the 10% treatment.⁴⁹ Unlike topical antibiotics, no studies to date have documented bacterial resistance to BPO.^{6,44,48} BPO has not been linked to systemic toxicity, and its effects on fetal development and lactation are unknown, so it is an FDA Pregnancy Category C drug.¹⁷

Efficacy

Eady and colleagues³¹ found BPO to be as effective as topical antibiotics in the treatment of inflammatory acne lesions, and superior in treating non-inflammatory lesions. Many randomized controlled trials have confirmed this finding that BPO is effective for reduction of both inflammatory and non-inflammatory lesion counts.^{38,50} Concentrations of 2.5%, 5%, and

10% BPO gel were found to be similarly effective at reducing inflammatory papules in pustules in a randomized, double-blind study of 153 patients.⁴⁹ A comparison study of BPO vs. adapalene found that BPO led to a greater reduction of inflammatory and non-inflammatory lesions early in therapy (weeks 2 and 5). However, the two monotherapies led to a similar reduction in all lesion counts at week 11.⁵¹

Patient preference

One adverse effect that patients should be made aware of is that BPO can cause bleaching of hair, clothes, or other fabrics.⁴⁸ The most common reason for patients to discontinue BPO therapy is cutaneous irritation. A number of new formulations and drug delivery systems have been developed in an attempt to mitigate this problem; however, studies comparing these newer products are lacking.⁴⁴ While leave-on products may be more effective, washes or cleansers are available, which are rinsed off in order to prevent irritation and bleaching.^{44,48} These may be especially popular with adolescents as they can be easily applied to large areas of affected skin while in the shower.³⁴ It should be recommended that patients avoid other skin irritants.

Place in therapy

As discussed above, BPO has a rapid onset of action, good efficacy, and is generally well-tolerated. Additionally, no bacterial resistance to BPO has been documented.^{6,44,48} It can therefore be used effectively as monotherapy for mild to moderate acne.⁴⁸ Clinically, BPO is the most commonly used first line product, in combination with a topical antibiotic or a retinoid (see below).^{6,48} Additionally, BPO can be used concurrently with topical or oral antibiotics to reduce the chance of bacterial resistance.³ BPO can be applied once or twice a day (morning and evening) and should not only be applied to visible lesions, but to the entire affected area.³⁴

Topical combination products

A number of fixed-dose topical combination products are available including adapalene-BPO (0.1%/2.5%), clindamycin/BPO (1%/5% gel), erythromycin/BPO (3%/5% gel), erythromycin/tretinoin (4%/0.025% solution), and Clindamycin/tretinoin (1.2%/0.025% gel).



Mechanism of action, metabolism and pharmacokinetic profile

As described above, topical retinoids are primarily effective because of their anticomedogenic and comedolytic effects (with some anti-inflammatory activity). Topical antibiotics reduce *P. acnes* and have additional anti-inflammatory properties, and BPO, while mainly antibacterial, also has anti-inflammatory and keratolytic effects. These overlapping effects suggest that these medications have not only complementary but also synergistic biological properties.^{6,48} Additionally, through their effects on follicular keratinization, topical retinoids increase the penetration of other topical medications when used in combination, thus potentiating their effectiveness.^{11,46}

Safety

A large number of high quality clinical trials have established that the various topical combination products currently available have excellent safety profiles. In a study of 492 patients with moderate to severe acne, treatment with clindamycin/BPO combination therapy compared to either agent alone demonstrated similar tolerability between all three treatment groups, with the most common adverse effect being dry skin.⁵⁰ A large trial examining adapalene/BPO compared to each product as monotherapy found that the tolerability and rates of adverse effects were the same.⁵²

Literature suggests that combining topical or oral antibiotic therapy with BPO can help prevent the emergence of resistant *P. acnes*.⁵³ One study found that the topical combination of erythromycin/BPO was not only effective for acne improvement, but that it also led to decreased counts of resistant bacteria.⁵³ In a study comparing clindamycin/BPO gel with clindamycin monotherapy, the counts of clindamycin resistant *P. acnes* steadily increased over the course of 16 weeks, while they remained at or below baseline with combination therapy.²⁸

Efficacy

Combining topical retinoids with topical antimicrobials significantly increases the efficacy of treatment and leads to a faster onset of action.^{34,54} Two large double-blind randomized controlled trials found that combination clindamycin/tretinoin gel was more efficacious than either agent alone or the vehicle, as the

combination resulted in lower inflammatory and total lesion counts.⁵⁵ Similar efficacy has been demonstrated in the literature for the combination of erythromycin and tretinoin.⁵⁶

Similarly, several studies have demonstrated the efficacy of topical combinations including BPO. Multiple randomized controlled trials comparing combination clindamycin/BPO and clindamycin or BPO monotherapy found that combination therapy resulted in greater reductions in total lesion counts, as well as numbers of inflammatory and comedonal lesions.^{28,50,38,57} A double-blind controlled study demonstrated superior efficacy using erythromycin/BPO combination product compared to either agent alone or the vehicle.⁵⁸ A study comparing clindamycin/BPO to erythromycin/BPO found no significant differences in effectiveness.⁵⁰ Topical retinoid/BPO combinations have also been investigated. Adapalene/BPO gel used once daily resulted in greater reductions in both inflammatory and comedonal lesions, with a faster onset of action compared to either monotherapy.^{52,59}

A comparative trial of erythromycin 3%/BPO 5% and erythromycin 4%/tretinoin 0.025% each applied twice daily in patients with moderate acne found no significant difference between the two treatment groups in reducing counts of comedones, papules and pustules.⁶⁰ No comparative studies of retinoid/BPO versus antibiotic/BPO combination products have been done, however both show similar reductions in lesion counts.⁴⁸

Patient preference

Many large clinical trials have demonstrated that the tolerability of topical clindamycin/BPO combination therapy is similar when compared to either agent alone.^{28,38,50,57} In a study of 2813 patients treated with clindamycin/BPO, either agent alone, or the vehicle, only 1% of patients dropped out due to adverse events.⁵⁷ Similarly, a combination adapalene/BPO product was studied in 452 patients with a dropout rate of only 2.0% due to mild adverse effects.⁵⁹ The tolerability of the adapalene/BPO combination product was found to be the same as either treatment alone.⁵² Patients found combination erythromycin/BPO therapy to be superior to combination erythromycin/tretinoin at reducing redness, oiliness, burning, and dryness, in a study that found these two treatments to be objectively similar in efficacy.⁶⁰



Overall, various topical combination products have been found to be more efficacious than monotherapy regimens, and tolerability has been found to be similar. As adherence depends on efficacy, safety, and ease of use, it is easy to conclude that combination products are a highly preferable treatment option in patients with acne.

Place in therapy

International guidelines on acne therapy recommend that topical combination therapy be used in mild to moderate inflammatory acne.⁶ Topical combinations of antibiotics/BPO, antibiotics/retinoids, and retinoids/BPO are all efficacious, safe, and tolerable, and so the decision of which to use can be determined by the patient's skin characteristics and the provider's experience. Although fixed-dose combination products are available, each component can be prescribed separately. If a topical antibiotic is used, it is recommended that BPO be used concomitantly or intermittently for between courses of therapy to prevent bacterial resistance.³ Once clinical improvement has been reached, monotherapy with a topical retinoid is effective for maintenance.³

Azelaic acid

Mechanism of action, metabolism and pharmacokinetic profile

Azelaic acid slows *P. acnes* growth, regulates abnormal keratinization and decreases inflammation.^{61–63}

Safety

Side effects of azelaic acid include burning, pruritus, scaling and erythema. Katsambas and colleagues⁶⁴ demonstrated in their azelaic acid versus vehicle study that of their 92 subjects, 9% of azelaic acid recipients reported burning, 5% reported pruritus and 5% reported erythema.

Efficacy

One study of 92 patients with moderate inflammatory acne tested 20% azelaic acid cream with its vehicle over a 3-month period, and found that the azelaic acid preparation significantly reduced the number of acne lesions. The same research team carried out an additional single-blind study of 289 comedonal acne patients and compared the effect of 20% azelaic acid cream with 0.05% tretinoin cream over a 6-month period.

The latter study demonstrated that both preparations were equally effective. Notably, however, the azelaic acid preparation was better tolerated.⁶⁴

Other studies have compared the effectiveness of azelaic acid to BPO. One study recruited 30 subjects suffering from papulopustular acne and treated subgroups with either azelaic acid or BPO for a period of 6 months. 75% of BPO recipients and 71% of azelaic acid recipients reported good to excellent efficacy. In a later study, investigators found that in 306 patients with papulopustular acne treated with either erythromycin or azelaic acid over a 5 month period, 72% of azelaic acid recipients and 67% of erythromycin recipients reported a good to excellent effectiveness.⁶⁵

Patient preference

Azelaic acid has been demonstrated to be a generally well-tolerated therapy, especially in comparison to already well-established treatment options. Overall, unwanted side effects to this drug are localized and mild, including erythema and scaling.⁶⁴ As noted, however, the incidence of these side effects is greater with tretinoin cream or benzoyl peroxide gel.^{64,65}

Place in therapy

In a 12 week study of 150 subjects receiving either topical 5% azelaic acid, topical 2% clindamycin, or both combined, Pazoki-Toroudi and colleagues⁶⁶ found the combination treatment of azelaic acid and clindamycin to be significantly more effective in reducing acne severity. A similar study comparing azelaic acid and erythromycin monotherapy effectiveness with combination therapy found that the combination of azelaic acid and erythromycin was better tolerated than either monotherapy.⁶⁷ Many other studies, including studies by Solomon and colleagues⁶⁸ and Shrager and Webster,⁶⁹ also suggest that azelaic acid works best in combination therapy for mild to moderate acne.

Oral antibiotics

There are several situations in which prescribing oral antibiotics for acne is clinically sound. These include situations where patients suffer from inflammatory acne that is moderate to severe, where patients have attempted topical treatments without success, or where the acne covers a substantial surface area of the skin, thereby precluding the practicality of applying topical therapies.⁷⁰ Essentially, there are two major



classes of antibiotics that are commonly used, being tetracyclines, and macrolides. In addition, several other medications, including trimethoprim (TMP)/Sulfamethoxazole (SMX), and ciprofloxacin can be used.

Mechanism of action, metabolism and pharmacokinetic profile

In general, antibiotics treat acne through either an anti-inflammatory effect or an antibacterial one. Which mode of action an antibiotic predominately uses depends on the antibiotic class. For instance, macrolides exert a primarily antibacterial effect. These antibiotics work by irreversibly binding the bacterial 50S ribosomal subunit, and consequently halting protein synthesis.⁷¹ Conversely, tetracyclines exert an antibacterial effect and an anti-inflammatory effect.⁷⁰ Tetracyclines exert their antibacterial effect by binding the 30S subunit of the bacterial ribosome.⁷² This class of drugs exert their anti-inflammatory effect through a variety of mechanisms: by inhibiting neutrophil and monocyte chemotaxis, granuloma formation, matrix metalloprotease and collagenase activity, as well as the formation of reactive oxygen species. They also modulate nitric oxide formation.⁷²⁻⁷⁷ Ciprofloxacin, a fluoroquinolone, works by inhibiting topoisomerase enzymes, thereby inhibiting bacterial DNA replication. Lastly, TMP/SMX blocks dihydrofolate reductase/dihydropteroate synthetase, which ultimately diminishes bacterial purine and pyrimidine synthesis.⁷⁸

Safety

Erythromycin is safe in pregnancy and in women who are lactating. Patients in general should take erythromycin with food to avoid gastrointestinal upset. Pharmacokinetically, erythromycin can inhibit clearing of theophylline, warfarin, carbamazepine, and cyclosporine. Up to 30% of patients on oral clindamycin report diarrhea. In addition, the use of clindamycin is further limited by its potential to increase *Clostridium difficile* growth.^{71,79}

Tetracycline commonly causes gastrointestinal discomfort and, less commonly, photosensitivity. It rarely can induce esophagitis, pancreatitis and pseudoporphyria.⁸⁰ Doxycycline is more likely to induce a phototoxic reaction than tetracycline.⁸¹ Minocycline can cross the blood-brain barrier and as a

result could cause vestibular disturbances. Long-term minocycline use can cause hyperpigmentation. Rarely, minocycline can induce a serum-sickness-like reaction, a lupus-like reaction, vasculitis or hepatic failure.^{82,83}

Tetracyclines in general should not be prescribed in pregnant women as they can adversely affect the fetus, and should not be prescribed for acne treatment in patients younger than 9 years old as they can leave deposits in and discolor developing teeth.

Lastly, TMP/SMX has potential side effects of thrombocytopenia, agranulocytosis and anemia. It also has the potential to cause a reaction of hypersensitivity.⁷⁸

Efficacy

Studies have shown that minocycline and doxycycline at sub-anti-microbial doses can still inhibit inflammation and subsequently improve acne.⁸⁵ Notably, one study demonstrated no change in doxycycline activity amongst doxycycline-treated patients who were extremely heavy compared to those with low body weight.⁸⁶

One study found that lymecycline (a semi-synthetic tetracycline) had a similar effectiveness and safety profile as minocycline, with lymecycline being more cost-effective. Another study found no clear evidence in the literature to support the use of minocycline as a first line agent over other tetracyclines.⁸⁷

In one randomized, double-blind trial, 100 patients suffering from moderate acne were treated with oral azithromycin or oral doxycycline for three consecutive months. The number and types of lesions all over the body were quantified at baseline, at the end of each month and 90 days following treatment. The results indicated that both drugs were comparably effective in treating moderate acne, with doxycycline being more effective in patients over the age of 18.⁸⁸ A 2006 randomized control trial of 290 patients compared azithromycin with tetracycline, again finding comparable efficacies between the two.⁸⁹

Patient preference

Both minocycline and doxycycline have low occurrences of adverse events, with fewer reported adverse events for doxycycline.⁷⁰ In the previously discussed study comparing effectiveness of azithromycin and doxycycline, azithromycin had no significant side effects, and the side effects reported with doxycycline were deemed minor.⁸⁸ Even in Rafiei and



Yaghoobi's study,⁸⁹ azithromycin was better tolerated than tetracycline. Overall, oral antibiotics are safe treatment options for most patients, with common side effects being minor or tolerable.

Place in therapy

Oral antibiotics should be held for those patients suffering from moderate to severe inflammatory acne. In general, medications from the tetracycline class of antibiotics are first line. Additionally, oral antibiotics should only be tried once topical therapy options have been exhausted, or are impractical.⁹⁰ Even when the decision to start oral antibiotics has been made, topical BPO or azelaic acid should be continued. Finally, antibiotic resistance should always be kept in mind when prescribing systemic antibiotics.⁷⁰ Notably in acne, the simultaneous use of topical BPO may have some role in preventing *P. acnes* resistance (see Benzoyl Peroxide section).

Hormonal medications

Mechanism of action, metabolism and pharmacokinetic profile

Androgen hormones instigate acne formation primarily by stimulating sebum production.⁹¹ Since androgens play a clear role in acne pathogenesis, it is logical that medications with anti-androgen effects could improve acne. In fact, many studies have demonstrated such an effect with oral contraceptive pills (OCPs). Oral contraceptive pills work by increasing sex hormone-binding globulin and by decreasing levels of freely circulating testosterone. Additionally, they inhibit ovarian androgen production.⁹² In general, OCPs contain ethinyl estradiol with a progestin. Despite the potentially androgenic effect of progestin, the combined effect with ethinyl estradiol is anti-androgenic.⁹³

OCPs have been shown to have drug interactions with rifampin and griseofulvin. These medications potentiate the metabolism of OCPs at cytochrome p450.⁹⁴

An additional anti-androgen drug is spironolactone. It is often used to treat acne as an adjunctive treatment. It works by acting as an androgen receptor blocker.^{95,96}

Safety

Common side effects of oral contraceptive pills include nausea, mood changes, breast tenderness and

breakthrough bleeding.⁹⁷ In addition, particularly in those patients who smoke, have hypertension, diabetes or migraines, the use of OCPs increases risk of stroke, venous thromboembolism, and myocardial infarction. Finally, while on these medications there is some debate as to whether patients are at an increased risk of developing breast cancer.⁹⁷

OCPs are contraindicated in pregnancy, and in breast-feeding women less than 6 weeks post-partum.⁹²

Possible adverse effects of spironolactone include menstrual irregularities, lethargy, fatigue, and headache.⁹⁸

Efficacy

One multicentre, double-blind, randomized, placebo-controlled study by Lucky and colleagues⁹⁹ on 257 females with moderate acne involved treatment with either 6 months of Ortho Tri-Cyclen (norgestimate and ethinyl estradiol) or placebo. The mean reduction in inflammatory lesion count from baseline was 62% in the Tri-Cyclen group compared to 38.6% in the placebo group. Similarly, the mean total decrease in lesions was 53.1% versus 26.8% respectively. Finally, global assessment indicated 93.7% versus 65.4% improvement at study close, for the Tri-Cyclen group and placebo group, respectively. Thus, Tri-Cyclen is deemed an effective therapy for moderate acne.⁹⁹ Redmond and colleagues¹⁰⁰ reported similar findings for Tri-Cyclen efficacy.

Another notable study demonstrated efficacy for 3 mg drospirenone/20 mcg ethinylestradiol OCP (Yaz). This randomized, double-blind, parallel-group study took 334 healthy females suffering from moderate acne vulgaris and treated them with either Yaz or placebo for six cycles of 28 days. Overall, there was a greater reduction in inflammatory, non-inflammatory and total lesions in the Yaz-receiving group compared to placebo. Additionally, members of the Yaz-receiving group were four times more likely to receive a global score of 'clear' or 'almost clear' skin ratings at the end of the investigation.¹⁰¹

Overall, in regards to estrogen-containing OCPs, James¹⁰² summarizes that after 6–9 months of OCP use, in general there is a 30%–60% decrease in inflammatory lesion counts and that overall improvement is observed in 50%–90% of patients.



In regards to spironolactone, a retrospective study by Shaw⁹⁸ investigated records from 85 women with acne treated with spironolactone at 50–100 mg/day as a monotherapy or as an adjunct for a time period lasting up to 2 years. They found that 33% of patients on low dose spironolactone experienced acne resolution, 33% showed marked improvement and 27.4% showed partial improvement. The remaining 7% demonstrated no change. This study suggests that spironolactone is a reasonable treatment option to consider.

Patient preference

In the study by Koltun and colleagues,¹⁰¹ 63.9% of Yaz-recipients compared to 48.1% of placebo-recipients reported at least one adverse event (57.9% and 43.6% of which were deemed mild to moderate, respectively). Also, adverse events caused a dropout rate of 6.4% of Yaz-recipients and 4.9% of those receiving placebo.

In regards to spironolactone tolerability, in the retrospective study by Shaw⁹⁸ discussed previously, the drug was tolerated very well, with 57.5% of patients reporting no adverse events at all. Menstrual irregularities were noted in 17.5% of patients, whereas 16.3% of patients reported symptoms of lethargy, fatigue, dizziness or headache.

Place in therapy

Lynde¹⁰³ insists that hormonal treatment of acne is an appropriate choice for women who seek contraception, as well as women with late-onset acne, menstrual irregularities, or acne that waxes and wanes with menstruation, and those suffering from concomitant endocrine problems. It can be argued that hormonal therapy for acne should not be used as a monotherapy, and should be combined with traditional approaches to acne management (for instance, topical antibiotics or BPO) that would act against components of acne pathogenesis that OCPs do not act against.¹⁰⁴ It is also important to continue other forms of acne treatment because OCPs generally take at least 3 months to exhibit an effect on acne.⁹²

Oral retinoids

Retinoids are synthetic derivatives of vitamin A. The oral or systemic retinoid used in the treatment of acne is isotretinoin (13-cis retinoic acid).^{105,106}

Mechanism of action, metabolism and pharmacokinetic profile

The exact mechanism of isotretinoin is not entirely elucidated. Isotretinoin is a non-selective retinoid that acts mainly on gamma-retinoic acid receptors (RAR- γ) in the nuclei of keratinocytes;¹⁰⁷ however, this binding has been demonstrated to be weak and thereby is likely not isotretinoin's main mechanism of action.¹⁰⁸ Additionally, isotretinoin regulates keratinocyte-keratinocyte adhesion; it has an anti-inflammatory effect and it appears to control *P. acnes* proliferation.¹⁰⁶ According to Chivot,¹⁰⁶ isotretinoin's central mechanism of action is its indirect suppression of the sebaceous gland itself.

Safety

The major adverse effect of oral isotretinoin is teratogenicity in pregnancy.¹⁰⁹ Much attention has been captured regarding the effect isotretinoin can have on premature epiphyseal closure in young children^{110–112} and bone growth and metabolism in general.¹⁰⁵ Notably, however, the doses and length of treatment in the specified cases were well beyond the parameters for the treatment of acne.¹⁰⁶ Since some of these bone changes are asymptomatic and can persist following treatment,¹¹³ it is important to establish baseline and subsequent regular skeletal surveys in patients who will be on prolonged courses and high doses of isotretinoin.¹¹⁴

Oral isotretinoin has been demonstrated to cause asthma exacerbation, due to a dried pulmonary mucosa.^{115,116} Additionally, there have been reports of associations with skin fragility,¹¹⁷ acne flare,¹¹⁸ nail changes,¹¹⁹ and mild hair loss.¹²⁰ Moreover, up to 15% of patients can experience myalgias.¹²¹ Prescribing physicians should also be aware that a spectrum of ophthalmological disturbances can occur, from dry eyes to optic neuritis.^{109,122} As a result, it is clinically prudent to ask questions regarding visual disturbances at regular follow up while on treatment and afterwards.

Notably, isotretinoin has been linked, although still controversially, to depression and suicide, so it is therefore important for the primary care physician to screen for depression at regular visits. Finally, isotretinoin has been associated with neurological, gastrointestinal, pulmonary, renal/urinary and menstrual side effects.¹⁰⁵ Appropriate and regular



screening and laboratory blood work is therefore recommended.

Efficacy

A study by Bener and colleagues¹²³ took 198 subjects with severe acne and treated them with oral isotretinoin. Overall, 32.8% were cured, 19.1% markedly improved, 11.1% moderately improved and 24.2% of patients were advised for further treatment. Notably, any change in serum lipids was found to be transient, especially in young patients with normal liver function.

A literature review on the efficacy of isotretinoin determined that a dose of 0.5 mg/kg/day for mild to moderate acne is comparably effective to the directed dosage of 1 mg/kg/day for severe acne. It is thereby suggested that isotretinoin effective dosage be dictated by the severity of the presentation itself.¹²⁴

In a retrospective study by Warren and Cruz,¹²⁵ investigators sought to compare the effectiveness of oral isotretinoin to conventional treatments (89% on a combination of one oral antibiotic and one or more topical preparations and the other 11% on either one oral antibiotic or one topical preparation) for moderate acne. They measured efficacy as ‘complete clearing’ of acne and on the duration of treatment required to reach it. In the group receiving oral isotretinoin, 82% of patients experienced complete clearing over an average of 5.2 months. In the group receiving conventional treatment only 9% of patients experienced complete clearing, taking an average of 15.8 months to do so. This study further reinforces the premise that oral isotretinoin is superior in its effectiveness for acne treatment.

Patient preference

The most common non-serious adverse effect experienced by patients on oral isotretinoin is mucocutaneous cheilitis and more than 90% of patients will experience it within the first week of treatment.^{109,126} Epistaxis is another less common side effect.¹⁰⁵ Both of these can be treated by moisturizing or lubricating the affected area.¹²⁷ Additionally, patients may experience dermatitis (which is more common in winter months or in dry climates).¹²⁰ Xerosis is also commonly experienced; however, less than half of the patients on isotretinoin will experience xerosis that is

clinically significant, and most of those patients will have a prior history of atopy.¹²⁸

In the retrospective study by Warren and Cruz¹²⁵ discussed previously, the investigators found that 94% of patients receiving oral isotretinoin reported an adverse event; however, none had to discontinue the medication. Interestingly, the group that received conventional treatments only had 20% of its members report adverse events, but in this group 12% ultimately discontinued the medication as a result. Again, the isotretinoin side effects experienced were mostly dryness and transient elevation in lipids and liver enzymes—side effects that are well-tolerated by patients. Indeed, oral isotretinoin has a vast array of potential side effects; however, the common ones are typically mild and tolerable considering the potential for excellent results.

Place in therapy

Charakida and colleagues¹⁰⁵ recommend that combining an antibiotic with isotretinoin for the first month of treatment can prevent the acne flare event discussed previously. Isotretinoin should be prescribed at 1 mg/kg/day. If the patient suffers from severe inflammatory acne, putting them at risk for an initial flare once on isotretinoin, a dose of 0.5 mg/kg/day for the first 6 weeks is acceptable. No matter which approach is taken, a cumulative dose of 120 mg/kg/day is the goal for a single course of treatment of isotretinoin. Although an effective treatment for acne, considering its immense profile of potential side effects, isotretinoin should be reserved for cases of severe acne or acne that is not responding to other traditional acne treatments. Also, it should be noted that relapses can occur at any point following a course of treatment in up to 21% of patients,^{129,130} and thus additional courses may be required.¹⁰⁵

Conclusion

Acne is a common and complicated dermatological problem. It has a spectrum of presentations and, at the same time, a myriad of treatment options. The purpose of this review is to provide the primary care physician with a framework to managing acne effectively. Every patient is different, and as this review has made clear, there is no single protocol or order of acne treatment options. Here we provide a basic starting point. In general, the first step is to characterize



the patient's acne as mild, moderate or severe. For mild acne that is predominately comedonal (multiple black or white heads with little to no associated inflammation), a topical retinoid is a good place to start. Once the acne progresses to a papulo-pustular form (where inflamed and infected lesions predominate), the addition of a topical antibiotic is prudent. If acne is moderate, and nodules become apparent, adding BPO is a good option.¹³¹ As stated previously, some studies suggest it is best to add BPO as soon as an oral antibiotic is administered, as it may help combat resistance. When acne becomes severely nodular or conglobate, oral isotretinoin should be considered. Again, however, as some studies discussed, prescribing oral isotretinoin earlier in the progression of acne or in moderate acne is not an unreasonable consideration.

Author Contributions

Conceived and designed the experiments: JR. Analysed the data: JR. Wrote the first draft of the manuscript: NM. Contributed to writing the manuscript: TP. Agree with manuscript results and conclusions: JR. Jointly developed the structure and arguments for the paper: NM, TP, JR. Made critical revisions and approved the final version: JR.

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