Pharmacologic Therapy for Acne

A Primer for Primary Care

Many of the 50 million persons affected by acne in the United States present to primary care. Acne severity guides treatment choices, which include topical antibiotics and retinoids, hormonal agents, and systemic antibiotics and retinoids. Formulating a treatment plan requires a thorough understanding of the dosing, mechanism of action, and potential adverse effects of available medications.

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LEARNING OBJECTIVES

- Describe the main factors involved in the pathogenesis of acne.
- Assess acne severity and classify acne as mild, moderate, or severe.
- Describe available acne therapies, including their mechanisms of action, indications, and potential adverse effects.
- Identify strategies patients can employ to mitigate the adverse effects of acne treatments.

Acne vulgaris (acne) is a common skin condition that is frequently encountered in primary care. Acne affects up to 50 million people in the United States, and about 85% of teenagers experience it at some point.[1] Costs for treatment exceed $3 billion per year.[2] Although commonly considered a condition of adolescence and young adults (85% prevalence), acne may persist in both men and women well into their 30s and 40s (43% prevalence). In fact, 5% of women ages 40 and older may experience acne.[3]

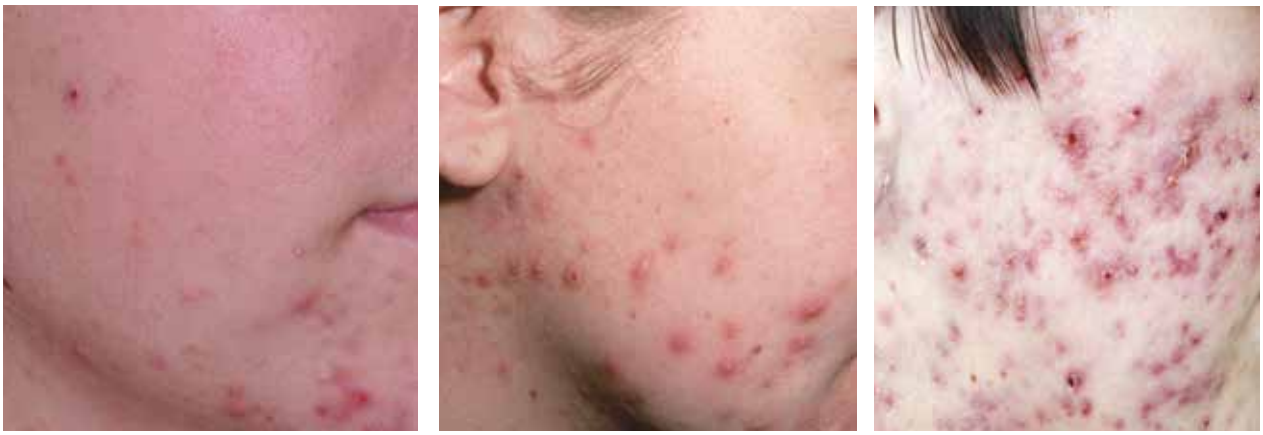
Acne is associated with considerable, long-lasting psychological sequelae, even in those with mild conditions, as many affected patients experience self-esteem issues and may avoid social interactions.[4] Recognition of patients' concerns about acne will help to promote a trusting patient-provider relationship. This article describes the pathophysiology and classifications of acne and reviews therapeutic options, enabling the practitioner to initiate treatment.

PRESENTATION AND ASSESSMENT

Acne lesions may occur on the face, neck, trunk, and extremities. The severity of acne is assessed based on lesion type, number, and size, and this grading is used to inform decisions about treatment options. Mild acne is characterized by plugging of the sebaceous gland (comedones), with small numbers of inflammatory pap-

FIGURE 1

Acne Severity



Severity is based on lesion type, number, and size. Mild acne (left) is characterized by plugging of the sebaceous gland; moderate acne (center) involves a larger number of inflammatory papules/pustules and small cystic nodules; and severe acne (right) is marked by large numbers of noninflammatory and inflammatory lesions and cystic nodules.

Credit (l to r): Reprinted with permission from *Cutis* (2017;100[1]:23); Biophoto Associates, Science Source; SPL, Science Source

ules and pustules. Moderate acne involves a larger number of inflammatory papules/pustules as well as the presence of small cystic nodules. Severe acne is marked by the presence of large numbers of noninflammatory and inflammatory lesions and cystic nodules or widespread involvement of these lesions.[5] Examples of mild, moderate, and severe acne are shown in Figure 1. Assessment should include questions about the patient's experiences with prior therapies.

PATHOGENESIS

The pathogenesis of acne is a complex process involving multiple factors (see Figure 2, page 25). Knowledge about acne pathogenesis continues to evolve, but the current view is that a combination of simultaneous noninflammatory and inflammatory events involving pilosebaceous units (which consist of sebaceous glands and hair follicles) contribute to its development.[6] Activation of the sebaceous glands is influenced by androgens, which increase sebum production and shedding of the keratinocytes lining the gland. Plugging of the pilosebaceous canal ensues, leading to the development of a microcomedone. Increased proliferation of *Propionibacterium acnes* occurs within the obstructed gland. The inflammatory response to this process includes a cascade of numerous cytokines, most notably toll-like receptor 2 (TLR-2).[7] The plug at the opening of the sebaceous gland creates either an open comedone (blackhead) or a closed comedone (whitehead). Eventually, the follicular wall ruptures, leading to the formation of erythematous papules and pustules on the skin surface or deep-seated cystic structures under the skin surface. Current pharmacologic agents target one or more of these identified factors underlying acne pathogenesis.

THERAPEUTIC OPTIONS

Pharmacologic treatment options for acne include topical, systemic, and hormonal agents. Topical and systemic therapies reduce inflammation and follicular plugging. Topical treatments include antibiotics, anti-inflammatories, and retinoids. Oral treatments include antibiotics, hormones, and retinoids. The clinician must have a thorough understanding of the actions, potential adverse reactions, and drug interactions of each proposed therapy prior to formulating a treatment plan.

Topical retinoids

Topical retinoids are the most effective comedolytic agents available.[1] Since com-

TABLE 1

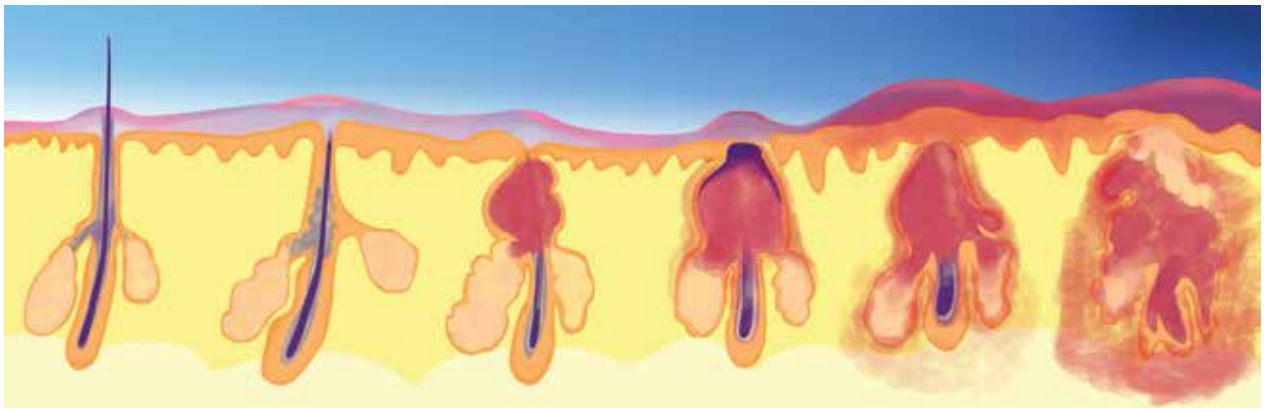
Topical Agents for Treatment of Acne

Medication	Mechanism of action	Available preparations	Potential adverse effects
Topical retinoids			
All retinoids	Normalizes follicular epithelial desquamation and keratinization, exhibits anti-inflammatory activity, promotes comedolysis		Erythema, skin irritation, peeling, pruritus, photosensitivity
Tretinoin*		Cream 0.025, 0.0375, 0.05, 0.075, 0.1% Gel 0.01, 0.25, 0.0375, 0.04, 0.05, 0.1% Micronized 0.04, 0.08, 0.1%	
Adapalene*		Cream, lotion 0.1% Gel 0.1%, 0.3%	
Tazarotene†		Cream 0.05%, 0.1% Gel 0.05%, 0.1% Foam 0.1%	Worsening of psoriasis via koebnerization (appearance of psoriasis at areas of trauma)
Other topical agents			
Benzoyl peroxide*	Bactericidal against *P acnes*, exhibits comedolytic and keratolytic actions and anti-inflammatory activity	Washes, creams, gels, foams, solutions, and bar soaps with concentrations ranging from 2.5% to 10%	Erythema, scaling, dryness, bleaching of hair and clothing
Clindamycin phosphate‡	Inhibits protein synthesis by binding to ribosomal 50S subunit of *P acne*	Lotion, gel, solution, foam, all 1%	Skin irritation, rare cases of pseudomembranous colitis, resistance
Erythromycin‡	Inhibits protein synthesis by binding to ribosomal 50S subunit of *P acnes*	Gel, solution, ointment, pledgets, film, all 2%	Resistance, irritant dermatitis from drug
Azelaic acid‡	Disrupts mitochondrial respiration and DNA synthesis in *Propionibacterium acnes*; exhibits anti-inflammatory, antimicrobial, and comedolytic properties; can inhibit tyrosinase, which may help lighten post- inflammatory hyperpigmentation	Gel, foam 15%, Cream 20%	Tingling or itching application, irritant dermatitis
Dapsone*	Inhibits dihydropteroate synthetase and nucleic acid synthesis	Gel 5% and 7.5%	Irritant dermatitis, signs of methemoglobin discoloration of clothing and skin when used in conjunction with benzoyl peroxide
Sodium sulfacetamide*	Exerts a bacteriostatic effect on *P acnes* through inhibition of dihydropteroate synthetase	Lotion, suspension 10%	Irritant dermatitis, may have a sulfuric odor

* Risks in pregnancy not ruled out; human studies lacking; potential benefits may justify potential risk.
† Contraindication in pregnancy. There is NO reason to risk use of drug in pregnancy.
‡ No risk to human fetus. No risk in animal studies, and human studies have not yet been done.
Sources: Zaenglein et al. *J Am Acad Dermatol.* 2016[1]; Canavan et al. *Dermatol Ther.* 2016[6]; Sami. *Comprehensive Dermatologic Drug Therapy.* 2013[9]; Smith. *Acne in Review Guide.* 2013[10]; Sagransky et al. *Expert Opin Pharmacother.* 2009[11]; Motoparthi and Hsu. *Comprehensive Dermatologic Drug Therapy.* 2013[12]; Thiboutot et al. *J Clin Aesthet Dermatol.* 2016[13]; Wolf and Silapunt. *Cutis*. 2015[14]; Hassoun L et al. *Semin Cutan Med Surg.* 2016[15]; Patton and Ferris. *Comprehensive Dermatologic Drug Therapy.* 2012.[16]

FIGURE 2

Pathogenesis of Acne



This illustration depicts the pathogenesis of acne as a landscape. From left to right, it shows a normal pore; the microcomedone stage; a closed comedone; an open comedone (dark purple on top); a papule; and a pustule (or cyst) with inflammation.

Credit: Shelia Herman / Science Source

edones are thought to be the precursor of all other acne lesions, retinoids are appropriate for cases in which comedones are seen.[1] Retinoids belong to a class of compounds structurally related to vitamin A. Topical retinoids act by promoting normal follicular keratinocyte desquamation, which prevents obstruction of the pilosebaceous canal and thereby inhibits the formation of microcomedones.[8]

They also exhibit anti-inflammatory action via inhibition of TLR-2.[9] The comedolytic and anti-inflammatory actions of topical retinoids make them a mainstay of acne treatment, although some patients are unable to tolerate their adverse effects, which include erythema and dryness related to increases in transepidermal water loss. Application of noncomedogenic emollients can improve these common effects.[10] The newer micronized and time-release retinoid formulations may have less potential for irritation.[8] Vehicle formulation and concentration also play a role in skin irritation, with gels and liquids and formulations with higher concentrations of retinoids generally causing more drying than creams and lower potency formulations.[8] Table 1 summarizes the mechanisms of action, available formulations, and potential adverse effects of the topical retinoids and other topical agents.[1,6,9-16]

It is important to note that retinoids can adversely affect the developing fetus when absorbed in large quantities. Notably, tazarotene is assigned to pregnancy category X because when it is used to treat psoriasis, one of its approved indications, large surface areas may be treated, increasing absorption. Absorption amounts are extremely low when tazarotene is used to treat acne. Nevertheless, verification of a negative pregnancy test is recommended prior to initiating tazarotene therapy. Effective birth control measures should be utilized throughout therapy. Even though other commonly used retinoids (tretinoin and adapalene) are assigned to pregnancy category C, all topical retinoids should be avoided during pregnancy.[9]

As noted, patient education is key for increasing patient adherence to therapy. Patients should be instructed to use a small (pea-sized) amount of medication for the entire face. Providers should also inform patients that transient erythema and dryness can be expected, and that application of a noncomedolytic moisturizer may reduce irritation. Tretinoin is best used at night,[1] and it is useful to advise that erythema and irritation associated with retinoid use can be reduced by initially using the medication every other night to every third night, gradually building up to nightly use.[1]

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TABLE 2

Oral Antibiotics Used in Acne Treatment

Medication	Class	Usual dosage	Potential adverse reactions
Doxycycline*	Tetracycline	50-200 mg/d	Antibiotic resistance, gastrointestinal upset, esophagitis, tooth discoloration in the developing fetus and in children under age 8, photosensitivity, pseudotumor cerebri (rare), hepatic dysfunction (rare)
Minocycline*	Tetracycline	50-100 mg every 12-24 h Extended-release formulations 45-135 mg once daily	Antibiotic resistance, gastrointestinal upset and photosensitivity but each less than doxycycline, dizziness, urticaria, hepatic dysfunction (uncommon), pseudotumor cerebri (rare), bluish grey to brown hyperpigmentation
TMP- SMX†	Folate synthesis inhibitor	Single strength 80 mg TMP and 400 mg SMX Double strength 160 mg TMP and 800 mg SMX	Photosensitivity, urticaria, hypersensitivity syndrome, bone marrow suppression, erythema multiforme ranging from Stevens-Johnson syndrome to toxic epidermal necrolysis

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole.
*Positive evidence for risk to human fetus. However, benefits may outweigh risks of the drug.
†Risks in pregnancy not ruled out; human studies lacking; potential benefits may justify potential risk.
Sources: Zaenglein et al. *J Am Acad Dermatol.* 2016[1]; Yan and Del Rosso. *Acne in Review Guide.* 2013[19]; Kim et al. *Comprehensive Dermatologic Drug Therapy.* 2013.[20]

Topical antibiotic and anti-inflammatory agents

Topical agents used to treat inflammatory lesions include benzoyl peroxide, erythromycin, clindamycin, dapsone, azelaic acid, and sulfacetamide (Table 1, page 24).[1,6,9-16] These topical agents are generally well tolerated, with most adverse reactions limited to facial irritation and erythema. They come in an array of vehicle formulations, including washes, creams, gels, solutions, foams, and lotions. Vehicle selection should be based upon patient preference and skin type. Gels and solutions have a drying effect, making them more appropriate for individuals with oily skin, whereas creams are moisturizing and appropriate for individuals with dry skin. Lotions are appropriate for all skin types.[11]

Benzoyl peroxide (BPO) has both keratolytic and comedolytic activity and is available in concentrations ranging from 2.5% to 10%. It is available OTC, as well as by prescription, and is thus readily accessed by the patient. Because BPO is bactericidal for *P acnes*, resistance to BPO among *P acnes* has not occurred.[1] All concentrations are equally effective, but the higher concentrations are more likely to cause skin dryness and other adverse effects.[12] Combination therapy with topical antibiotics, tretinoin, and BPO is more clinically effective than monotherapy.[17] Combination products reduce the complexity of acne treatment and likely increase therapy adherence.[11] Currently available combination products in various percentages are erythromycin with BPO, clindamycin with BPO, adapalene with BPO, and clindamycin with tretinoin.[1]

Oral antibiotics

Oral antibiotics should be reserved for use in situations where topical therapy is ineffective. All antibiotics are effective in treating acne due to their antimicrobial activity against *P acnes*.[1] These agents play a key role in managing moderate to severe acne that is likely to scar, as well as in cases of widespread acne involving the face, arms, and trunk. Note that the use of oral antibiotics in acne treatment is controversial, as chronic use contributes to rising rates of bacterial resistance.[18] For this reason, antibiotic therapy for acne should be limited to a duration of three months or

less, and these agents should not be used as monotherapy.[6] In particular, recent recommendations restrict the use of erythromycin for acne treatment due to an increase of *P acnes* resistance.[1] Cephalosporins, macrolides, and penicillin class antibiotics are not routinely recommended due to lack of data regarding their clinical effectiveness in treating acne.[1]

Tetracycline class antibiotics are the most commonly used oral antibiotics for acne therapy, particularly doxycycline and minocycline.[5] Common adverse effects include gastrointestinal upset, photosensitivity, and some pigmentation issues.[19] Trimethoprim-sulfamethoxazole (TMP-SMX) is a folate synthesis inhibitor class antibiotic also used to treat acne. Its use should be reserved for individuals who are allergic to tetracyclines or in cases of acne resistant to other antimicrobials.[1] Potential adverse reactions include photosensitivity and severe hypersensitivity conditions ranging from a mild rash to toxic epidermal necrolysis.[19] Table 2 summarizes the dosage ranges, pregnancy category risk, and potential adverse effects of oral antibiotics used to treat acne.[1,19,20]

The firstline choice for treating *moderate acne* with papules and pustules is oral antibiotics with topical retinoids and BPO.[5] Patients should be educated about potential adverse effects of these agents, including the development of antibiotic resistance.

Hormonal agents

Hormonal therapies should be reserved for females with acne lesions influenced by fluctuations in hormone levels.[21] Pubertal changes initiate the production of adrenal dehydroepiandrosterone, which leads to increased testosterone production. Testosterone is converted to dihydrotestosterone (DHT), which binds to androgen receptors in the sebaceous glands, stimulating the glands and potentially increasing production of sebum. Hormonal agents act by reducing androgen activity in the sebaceous gland. Combined oral hormones, those containing both estrogen and progesterone, reduce the amount of free testosterone and ovarian androgens by suppressing ovulation.[1] Hormonal therapy can be quite effective for females of childbearing age. Females who report acne flares with their menstrual cycles may be good candidates for hormonal therapy.[1]

The estrogen agent most frequently used in oral contraceptives is ethinyl estradiol. Numerous progesterone agents can also be used, but those with low androgenicity or antiandrogenic properties are more effective for acne therapy.[21] It is prudent to screen patients for thromboembolic risks, as this is a major adverse effect of combined hormonal agents. Risks of thromboembolic episodes are increased in obese persons, those who smoke, and those older than age 35.[15] Other contraindications for combined hormonal therapy are pregnancy, liver disease, current breast cancer, heart disease, hypertension, and migraines with neurologic symptoms. Minor adverse effects include nausea, breast tenderness, cyclic weight gain, and headaches.[15] Although many combined oral contraceptives improve acne, only four have FDA indications for the treatment of acne: ethinyl estradiol/norgestimate, norethindrone acetate/ethinyl estradiol, drospirenone/ethinyl estradiol, and drospirenone/ethinyl estradiol/folate.[5]

Spironolactone, a potassium-sparing diuretic, may also be appropriate for treating acne in women due to its antiandrogenic properties. The drug binds androgen receptors in the skin, which then blocks testosterone and DHT. Spironolactone can be an effective firstline agent in treating hormonal-pattern acne, which presents as inflammatory lesions located on the lower face and neck. In particular, it can be an appropriate choice for women with adult-onset acne.[15] Spironolactone is not approved by the FDA for acne treatment, but it has been used successfully for many years.[5] Spironolactone was found in rodent studies to cause feminization of the male rat fetus, so patients taking this drug should use reliable birth control methods. It can be used concomitantly with oral contraceptives.[5] Common side effects include breast tenderness,

diuretic effects, headaches, and menstrual irregularities. Although the risk for hypokalemia is low in healthy young women, it may be prudent to periodically assess potassium, sodium, and renal function in patients.[1] Spironolactone should be avoided in patients with renal disease and those on other diuretics.[15]

Isotretinoin

Isotretinoin is an oral systemic retinoid that modulates nuclear receptors and regulates gene transcription in the epidermis.[16] Isotretinoin's mechanisms of action target the main pathogenic factors underlying acne, including reduction of follicular hyperkeratosis, comedogenesis, sebum production, and inflammation and suppression of *P acnes*.[22] These combined actions make isotretinoin a highly effective treatment option for acne.

The drug is approved by the FDA for treatment of nodular acne refractory to traditional acne therapies.[23] Isotretinoin is available in 10, 20, 25, 30, and 40 mg capsules, and the recommended dosing is 0.5 to 2.0 mg/kg/d. The usual course of therapy is 15 to 20 weeks or until an accumulative dosage of 120 to 150 mg/kg is attained.[23] Patients should be instructed to take isotretinoin with meals, as oral availability is increased with high-fat foods.[23]

Isotretinoin has major adverse effects. It is a teratogenic medication that can cause congenital anomalies in exposed fetuses, including craniofacial, cardiac, and neurologic issues.[16] Due to the seriousness of the congenital anomalies, all prescribers must be registered in the iPledge program, a computer-based risk management program instituted in 2006 by the FDA and the companies that manufacture isotretinoin to eliminate congenital risks associated with isotretinoin. All patients, both male and female, must sign an informed consent form when they register in the program.

Although the iPledge program does not mandate consistent condom use for male patients, they should be informed that minute amounts of isotretinoin can be found in semen. The risk for fathering a fetus with congenital anomalies when taking isotretinoin appears to be extremely low.[16] Women of childbearing potential must commit to the use of two highly reliable forms of birth control when taking the medication, including one month before starting therapy and one month after completing therapy.[16] Monthly pregnancy testing is mandatory throughout the course of treatment.[24] Further information regarding the risk management program can be found at **iPledgeprogram.com.**

Isotretinoin is metabolized by the liver and may cause lipid abnormalities and hepatic enzyme elevations. Baseline and monthly laboratory monitoring of liver enzymes and cholesterol and triglyceride levels are recommended.[24] The process of initiating and monitoring isotretinoin therapy is quite complex, and unless the practitioner plans to routinely prescribe this medication, patients needing isotretinoin therapy should be referred to a dermatology practice.

PATIENT EDUCATION

Patients are more likely to adhere to treatment when simplified regimens are used and when they have realistic expectations for therapy outcomes. Providers need to educate patients that all treatments may require at least two to three months of use before visible results occur. Initial and subsequent visits should include discussions about clear expectations and strategies to reduce potential adverse effects.

PUTTING IT ALL TOGETHER

Acne therapy starts with the use of a topical retinoid in mild acne cases, unless the patient is unable to tolerate the associated skin irritability. Addition of a topical antibiotic or anti-inflammatory agent, preferably BPO, either alone or with a combination product, is also recommended for mild to moderate acne. Patients with moderate to severe acne may benefit from a short course (three months or less) of antibiotics.

Oral hormones may be an excellent therapy choice when acne treatment is needed for women of childbearing age. Isotretinoin

is indicated in select cases of severe acne resistant to other treatments. **CR**

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