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Challenges in the Treatment of Acne in the United States

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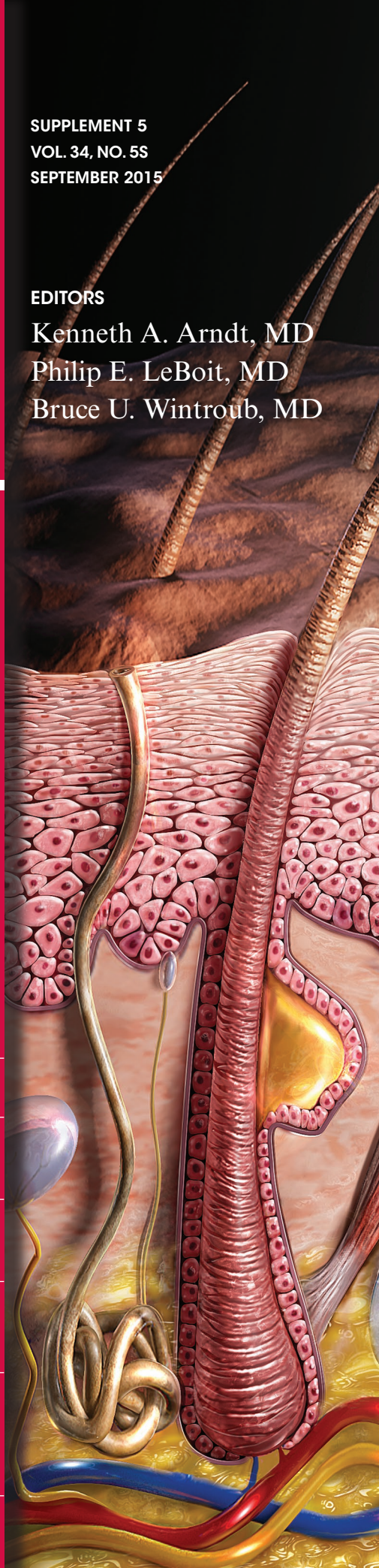

Challenges in the Treatment of Acne in the United States

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Target Audience

This supplement is intended for dermatologists, family practitioners, internists, nurse practitioners, physician assistants, and other clinicians who treat patients with with acne vulgaris.

Educational Needs

Acne vulgaris, once thought of as an infectious dermatologic condition, now is recognized as a chronic inflammatory disease with a multifactorial pathogenesis. Research within the past decade has enhanced the understanding of several pathways involved in the expression of the underlying disease, including how *Propionibacterium acnes* induces inflammation, the role of the innate immune system in acne, and how aberrations in the immune response may be better addressed to manage this disease. As a result of this improved understanding, the goals of therapy also have evolved, and now include—in addition to managing acute outbreaks of acne lesions—prevention of visible lesions by reducing the development of microcomedones, managing underlying inflammation, reducing the risk for scarring, and minimizing the psychosocial burden of acne. Achieving these goals demands that clinicians remain up to date on the treatment recommendations of dermatology researchers and clinical experts, including which patients are candidates for isotretinoin therapy and what strategies can be helpful in promoting patient and family acceptance of this treatment and—for best results—adherence to a therapeutic regimen.

Learning Objectives

After reading and studying this enduring journal, participants will be better able to:

- Discuss the safety and efficacy of the various classes of agents used for treating acne
- Explain the mechanisms of action of systemic and topical agents used to treat acne
- Diagnose and determine appropriate systemic and topical treatment options for patients with mild to severe acne
- Describe the appropriate candidates for isotretinoin therapy, and incorporate improved protocols for the optimum use of this agent
- Discuss strategies for minimizing the risk of acne scarring
- Recognize the urgency of prompt treatment of acne to prevent physical and psychological scarring
- Advise patients regarding the nature and management of their diseases and suggest practical psychosocial coping techniques
- Implement educational strategies to improve adherence with treatment plans, including ways to help reduce relapse rates in adolescent patients

Disclosure Declarations

As a provider accredited by the ACCME, the Office of CME & PD, School of Medicine, University of Louisville must ensure balance, independence, objectivity, and scientific rigor in all its sponsored educational activities. All planners, faculty, reviewers, and other persons that affected the content of this CME activity were required to submit a financial disclosure form from which relevant conflicts of interest were determined. The persons below disclosed the following:

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This activity discusses the off-label use of spironolactone for acne and isotretinoin for acne that may be physically or psychologically scarring.

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Seminars in Cutaneous Medicine and Surgery

EDITORS

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Seminars in Cutaneous Medicine and Surgery presents well-rounded and authoritative discussions of important clinical areas, especially those undergoing rapid change in the specialty. Each issue, under the direction of the Editors and Guest Editors selected because of their expertise in the subject area, includes the most current information on the diagnosis and management of specific disorders of the skin, as well as the application of the latest scientific findings to patient care.

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INTRODUCTION

Reframing the Isotretinoin Discussion

Hilary E. Baldwin, MD*

■ Keywords
Acne; isotretinoin.

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The effective treatment of most patients with mild-to moderate acne vulgaris is readily accomplished using evidenced-based guidelines. At a recent clinical round-table—from which this educational supplement was derived—the faculty reviewed the most current acne treatment guidelines, the mechanisms of action of topical and systemic medications, the burden of acne, and strategies and techniques to promote adherence with therapeutic regimens. We offer two articles as succinct updates on these topics.[1,2]

However, we devoted most of our time at that meeting to discussing three important topics that we believe need special attention in acne care: dilution of the term "severe acne" to the point at which a new term is needed to describe "isotretinoin-worthy" acne; understanding and preventing scarring[3]; and—given the advances in understanding acne pathophysiology—how and when isotretinoin should be used and into which category this medication should be placed.[4]

Introduced in 1982 as an "oral retinoid," isotretinoin rapidly became the most effective treatment available for acne; it remains so today. However, with advances in our understanding of acne pathophysiology has come new insights about how isotretinoin works. Its classification as an oral retinoid does not begin to describe isotretinoin's mechanism of action, much as aspirin's categorization as a "pain reliever" does not do justice to this drug. Furthermore, the classification of isotretinoin as, simply, an oral retinoid has caused confusion among some treatment stakeholders—including clinicians, pharmacists, insurance providers, parents, and patients—who have assumed that isotretinoin is merely an oral form of medications such as topical adapalene, tazarotene, or tretinoin. This is a misperception that must be corrected, especially because this inaccurate view can result in barriers to the timely initiation of isotretinoin therapy in patients who would benefit from its use. As we discuss in the article "Isotretinoin: Mechanism of Action and Patient Selection,"[4] isotretinoin's mechanism of action in acne indicates the need for a more accurate subclassification under the retinoid umbrella. We propose "sebocyte modulator" as a more accurate descriptor.

We have recently seen an upsurge in topical medications and non-isotretinoin oral medications that have been approved by the US Food and Drug Administration for "severe acne." However, patients with a large number of nodules were expressly excluded from clinical trials of these medications and it is precisely this clinical presentation that makes patients isotretinoin-worthy. Therefore, what are we to call isotretinoin-worthy acne? We propose that new terminology is needed. We are concerned that the absence of a more specific term increases the likelihood of step edits, complicating the task of acquiring isotretinoin in a timely way for appropriate patients.

Finally, the prevailing notion for many years was that only patients with severe acne were at risk for scarring and the current labeling for isotretinoin reflects this view: isotretinoin is indicated for patients with resistant scarring nodular acne. However, some patients with less severe acne are at risk for significant emotional scarring, and evidence shows that physical scars can develop in patients in whom inflammation is relatively mild. Studies also show that time to initiation of treatment is an important factor in whether a susceptible patient develops scars: the longer the delay in instituting effective treatment, the greater the risk for scarring and its potentially profound, life-long consequences. The stakes are high for patients who can benefit from isotretinoin. Emotional and physical scarring is common and has been shown to worsen with delay in treatment. If patients need isotretinoin, they should experience no barriers to its acquisition.

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References

1. Baldwin HE, Zaenglein AL, Leyden JJ, Webster GF. Pharmacologic treatment options in mild, moderate, and severe acne vulgaris. *Semin Cutan Med Surg*. 2015;34(suppl 5):S82-S85.
2. Zanglein AL, Baldwin HE, Webster GF, Leyden JJ. Psychosocial issues in acne management: Disease burden, treatment adherence, and patient support. *Semin Cutan Med Surg*. 2015;34(suppl 5):S92-S94.
3. Leyden JJ, Webster GF, Zaenglein AL, Baldwin HE. Understanding and reducing the risk for acne scarring. *Semin Cutan Med Surg*. 2015;34(suppl 5):S89-S91.
4. Webster GF, Leyden JJ, Baldwin HE, Zaenglein AL. Isotretinoin: Mechanism of action and patient selection. *Semin Cutan Med Surg*. 2015;34(suppl 5)S86-S88.

Pharmacologic Treatment Options in Mild, Moderate, and Severe Acne Vulgaris

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Abstract

Most patients with acne have a disease that responds to acute treatment and can be controlled long term with a maintenance regimen of topical therapy. It is the minority of patients—generally, but not exclusively—the most severely affected, who respond poorly to acute therapy and require continued systemic therapy. The goals of therapy are resolution of visible lesions, prevention of new lesions, avoidance of scarring, and improvement of patient quality of life. Treatment choices are made on the basis of lesion type, number, and size, with consideration given to the presence of physical and psychological scarring.

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Keywords

Acne vulgaris; adapalene; antibiotics; antimicrobials; benzoyl peroxide; hormonal therapy; isotretinoin; topical retinoids; oral contraceptives; spironolactone; tazarotene; tretinoin

A broad range of medications currently are available to treat patients with acne. The choice of agents—as monotherapy or in combination—is made on the basis of lesion type and distribution, disease severity, psychosocial consequences, and the presence of scarring, with consideration of individual patient characteristics such as gender, age, and patient preference and lifestyle. Thoughtful consideration to the mechanism of action of each agent utilized maximizes efficacy while minimizing regimen complications and intolerance.

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Determining Acne Severity

The assessment of acne severity remains a subjective judgment in the absence of a single evidence-based, objective, and widely accepted grading system. This is a shortcoming primarily in the realm of clinical trials. Experienced clinicians can gauge acne severity rapidly and accurately within their own framework and derive an optimal therapeutic plan within the first moments of the patient encounter. However, to facilitate comparisons in discussions with colleagues, a common language is needed.

The Global Alliance to Improve Outcomes in Acne (hereafter referred to as the Global Alliance) and the American Acne and Rosacea Society (AARS)—both panels of dermatologists with extensive expertise in treating patients with acne—have devised evidence-based treatment algorithms for the care of mild, moderate, and severe disease, describing the general characteristics of these designations (**Figure 1**).[1-3] Mild disease includes comedonal and mixed and papular/pustular lesions; a larger number of mixed and papular/pustular lesions as well as small nodules (defined as <0.5 cm) are indicators of moderate disease (**Figure 2**); and severe disease is the designation used when a large number or widespread involvement of noninflammatory and inflammatory lesions and/or nodules are present. These designations are considered to be on a continuum, allowing for descriptions such as "mild-to-moderate" and "moderately severe" disease.

Although these methods of grading are useful for the purposes of comparative and clinical trials, they do not take into account psychological and psychosocial issues or the presence of physical scars. In clinical practice, patients whose moderate acne causes considerable distress may require more aggressive acute management; regardless of severity, scarring acne also warrants aggressive therapy. In such patients, systemic therapy, even isotretinoin, may be warranted as the initial treatment choice.

Therapeutic Options: Mechanisms of Action and Recommendations

The Global Alliance and AARS guidelines are built on evidence-based and clinically proven outcomes that follow from an understanding of the mechanism of action of the drugs recommended for use. The treatments to be discussed below are utilized because of their activity in targeting one or more of the pathogenic factors involved in the development of acne—that is, excess production of sebum, colonization by *Propionibacterium acnes* of the pilosebaceous duct, and resultant release of inflammatory mediators, inflammation, and abnormal follicular keratinization. The goals of acne treatment are the resolution of existing acne lesions, the prevention of new lesions, and the reduction of the sequelae of persistent hyperpigmentation, erythema, and scarring.

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Topical Retinoids

Therapy with a topical retinoid—adapalene, tazarotene, and tretinoin—is recommended across the spectrum of acne severity and in both acute and maintenance phases. As monotherapy, these agents are often used as first-line choices for mild or primarily comedonal acne. For patients with mixed comedonal and inflammatory lesions, topical retinoid monotherapy or a combination of topical retinoid and an antimicrobial agent or topical dapsone is recommended. For patients with moderate to severe disease, a combination of a topical retinoid and an antimicrobial/dapsone are recommended, often in combination with oral antibiotics or hormonal therapy.

The maintenance phase for acne of any severity includes a topical retinoid as monotherapy or in combination with benzoyl peroxide.

The mechanism of action of topical retinoids in acne is broad. These agents normalize keratinization within the follicle, eradicating existing and preventing the formation of new microcomedones. In addition, topical retinoids have anti-inflammatory activity and have been shown to enhance the penetration of antimicrobials applied at the same time.

Benzoyl Peroxide

Benzoyl peroxide (BP) has antibacterial and mild keratolytic activity. In addition to its effectiveness in treating acne, BP also plays a role in the prevention of antibiotic resistance. *P. acnes* resistance to BP has not been reported. The combination of BP and topical clindamycin prevents the development of resistance to clindamycin, which occurs rapidly in the absence of BP.[4] In one study, the addition of a 6% BP wash to an acne regimen was shown to greatly reduce antibiotic resistance *P. acnes* strains after only 3 weeks of use.[5]

In mild disease, BP often is used as first-line monotherapy. In moderate disease, it is used in combination with a topical retinoid and/or topical antibiotic. In severe disease, BP often is included in a combination therapy regimen along with oral antibiotics/hormonal therapies and topical retinoids.

Topical Antimicrobials

Topical antimicrobial therapy—clindamycin, primarily—is recommended in combination with BP and/or a topical retinoid and BP for mild-to-moderate inflammatory acne. Topical antimicrobial agents also are used for more severe disease along with oral medications, in a multitherapy approach. Topical clindamycin has demonstrated in vitro bactericidal activity against *P. acnes*, and also has numerous anti-inflammatory properties. Clindamycin should not be used as monotherapy in acne as antibiotic resistance occurs rapidly; instead, it should be combined with BP. In a meta-analysis of 23 studies that included more than 7,000 patients with mild-to-moderate acne, Seidler and Kimball[6] compared the efficacy of BP alone, clindamycin alone, BP with salicylic acid, and BP plus clindamycin. The combination of BP and clindamycin was superior to clindamycin alone but was only slightly better than BP alone, the authors reported. After 10 to 12 weeks, the efficacy of the BP/clindamycin combination was similar to that seen with 5% BP plus salicylic acid.

Topical Dapsone

Topical dapsone gel has been shown to be effective as monotherapy or in combination with a topical retinoid.[7,8] It is most effective in the treatment of inflammatory lesions. A post hoc analysis of the phase III data suggests that it is particularly effective in adult women with acne.[9] The mechanism of action is unknown, but it is believed to act as an anti-inflammatory agent by suppression of neutrophil activity.

Oral Antibiotics

The tetracycline class of antibiotics, particularly minocycline and doxycycline, are the most commonly prescribed antibiotics for patients with acne. Their use is recommended for patients with moderate to severe inflammatory acne in whom topical therapy is ineffective, or in patients with widespread disease. The mechanism of action of the tetracyclines in acne is believed to be twofold: suppression of proliferation of *P. acnes* and numerous anti-inflammatory actions.

Acne Severity	**Mild**		**Moderate**		**Severe**
	Comedonal	**Mixed and Papular/Pustular**	**Mixed and Papular/Pustular**	**Nodular*†**	**Nodular/ Conglobate**
1st Choice	Topical retinoid	Topical retinoid + topical antimicrobial	Oral antibiotic + topical retinoid ± BP	Oral antibiotic + topical retinoid + BP	Oral isotretinoin
Alternatives‡	Alt. topical retinoid or dapsone or salicylic acid	Alt. topical retinoid antimicrobial agent + alt. topical retinoid or dapsone	Alt. oral antibiotic + alt. topical retinoid ± BP	Oral isotretinoin or alt. oral antibiotic + alt. topical retinoid ± BP/Dapsone	High dose oral antibiotic + topical retinoid + BP
Alternatives for Females‡§	See 1st choice	See 1st choice	Oral antiandrogen† + topical retinoid/ dapsone ± topical antimicrobial	Oral antiandrogen† + topical retinoid + oral antibiotic ± topical antimicrobial	High dose oral antiandrogen† + topical retinoid + alt. topical antimicrobal
Maintenance Therapy	Topical retinoid		Topical retinoid ±BP		

*With small nodules (<0.5 cm). †Second course in case of relapse. ‡Consider physical removal of comedones. §For pregnancy, options are limited.
Alt.=alternate; BP=benzoyl peroxide.

FIGURE 1 Global Alliance Treatment Algorithm.

Source: Adapted from Gollnick H, et al.[1]

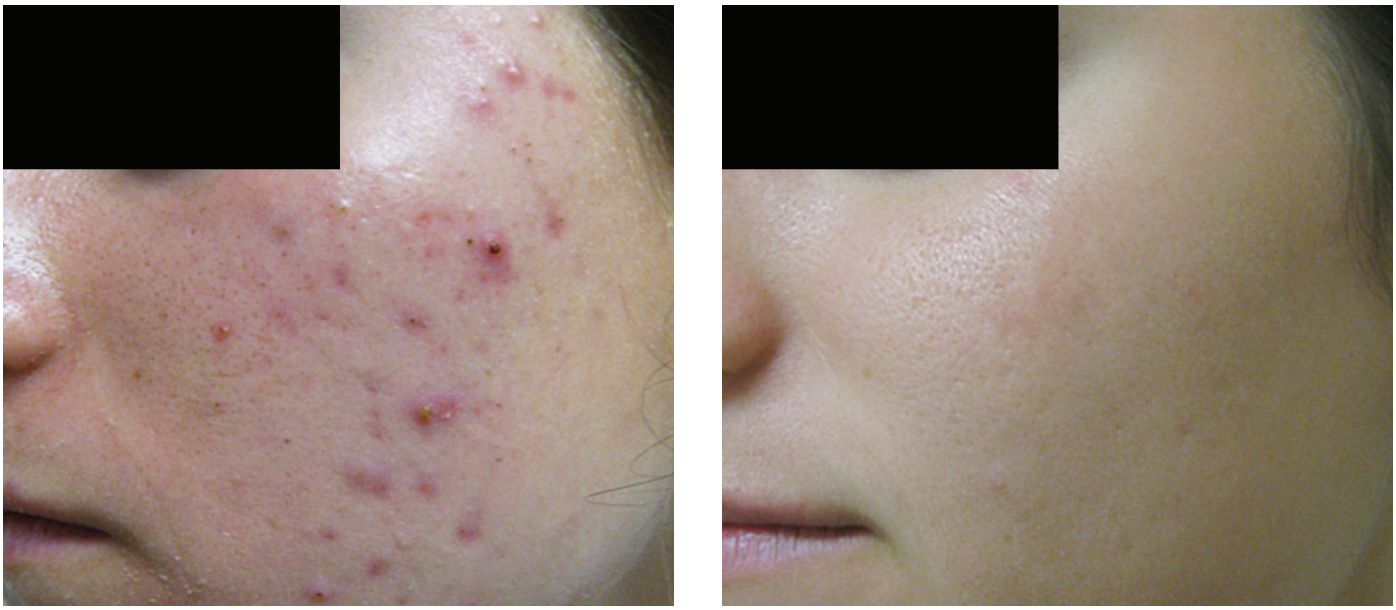

FIGURE 2 Moderate Acne.
This patient had mixed noninflammatory and inflammatory acne that was refractory to a topical retinoid plus benzoyl peroxide (left). Doxycycline was added to the regimen for 3 months, resulting in clearance of lesions (right).
Source: Photos courtesy of Hilary E. Baldwin, MD.

Because of concerns about bacterial antibiotic resistance, oral antibiotics should be used only after careful consideration, discontinued as soon as possible, and used as part of a combination regimen that also includes a topical retinoid and BP. Antibiotic resistance is a pressing international health care concern and is discussed in more detail in the next section.

Hormonal Therapy

For female patients with moderate to severe inflammatory acne, treatment with oral contraceptives (OCs) or spironolactone can be used as monotherapy or as part of a multitherapy approach. Often these agents are chosen as alternatives to or are used in combination with antibiotics or isotretinoin.

Oral Contraceptives

Oral contraceptives work by blocking the production of androgens by the ovaries and adrenal glands and also by increasing sex hormone binding globulin, which further reduces free circulating testosterone. This, in turn, reduces sebum production. Four OC formulations currently are approved by the FDA for the treatment of acne: norethindrone acetate/ethinyl estradiol, norgestimate/ethinyl estradiol, drospirenone/ethinyl estradiol, and drospirenone/ethinyl estradiol/folate. Other third- and fourth-generation OCs probably are also effective, although formal studies are lacking and they have not received FDA approval for use in acne.

Spironolactone

Spironolactone, an aldosterone antagonist, blocks androgen receptors and inhibits 5α-reductase (an enzyme involved in processing androgens), resulting in reduced sebum production. Although not FDA-approved for the treatment of acne, spironolactone has been available for more than 50 years and has been used for more than 20 years to treat women with acne. Spironolactone may be particularly useful in so-called hormonal-pattern acne (characterized by a preponderance of painful inflammatory papular lesions typically located on the lower face and front and sides of the neck), and in women who cannot or choose not to use isotretinoin.[10] As with all antiandrogen medications, it is possible that spironolactone could have feminizing effects on a developing male fetus, so it is prudent to consider concomitant contraception use.

Isotretinoin

Since its introduction in the United States in 1982, oral isotretinoin has been the most effective acne treatment available. Additionally, it is the only pharmacologic therapy with the ability to produce acne remission. Due to its side effect profile and teratogenic potential, isotretinoin is FDA-approved for severe acne that is unresponsive to conventional therapy. In clinical practice, its use is often broadened to include patients who have physical or psychological scarring, which warrants a more aggressive treatment plan.

Isotretinoin's efficacy is attributed to its four-pronged mechanism of action, targeting all of the recognized factors in acne pathogenesis. Layton[11] reviewed the evidence on isotretinoin's mechanism of action and noted that it markedly and rapidly reduces sebum secretion and affects cell-cycle progression, cell differentiation, cell survival, and apoptosis in sebocytes. Isotretinoin also produces a decrease in the induction of proinflammatory cytokines, reducing inflammation. Finally, isotretinoin inhibits comedogenesis by fostering keratinocyte differentiation and normalizing the process of desquamation.

Laser and Light Therapy

Although this article is intended to discuss pharmacologic therapy, it is nonetheless important to recognize that laser and light modalities may be effective in moderate to severe acne. The mechanism of action is thought to be reduction in *P. acnes* and/or sebum excretion.

Rational Use of Topical Antimicrobials and Oral Antibiotics

Dermatologists comprise less than 1% of the population of healthcare providers in the United States but, according to unpublished prescription monitoring data from the pharmaceutical industry, are responsible for writing about 5% of prescriptions for antibiotics. Most of these are in the tetracycline class. The use of oral antibiotics has been associated with the development of resistance in normal flora at all body sites, whereas the resistance that develops from exposure to topical antibiotics generally is limited to the site of application.[8] The rational position is moderation: avoid overuse, but do not hesitate to use topical or oral antibiotic agents to achieve disease control in appropriately selected patients.

To avoid contributing to antibiotic overuse and the development of resistant microbes, clinicians should follow the strategies recommended by the Global Alliance and the AARS. Among these recommendations is limiting the duration of either topical or oral antimicrobial therapy to as short a treatment phase as possible, followed by a maintenance regimen of nonantibiotic topical treatment. The feasibility of this practice was demonstrated in three papers, in which topical retinoid or retinoid and BP therapy was used along with oral antibiotic treatment for the acute phase (3-4 months). After this time, the oral antibiotic was discontinued and either a topical retinoid alone or a topical retinoid plus BP was used as maintenance. In the vast majority of patients—75%—disease control was maintained (or even continued to improve) for the duration of the 3- to 6-month study period, without further antibiotic use.[12-14]

Conclusion

Most patients have mild-to-moderate acne that can be effectively treated with topical retinoids and antimicrobials. Patients with more significant disease may need a course of therapy with oral antibiotics, which should be administered with BP and a topical retinoid. Hormonal therapy is a valid option in women. Most patients will require long-term management, including a maintenance regimen of topical therapy (retinoids, with or without BP). For severe acne, isotretinoin is the most effective agent available, resulting in resolution of lesions that is often permanent.

References

1. Gollnick H, Cunliffe W, Berson D et al. Management of acne: A report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2003;49 (suppl 1):S1-S37.
2. Thiboutot D, Gollnick H, Bettoli, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. *J Am Acad Dermatol*. 2009;60(suppl 5):S1-S50.
3. Eichenfield LF, Krakowski AC, Piggott C, et al; American Acne and Rosacea Society. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131(suppl 3):S163-S186.
4. Cunliffe WJ, Holland KT, Bojar R, Levy SF. A randomized, double-blind comparison of a clindamycin phosphate/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. *Clin Ther*. 2002;24:1117-1133.
5. Leyden JJ, Wortzman M, Baldwin EK. Antibiotic-resistant *Propionibacterium acnes* suppressed by a benzoyl peroxide cleanser 6%. *Cutis*. 2008;82:417-421.
6. Seidler EM, Kimball AB. Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne. *J Am Acad Dermatol*. 2010;63:52-62.
7. Draelos ZD, Carter E, Maloney JM, et al; United States/Canada Dapsone Gel Study Group. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *J Am Acad Dermatol*. 2007;56:439.e1-10.
8. Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: Focus on antibiotic resistance. *Cutis*. 2007;79(suppl 6):9-25.
9. Tanghetti E, Harper JC, Oefelein MG. The efficacy and tolerability of dapsone 5% gel in female vs male patients with facial acne vulgaris: Gender as a clinically relevant outcome variable. *J Drugs Dermatol*. 2012;11:1417-1421.
10. Kim GK, Del Rosso JQ. Oral spironolactone in post-teenage female patients with acne vulgaris: Practical considerations for the clinician based on current data and clinical experience. *J Clin Aesthet Dermatol*. 2012;5:37-50.
11. Layton A. The use of isotretinoin in acne. *Dermato-Endocrinol*. 2009;1(3):162-169.
12. Leyden J, Thiboutot DM, Shalita AR, et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: A multicenter, double-blind, randomized, parallel-group study. *Arch Dermatol.* 2006;142:605-612.
13. Thiboutot DM, Shalita AR, Yamauchi PS, et al. Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: A randomized, controlled, investigator-blind follow-up of a recent combination study. *Arch Dermatol*. 2006;142:597-602.
14. Gold LS, Cruz A, Eichenfield L, et al. Effective and safe combination therapy for severe acne vulgaris: A randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. *Cutis*. 2010;85:94-104.

Isotretinoin: Mechanism of Action and Patient Selection

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Abstract

Oral isotretinoin is a highly effective treatment for appropriately selected patients with acne. This medication is the only treatment that targets all four of the identified factors underlying acne pathogenesis. In addition to the approved indication of resistant nodular scarring acne, clinical studies and experience have shown that other categories of patients benefit from isotretinoin therapy, including those with resistant scarring papular acne, those with resistant acne that interferes with normal living, those who have severe acne-related psychological sequelae, and those with acne who have a skin picking habit or compulsion.

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Keywords

Acne; isotretinoin; topical retinoids; treatment barriers

An estimated 40 to 50 million Americans have acne vulgaris.[1] The pathogenesis of acne vulgaris is multifactorial, attributed to the interaction of four main factors: comedogenesis associated with obstruction of sebaceous follicles, production of sebum associated with androgenic stimulation of the sebaceous glands, proliferation of *Propionibacterium acnes*, and inflammation related—directly or indirectly—to *P. acnes* proliferation. Isotretinoin, which is the most effective therapy for severe acne, has been shown to affect all four of these factors.

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Mechanism of Action

The mechanisms of action of isotretinoin are fourfold: decreased comedogenesis, sebum suppression, suppression of *P. acnes* proliferation, and reduction of inflammation.

Decreased Comedogenesis

In early studies on isotretinoin's mechanism of action, it was demonstrated that isotretinoin use resulted in reduced follicular hyperkeratinization and decreased comedogenesis. In seeking to explain this effect, Melnik and colleagues[2] studied epidermal lipid composition in early, noninflamed comedones from patients using isotretinoin. These investigators found that, after 6 weeks of isotretinoin therapy, the glyceride fraction in the comedones had decreased by 36%, a significant change ($P<0.01$), and the levels of free sterols and total ceramides had increased by 34% ($P<0.10$). These changes in comedonal lipid composition began to approach the pattern of epidermal lipids found in normally desquamating stratum corneum cells, possibly explaining isotretinoin's beneficial effect on comedogenesis. Other early studies supported this hypothesis of comedogenesis, demonstrating that abnormal alterations in sebaceous lipids—arising from several possible mechanisms—seem to cause increased adherence in follicular cells.[3,4] Alternatively, anti-inflammatory effects of isotretinoin also could modulate comedo formation. Further studies are needed.

Sebum Suppression

The production of serum, regulated by androgens, has long been associated with the development of acne, and the rate of sebum production has been linked, to a degree, with acne severity. Nevertheless, sebum production itself is a recognized contributing factor in acne, and suppression of sebum production clearly is related to improvement in the disease.

Research to identify the mechanism that underlies isotretinoin's effects on sebum production has been ongoing for more than 3 decades. The more recently published work demonstrated that the most likely explanation is that isotretinoin has direct effects on sebocytic cell-cycle progression, cell differentiation, cell survival, and apoptosis.[5,6] Nelson and colleagues[5] demonstrated the possible role of the tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) gene. Clinically, isotretinoin use has been shown to markedly and rapidly reduce sebum secretion—in one study, sebum secretion was reduced by 90% within 6 weeks of treatment at dosages of 0.5 to 1.0 mg/kg/day.[6]

Suppression of *P. acnes* Proliferation and Inflammation

The role of *P. acnes* in the development of acne lesions was the first mechanism proposed to explain acne pathogenesis, which was initially believed to be an infectious, bacterial disease process. Research has demonstrated that acne vulgaris is a multifactorial disease, and that *P. acnes* proliferation is one of those factors.

It has been established that *P. acnes* proliferation in the microcomedo environment of sebum and corneocytes induces proinflammatory mediators by activating various facets of the innate immune system.[7] More recent work has enhanced the

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understanding of the inflammatory process; it is increasingly clear that the innate immune system is involved by means of activation of toll-like receptor 2 (TLR2)[8] and the inflammasome.[9,10] Dispenza and colleagues[11] showed that isotretinoin normalizes exaggerated TLR-2-mediated innate immune responses in patients with acne by significantly decreasing TLR-2 responses in monocytes and suppresses inflammatory cytokine responses to *P. acnes*.

Patient Selection for Isotretinoin Use

The approved labeling for isotretinoin states that this medication is indicated for patients with "resistant scarring nodular acne." However, limiting the use of isotretinoin to patients who fit this narrow category fails to appreciate the value of isotretinoin treatment for several other categories of patients with acne who, as clinical experience demonstrates, benefit greatly from its use (**Figure**).

Recognizing this, the American Academy of Dermatology[12] issued a position paper on isotretinoin (first issued in 2000, and amended in 2003, 2004, and 2010), which reiterated the effectiveness of isotretinoin in reducing acne and scarring in patients with "severe recalcitrant nodular acne"—the US Food and Drug Administration (FDA)-approved indication—but also acknowledged the existence of sufficient evidence to support the use of this agent in "severe forms of acne," including acne that is refractory to other treatment. In addition, the definition of "severe" is expanded to include "the impact of the disease on the patient, both physical and psychological."

Clinicians routinely prescribe isotretinoin for patients with resistant scarring papular acne, resistant acne that interferes with the ability to function normally (at home, socially, or in the workplace), and acne that results in severe psychological sequelae, as well as for patients who habitually—perhaps compulsively—pick at acne lesions.

Isotretinoin Re-treatment

Clinicians should be aware—and should advise patients (and, if appropriate, their parents)—that although isotretinoin treatment results in long-term clearance with one course of therapy in the majority of individuals (approximately two-thirds), some patients will experience clearance of lesions and later have a recurrence of acne (in most cases, a much milder presentation consisting of comedonal or mixed comedonal and inflammatory papular/pustular lesions). However, a small subset of patients may need one or more additional courses of treatment with isotretinoin for optimal clearance of lesions. Patients in the following categories seem to be most likely to require re-treatment:

- Patients younger than 16 years who may have inherently more severe disease[13]
- Women with hormonal imbalances
- Patients who take non-Lidose isotretinoin without a fatty meal
- Patients with concomitant use of competing medications
- "Hormonal athletes"—that is, patients with hyperandrogenism from using performance-enhancing substances such as anabolic steroids or supplements containing androgens.

With respect to the last category, many dietary supplements contain androgenic compounds. A discussion of this topic is instructive and is available on the FDA website, at http://www.fda.gov/newsevents/testimony/ucm184497.htm.

Barriers to Isotretinoin Treatment

Patients who are appropriate candidates for isotretinoin may not receive it for one or more reasons.

In some cases, parents refuse to consent to isotretinoin therapy, often because of news reports or information from other sources that have promoted inaccuracies about the "dangers" of this medication. Some patients themselves—adolescents as well as adults—say they are reluctant to use isotretinoin, often for the same reasons. Foremost among these is the perception that isotretinoin causes depression and suicide, with a causal relationship also alleged between isotretinoin and inflammatory bowel disease (IBD).

It has long been established that isotretinoin is teratogenic, and any risk for fetal exposure is unacceptable. The risk management program mandated by the FDA, iPLEDGE, was established

Clarifying the Retinoid Drug Classes

Although it is clear that adapalene, tazarotene, and tretinoin are topical retinoids and that isotretinoin is an oral retinoid, the mere distinction as topical or oral is not sufficient to prevent the confusion that has arisen among patients, insurance carriers, and even some clinicians. In addition to route of administration, topical agents differ from isotretinoin in mechanism of action and indication in the population of patients with acne, and topical retinoids are not interchangeable options when isotretinoin is indicated.

Topical retinoids normalize keratinization, promote comedolysis, and have anti-inflammatory activity. This group of agents represents the drugs of first choice for acute therapy in the following presentations:

- mild comedonal acne, as monotherapy
- mild-to-moderate mixed comedonal and inflammatory and papular/pustular acne, in combination with an oral antibiotic, and with or without the addition of benzoyl peroxide
- moderate to moderately severe acne with small (<0.5 cm) nodules present, with an oral antibiotic plus benzoyl peroxide.

Topical retinoids also are preferred as maintenance therapy for patients with mild-to-moderate acne, and also—with or without the addition of benzoyl peroxide—for maintenance in those with moderate to severe acne.

In contrast, oral isotretinoin works by targeting all four of the factors recognized in acne pathogenesis. In addition to normalizing desquamation and reducing the inflammatory response—the two mechanisms it shares with the topical retinoids—isotretinoin inhibits the growth of *P. acnes* and works directly on sebocytes, reducing sebum secretion by affecting cell-cycle progression, differentiation, and survival, and inducing sebocyte apoptosis. This latter property is perhaps the most important—and defining—difference: isotretinoin is a sebocyte-modulating, sebum-suppressing retinoid, whereas the topical agents have no effect on sebum or sebocytes.

Clinicians can assist in promoting an understanding of how these medications work, how they are used, and whom they help.

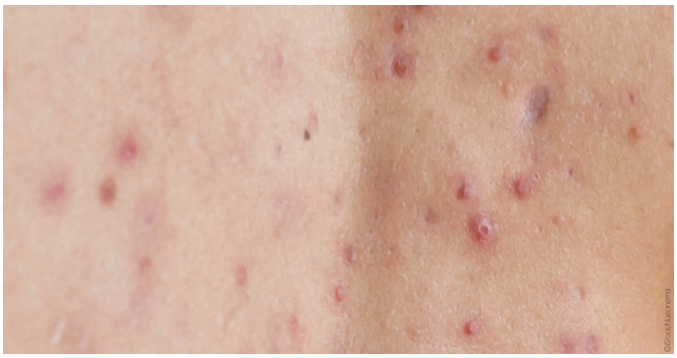

FIGURE Hypertrophic Scars on Back and Shoulder. Isotretinoin is approved for "resistant scarring nodular acne," and such treatment might have prevented the hypertrophic scarring on this patient's back and shoulders. However, patients in other categories can benefit greatly from isotretinoin: those with resistant scarring papular acne, resistant acne that interferes with the ability to function normally, acne that results in severe psychological sequelae, and in patients who pick at acne lesions.

to minimize the risk that patients of childbearing potential would become pregnant during therapy with isotretinoin. For some clinicians and patients, the requirements of the iPLEDGE program represent a barrier to isotretinoin prescription and use.

Most clinicians—dermatologists, in particular—are aware that the proposed associations between isotretinoin and either depression/anxiety or IBD lack scientific support. Indeed, Etminan and colleagues[14] performed a nested case-control study and a meta-analysis of both published an unpublished data exploring this relationship and concluded that isotretinoin use did not pose an increased risk for IBD, including Crohn's disease and ulcerative colitis. With respect to the potential psychiatric effects of isotretinoin, the phase III trial of the safety and efficacy of isotretinoin-Lidose included a careful study of psychiatric parameters.[15] No increase in depression was seen either in patients who took isotretinoin-Lidose formulation or in those who used non-Lidose isotretinoin. Of course, it is possible that a very small subset of patients might have a psychiatric reaction to the drug, but studies have not yet identified such individuals.

Moreover, the American Academy of Dermatology's position statement on isotretinoin noted that a causal relationship between isotretinoin and depression/anxiety symptoms has not been established, but that evidence does demonstrate improvements in psychiatric disturbances and quality of life in patients with acne who are treated with isotretinoin.[12]

Dermatologists recognize the urgency of providing this effective medication to patients whose condition warrants it, as well as the consequences to these patients who are treated less optimally. Despite this, many clinicians in the United States do not prescribe isotretinoin. Nagler and Orlow[16] recently published the results of a questionnaire-based study undertaken to explore dermatologists' opinions about isotretinoin controversies and about their patient counseling and prescribing practices. These investigators emailed a 25-question survey to 7,013 dermatologists, and collected anonymous responses from 591 board-certified physicians. Thirty-seven percent of the respondents said they believe that isotretinoin may cause psychiatric disturbances, and 2.7% believe it may cause IBD.

In the experience of the authors, some health insurance carriers present another barrier to isotretinoin therapy. Some patients have been advised that a topical retinoid would be covered rather than the oral retinoid (isotretinoin), with the implication that these agents are the same drug but formulated for different routes of administration. However, sharing the classification of "retinoid" in no way signifies that topical retinoids and oral isotretinoin are the same. Isotretinoin does share two mechanisms of action with topical retinoids (that is, normalizing desquamation and reducing the inflammatory response), but isotretinoin has an important—and defining—property in that it is a sebocyte-modulating, sebum-suppressing retinoid. The topical agents have no effect on sebum or sebocytes. (See also "Clarifying the Retinoid Drug Class" on page 87.)

Conclusion

Patients with severe acne represent a dermatologic urgency: to prevent scarring and long-term psychosocial sequelae and improve patients' current quality of life, severe acne should be treated using the most effective modality available. Isotretinoin has a 30+-year track record of efficacy and should be considered in appropriately selected patients and prescribed in compliance with iPLEDGE, the FDA-mandated risk management program.

References

1. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases, 2004: A joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55:490-500.
2. Melnik B, Kinner T, Plewig. Influence of oral isotretinoin treatment on the composition of comedonal lipids: Implications for comedogenesis in acne vulgaris. *Arch Dermatol Res*. 1988;280:97-102.
3. Kligman AM, Katz AC. Pathogenesis of acne vulgaris. *Arch Dermatol*. 1968;98:53-57.
4. Motoyoshi K. Enhanced comedo formation in rabbit ear skin by squalene and oleic acid peroxides. *Br J Dermatol*. 1983;109:191-198.
5. Nelson AM, Gilliland KL, Cong Z, Thiboutot DM. 13-cis Retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. *J Invest Dermatol*. 2006;126:2178-2189.
6. Layton A. The use of isotretinoin in acne. *Dermato-Endocrinol*. 2009;1:162-169.
7. Webster GF. Inflammation in acne vulgaris. *J Am Acad Dermatol*. 1995;33(2 pt 1): 247-253.
8. Kim J, Ochoa MT, Krutzik SR, et al. Activation of roll-like receptor 2 in acne triggers inflammatory cytokine responses. *J Immunol*. 2002;169:1535-1541.
9. Kistowska M, Gehrke S, Jancovic D, et al. IL-1 beta drives inflammatory responses to *Propionibacterium acnes* in vitro and in vivo. *J Invest Dermatol*. 2014;134:677-685.
10. Contassot E, French LE. New insights into acne pathogenesis: *Propionibacterium acnes* activates the inflammasome. *J Invest Dermatol*. 2014;134:310-313.
11. Dispenza MC, Wolpert EB, Gilliland KL, et al. Systemic isotretinoin therapy normalizes exaggerated TLR-2-mediacted innate immune responses in acne patients. *J Invest Dermatol*. 2012;132:2198-2205.
12. American Academy of Dermatology. *Position Statement On Isotretinoin* (Approved by the Board of Directors December 9, 2000; Amended by the Board of Directors March 25, 2003, March 11, 2004 and November 13, 2010). Available at https://www.aad.org/Forms/Policies/Uploads/PS/PS-Isotretinoin.pdf. Accessed June 5, 2015.
13. Leyden JJ, Del Rosso JQ, Baum EW. The use of isotretinoin in the treatment of acne vulgaris: Clinical considerations and future directions. *J Clin Aesthetic Dermatol*. 2014;7(suppl):S3-S21.
14. Etminan M, Bird ST, Delaney JA, Bressler B, Brophy JM. Isotretinoin and risk for inflammatory bowel disease: A nested case-control study and meta-analysis of published and unpublished data. *JAMA Dermatol*. 2013;149:216-220.
15. Webster GF, Leyden JJ, Gross JA. Results of a phase III, double-blind, randomized, parallel-group, noninferiority study evaluating the safety and efficacy of isotretinoin-Lidose in patients with severe recalcitrant nodular acne. *J Drugs Dermatol*. 2014;13:665-670.
16. Nagler AR, Orlow SJ. Dermatologists' attitudes, prescription, and counseling patterns for isotretinoin: A questionnaire-based study. *J Drugs Dermatol*. 2015;14:184-189.

Understanding and Reducing the Risk for Acne Scarring

James J. Leyden, MD,* Guy F. Webster, MD, PhD,† Andrea L. Zaenglein, MD,‡ and Hilary E. Baldwin, MD§

Abstract

Scarring is a lifelong, physically disfiguring and often emotionally debilitating sequela resulting from acne vulgaris. Nearly 80% of patients have some scarring and 50% have clinically relevant scarring. Although the extent duration and intensity of inflammation are important risk factors, scarring also can develop in patients with relatively mild inflammation. Assessment of scarring should be part of the evaluation in all patients with acne and should be a consideration in determining treatment.

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Keywords

Acne vulgaris; isotretinoin; scarring

Despite the profound effect that acne-associated scarring can have on patients, little attention has been devoted to the study of its pathophysiology. Most of the literature on scarring describes treatment modalities for mitigating acne scars once they have occurred. Nevertheless, prevention of scarring is a stated goal of acne therapy. To achieve this goal, more information is needed on which patients are prone to scarring, what nuances in pathophysiology account for this sequela of inflammation, and what treatments best counteract the scarring process.

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Incidence and Sites of Acne Scarring Predilection

Few studies have been published that provide insight into the occurrence and incidence of scarring. In an article focusing on the treatment options for post-acne scars, Goodman[1] reported a post-acne scar frequency of 11% in men and 14% in women, but in a survey of adult women in France, 49% of those who had a history of acne said they had acne scarring.[2] In a classic paper on the incidence and evaluation of acne scarring, Layton and colleagues[3] reported that 95% of the 185 patients in their study had some degree of facial scarring. In men, scarring on the back also was seen in almost 80% and chest scars were seen in about 70%; in contrast, less than 40% of women had truncal scarring.

In their study of 973 patients with a history of acne, Tan and colleagues[4] observed facial scarring in 87% of patients; scarring of the back was seen in 51% of patients, and 38% had scarring on the chest.

Certain anatomic areas have been identified as being more prone to scarring than other sites. The temples are prone to atrophic scars (having a "punched out" appearance), whereas the cheeks are prone to smaller, so-called icepick scars and larger "rolling" scars. Hypertrophic scars primarily occur on the lower mandible, shoulders, and trunk (**Figure 1**).

Types and Severity of Acne Scars

Two types of scarring are described in the literature: atrophic scars, caused by a loss of tissue, and hypertrophic and keloid scars, caused by an increase in tissue formation.

Atrophic scarring is more common, and, as noted above, has a propensity to occur in certain areas of the skin, particularly the temple. A classification system for atrophic scars proposed by Jacob and colleagues[5] has been widely discussed. In this system, three types of scars are described: *icepick*, which are narrow, punctiform, deep scars (0.5 to 1.5 mm), which are wider at the surface, suggesting a V shape; *rolling* scars, measuring at least 4 to 5 mm in width and characterized by an M-shaped, undulating appearance that results from subdermal, fibrotic tethering; and *boxcar* scars, which are round or oval with well-defined, vertical edges, suggesting a U shape (**Figure 2**). Although these designations are somewhat useful, identification of these types by visual inspection is a highly subjective exercise, and identification of scars using these descriptors is highly variable, even among experts.[6] For this reason, the Global Alliance to Improve Outcomes in Acne Group has determined that a new classification system is needed.[6]

Hypertrophic and keloid scars both result from excess deposition of collagen in response to inflammation and are seen most commonly in truncal areas. These scars differ in appearance and histology. Hypertrophic scars usually are pink in color and firm to the touch, and are limited to the borders of the original wound. In contrast, keloids appear as reddish-purple papular and nodular scars that typically extend beyond the borders of the original acne lesion.[7]

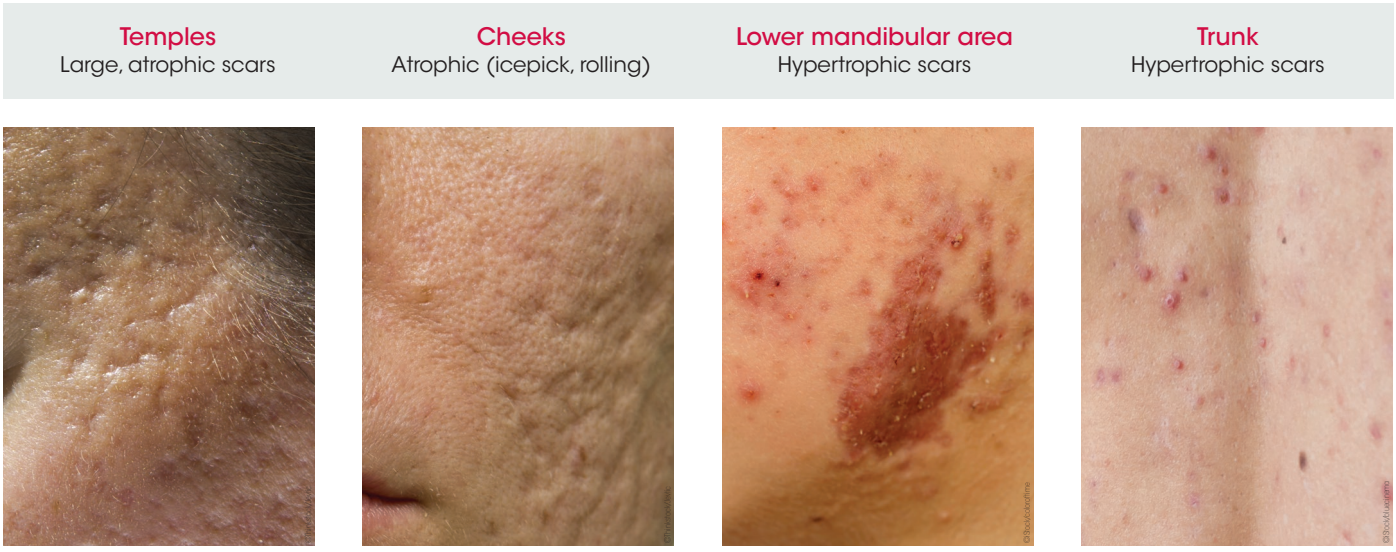

FIGURE 1 Moderate Acne. Risk Areas for Different Types of Scars.
Clinical observation has shown that certain types of scars are more likely to occur in specific anatomic areas, as shown.

Several groups have proposed grading scales for describing the severity of acne scars. Dreno and colleagues,[8] Goodman and Baron,[9] and Tan et al[4] have all developed validated scales for quantifying severity. In developing their Scale for Acne Scar Severity (SCAR-S), Tan et al[4] determined that scarring was mild in 63% of patients, moderate in 20%, and severe in 5%, and noted that scarring was frequent even in those who had mild-to-moderate acne. Layton and colleagues[3] concluded that both superficial inflamed papular acne lesions and nodular lesions could produce scars. Kang and colleagues[10] observed scars from closed comedones, inflammatory lesions, and in normal-appearing skin areas in patients with acne.

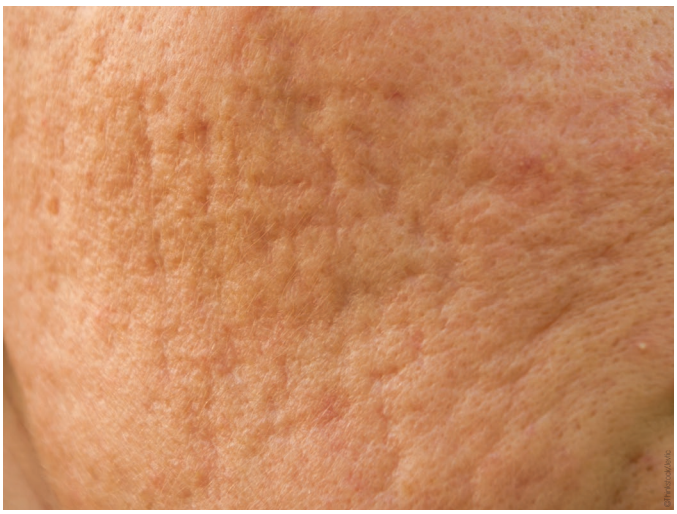

FIGURE 2 Mixed Atrophic Scars. It is common for patients to have multiple shapes and sizes of scars. In this patient photo, three types of atrophic scars can be seen: rolling U-shaped scarring in the temple area, boxcar scarring (resembling chickenpox) in the upper malar region, and narrow, deep "icepick" scarring on the mid-malar area.

Pathophysiology of Scarring

Acne scars arise as a result of imperfections in wound healing mechanisms seen in other skin injuries, progressing through the stages of inflammation, the formation of granulation tissue, and matrix remodeling.

In atrophic acne scarring, Kang et al[10] noted that the process of remodeling involves the activation of activator protein 1 (AP-1), which induces several matrix metalloproteinases (MMPs)—MMP-1, MMP-3, and MMP-9—and recruits neutrophils, which produce MMP-8. This results in imperfect wound healing responses, leaving clinically evident deficits in the organization or composition—or both—of the extracellular matrix. These findings are helpful in understanding the development of atrophic scars but they do not explain why some patients and certain areas of skin are prone to scarring. In the case of hypertrophic scarring, the mechanisms that account for the excessive production of collagen and fibrosis remain unknown.

Risk Factors for Scarring

In general, scarring is most likely to occur when acne is severe—that is, in the presence of large lesions and severe inflammation, but it is also clear that significant scarring can occur without severe inflammation. The reasons for this are unknown; familial or genetic factors may be involved, but this has not been established, and at this time it is not possible to determine an individual patient's risk for developing acne scars. Patients who have already developed scarring and still have active disease are at high risk for additional scarring.

Conclusion

Two risk factors have been identified that increase the risk for scarring regardless of other individual patient characteristics—the extent of inflammation and duration from onset of inflammation to effective anti-inflammatory response. In addition, frequent relapses have been associated with an increased risk for scarring. Thus, earlier, adequate therapy is crucial to reducing the risk for scarring.

References

1. Goodman GJ. Management of post-acne scarring: What are the options for treatment? *Am J Clin Dermatol*. 2000;1:3-17.
2. Poli F, Dreno B, Vershoore M. An epidemiological study of acne in female adults: Results of a survey conducted in France. *J Eur Acad Dermatol Venereol*. 2001;15:541-545.
3. Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. *Clin Exp Dermatol*. 1994;19:303-308.
4. Tan JK, Tang J, Fung K, et al. Development and validation of a scale for acne scar severity (SCAR-S) of the face and trunk. *J Cutan Med Surg*. 2010;14:156-160.
5. Jacob CL, Dover JS, Kaminer MS. Acne scarring: A classification system and review of treatment options. *J Am Acad Dermatol*. 2001;45:109-117.
6. Finlay AY, Torres V, Kang S, et al. Classification of acne scars is difficult even for acne experts. *J Eur Acad Dermatol Venereol*. 2013;27:391-393.
7. Thiboutot D, Gollnick H, Bettoli, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group. *J Am Acad Dermatol*. 2009;60(suppl 5):S1-S50.
8. Dreno B, Khammari A, Orain N, et al. ECCA grading scale: An original validated acne scar grading scale for clinical practice in dermatology. *Dermatology*. 2007;214:46-51.
9. Goodman GJ, Baron JA. Postacne scarring—A quantitative global scarring grading system. *J Cosmet Dermatol*. 2006;5:48-52.
10. Kang S, Cho S, Chung JH, Hammerberg C, Fisher GJ, Voorhees JJ. Inflammation and extracellular matrix degradation mediated by activated transcription factors nuclear factor-kappa B and activator protein-1 in inflammatory acne lesions in vivo. *Am J Pathol*. 2005;166:1691-1699.
11. Goodman G, Baron J. The management of postacne scarring. *Dermatol Surg*. 2007;33:1175-1188.

Psychosocial Issues in Acne Management: Disease Burden, Treatment Adherence, and Patient Support

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Abstract

Physical and emotional scarring are equally important burdens of acne vulgaris in patients of any age. Effective therapeutic regimens are readily available, and the consistent and correct use of these medications results in effective disease management, reduced risk for scarring, as well as improvement in various factors that affect quality of life. Nevertheless, adherence to treatment recommendations generally is poor. Clinicians can help improve adherence with a variety of strategies, including counseling, education, and choosing treatment options that are most consistent with a patient's lifestyle.

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Keywords

Acne; adherence; disease burden

Acne vulgaris is a common dermatologic disease that once was trivialized as a virtually inevitable part of the maturation process during the teen years. Teenagers of decades past were expected to accept what could not be cured and endure acne as a rite of passage to adulthood. However, acne vulgaris now is recognized as an important medical condition that is associated with physical and emotional consequences, both acute and potentially lifelong—all of which may be mitigated or prevented with early and accurate diagnosis and prompt initiation of appropriate therapy. Several treatment options are widely available, safe, and—when prescribed appropriately and used by patients according to recommendations—highly effective.

Psychological and Psychosocial Burden of Acne

The burden of acne may be considerable regardless of the severity of disease. It has long been recognized that even mild disease may result in psychological disturbance, including severe embarrassment and low self-esteem—responses that can affect patients at any age.[1-4]

The impact of acne on patients' lives has been compared to the effects experienced by patients with other diseases generally recognized as serious and debilitating, including psoriasis, chronic asthma, epilepsy, diabetes, chronic back pain, and arthritis.[2,3,5,6]

Studies have demonstrated that many adults with acne have clinically relevant anxiety and/or depression,[6] and acne can adversely affect employment.[7] Social relationships are affected because of patients' appearance.[1] Moreover, quality of life has been shown to be affected more by an individual's subjective opinion about his or her disease severity than by the clinician's assessment.[3,8]

Promoting Treatment Adherence

It may be intuitive to believe that individuals who are burdened by disease symptoms would adhere to a prescribed regimen that was likely to improve those symptoms or that had—in a patient's own experience—already resulted in improvement of symptoms. However, in two surveys, the reported compliance was 56% (among 396 patients)[9] and 64.7% ± 24% (among 687 patients).[10] Furthermore, as the Global Alliance to Improve Outcomes in Acne Group's review of the adherence literature showed, studies over a period of almost 30 years have demonstrated that adherence with prescribed acne regimens generally is poor, with many patients either not using medications as directed or missing appointments, or both.[11] Interestingly, some evidence suggests that patients may perceive their adherence to be high: In a telephone survey in France, 70% of 1,566 adolescent participants reported that they closely followed the regimen their clinicians prescribed.[4] The investigators suggested a disconnect between patients' and clinicians' definitions of adherence.

Examination of the medical literature on adherence to any treatment regimen—particularly when the nature of the disease requires long-term therapy—reveals that this is a complex topic that involves multiple factors, including demographics, lifestyle, psychological/psychiatric issues, and environment.[12] However, several recommendations can be made that can help improve the consistent and correct use of medication.

Establish a therapeutic partnership.

The perception of positive mutual regard is a strong motivator for adherence in a therapeutic relationship.[13-15] Adherence is enhanced further when patients are involved in the formulation

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of and agree to a treatment plan.[16] Teenagers, in particular, respond to the feeling of empowerment derived from the sense of having some control over their disease.[17] One way to include the patient in developing a treatment plan is to offer choices of medication route of administration or type of vehicle (ointment, cream, lotion, gel, or foam) whenever possible.

In addition, it is helpful for the clinician to ask about a patient's existing daily routine, and to discuss how an acne treatment regimen can be incorporated into those activities. Finally—and not surprisingly—it has been shown that simplicity of a regimen correlates positively with improved adherence.[18,19]

Make certain the patient understands the disease.
Much of what many patients believe about acne is inaccurate, including the perception that patients with acne cause or contribute to their disease because of poor hygiene, unwise dietary choices, and the use of cosmetics.[20] Clinicians should provide accurate information about the known causes of acne, explaining in easily understandable terms that the disease is caused by a combination of factors, including obstruction of sebaceous follicles, sebum production, proliferation of the bacterium *Propionibacterium acnes*, and inflammation. This information lays the foundation for discussing the therapeutic choices that are most appropriate for each patient.

Explain the choice of acne medication(s) in each patient's case.
Patients should understand how various medications work for each type of acne. The patient's specific presentation should be discussed, along with the recommendations—for example: "You have some inflamed as well noninflamed pimples, and the medication that usually works best for that is a combination of two topical medications, a retinoid and an antibiotic."

Thoroughly explain how to use the medications and provide these instructions in written form.[15,20]
Instructions should include when and how to apply topical agents—for example: "After cleansing your face and gently patting dry, apply the medication to the entire affected areas, not just the visible pimples." The timing and circumstances for taking oral medications should be specified in practical terms—for example: "Take this antibiotic every morning with breakfast." or "Take this antibiotic before breakfast."

Manage expectations.
Most patients with acne who are seeing a clinician for the first time usually have tried over-the-counter products prior to seeking medical attention. Therefore, at the time of the clinical encounter, it is common for most patients to feel an urgency and impatience about starting therapy that will clear their acne—preferably quickly. Some studies suggest that most patients expect to see significant improvement in 4 to 6 weeks.[21,22] Clinicians should discuss realistic expectations as well as a time frame for treatment results.

Patients also should understand that keeping appointments for follow-up visits is important so that improvements can be assessed and, if necessary, modifications can be made in the regimen to improve the response. However, appointment-keeping behavior may not be an indicator of adherence. In one study of missed appointments by 144 consecutive patients with acne seen in a private dermatology office, McEvoy and colleagues[23] found that only 28% of patients attended all four follow-up appointments, 10% kept three appointments, 15% kept two appointments, 13% kept one appointment, and 19% did not follow up at all; 15% of patients stopped coming for one or two appointments, then returned, and were not counted among the other groups. These researchers theorized that some patients who did not keep appointments continued self-treating, and others may have failed to follow up because their acne cleared to a satisfactory degree and these patients determined that additional professional contact was not necessary.

In addition to expectations about benefits, all discussions should include information about possible medication-related adverse effects. Patients should understand that adverse effects can occur with any medication, and they should know what to do if side effects occur. In addition, clinicians should discuss any measures patients can take to avoid adverse effects; for example, patients using topical medications should be instructed in proper gentle cleansing techniques and advised to use a recommended moisturizer to help prevent medication-related drying and irritation.

Finally, patients should understand from the start that there are two phases of acne therapy: acute and long-term (maintenance). Once acne lesions are cleared, maintenance with a topical retinoid, with or without benzoyl peroxide, usually is needed to prevent relapse.

Patients Who Need Extra Support

Some studies have attempted to define which patients are most likely to comply with a treatment regimen and which factors may adversely affect adherence. The Global Alliance reviewed the literature on adherence and identified factors that were associated with good and poor medication adherence in patients with acne. Those patients who have lifestyle, demographic, or other factors that are inversely associated with compliance (**Table**) may benefit from the adherence-promoting interventions described in the previous section.

Conclusion

Patients with acne—regardless of the severity of the clinical presentation—often perceive their disease as a significant physical and emotional burden. Nevertheless, and despite the availability of effective treatments for acne, adherence with clinicians' management recommendations often is poor. Certain demographic, patient preference, and medication-related factors are associated with improved adherence; other factors correlate with poor medication adherence. Several strategies can be used to support patients with acne who demonstrate good adherence; special attention to these strategies may be helpful as intervention techniques in managing patients with poor adherence.

TABLE Factors Negatively Associated With Adherence

• Younger (vs older) age
• Being single (vs married)
• Male (vs female)
• Alcohol use
• Cigarette smoking
• Unemployment
• Out-of-pocket medication cost (adherence drops with increasing costs)
• Psychiatric morbidity (anxiety/depression)

Source: Adapted from Thiboutot D, et al.[11]

References

1. Krowchuk DP, Stancin T, Keskinen R, Walker R, Bass J, Anglin TM. The psychosocial effects of acne on adolescents. *Pediatr Dermatol*. 1991;140:672-676.
2. Lasek RJ, Chren MM. Acne vulgaris and the quality of life of adult dermatology patients. *Arch Dermatol*. 1998;134:454-458.
3. Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY. The quality of life in acne: A comparison with general medical conditions using generic questionnaires. *Br J Dermatol*. 1999;140:672-676.
4. Pawin H, Chivot M, Beylot C, et al. Living with acne: A study of adolescents' personal experiences. *Dermatology*. 2007;215:308-314.
5. Aktan S, Ozmen E, Sanli B. Anxiety, depression, and nature of acne vulgaris in adolescents. *Int J Dermatol*. 2000;39:354-357.
6. Kellett SC, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. *Br J Dermatol*. 1999;140:273-282.
7. Cunliffe WJ. Acne and unemployment. *Br J Dermatol*. 1986;115:386.
8. Yazici K, Baz K, Yazici AE, et al. Disease-specific quality of life is associated with anxiety and depression in patients with acne. *J Eur Acad Dermatol Venereol*. 2004;18:435-439.
9. Renzi C, Picardi A, Abeni D, et al. Association of dissatisfaction with care and psychiatric morbidity with poor compliance of treatment compliance. *Arch Dermatol*. 2002;138:337-342.
10. Zaghloul SS, Cunliffe WJ, Goodfield MJD. Objective assessment of compliance with treatments in acne. *Br J Dermatol*. 2005;152:1015-1021.
11. Thiboutot D, Gollnick H, Bettoli, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol*. 2009;60(suppl 5):S1-S50.
12. Baldwin HE. Tricks for improving compliance with acne therapy. *Dermatol Ther*. 2006;19:224-236.
13. Parchman ML, Burge SK. The patient-physician relationship, primary care attributes, and preventive services. *Fam Med*. 2004;36:22-27.
14. Ferguson WJ, Candib LM. Culture, language, and the doctor-patient relationship. *Fam Med*. 2002;34:353-361.
15. Draelos ZK. Patient compliance: Enhancing clinician abilities and strategies. *J Am Acad Dermatol*. 1995;32(5 pt 3):S42-S48.
16. Weil A, Ganato E. Dealing with treatment adherence issues in acute conditions. *Resident Staff Physician*. 2005;8:32.
17. Koo J. How do you foster medication adherence for better acne vulgaris management? *Skinmed*. 2003;2:229-233.
18. Yentzer BA, Ade RA, Fountain JM, et al. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: A randomized controlled trial. *Cutis*. 2010;86:103-108.
19. Snyder S, Crandell I, Davis SA, Feldman SR. Medical adherence to acne therapy: A systematic review. *Am J Clin Dermatol*. 2014;15:87-94.
20. Katsambas AD. Why and when the treatment of acne fails: What to do? *Dermatology*. 1998;196:158-161.
21. Rasmussen JE, Smith SB. Patient concepts and misconceptions about acne. *Arch Dermatol*. 1983;119:570-572.
22. Tan JK, Vasey K, Fung KY. Beliefs and perceptions of patients with acne. *J Am Acad Dermatol*. 2001;44:439-445.
23. McEvoy B, Nydegger R, Williams G. Factors related to patient compliance in the treatment of acne vulgaris. *Int J Dermatol*. 2003;42:274-280.

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MUST BE COMPLETED ONLINE.

Challenges in the Treatment of Acne in the United States Post-Test

Original Release Date: September 2015 • **Most Recent Review Date:** September 2015
Expiration Date: September 30, 2017 • **Estimated Time to Complete Activity:** 2.5 hours; 3.0 contact hours

To get instant CME credits online, go to **http://tinyurl.com/acne2015**. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. Please add cmepd@louisville.edu to your e-mail "safe" list. If you have any questions or difficulties, please contact the **University of Louisville School of Medicine Continuing Medical Education (CME & PD)** office at cmepd@louisville.edu.

POST-TEST CME/CE QUESTIONS

1. According to the Global Alliance to Improve Outcomes in Acne, the presence of small nodules (<0.5 cm) indicates a disease severity of:

A. Mild
B. Moderate
C. Severe
D. Very severe

2. Both normalization of keratinization/comedolysis and reduction of inflammation are primary mechanisms of action of:

A. Oral antibiotics
B. Oral contraceptives
C. Spironolactone
D. Topical retinoids

3. An example of the recommended first-choice combination topical medication regimen for mild comedonal and mixed inflammatory comedones with papular/pustular acne is:

A. Adapalene plus clindamycin
B. Benzoyl peroxide plus tretinoin
C. Tazarotene plus salicylic acid
D. Tazarotene plus tretinoin

4. Which of the following factors regulates sebum production?

A. Androgens
B. Estrogen in females, androgen in males
C. Pituitary gland
D. Testosterone

5. Proliferation of *Propionibacterium acnes*, one factor in the pathogenesis of acne, activates various facets of the innate immune system, by means of activation of _____.

A. Cachectin
B. Interleukin-17 and prostaglandin E_2
C. Toll-like receptor 2 and the inflammasome
D. Tumor necrosis factor

6. The mechanisms of action of _____ are decreased comedogenesis, sebum suppression, suppression of *Propionibacterium acnes* proliferation, and reduction of inflammation.

A. Adapalene
B. Isotretinoin
C. Spironolactone
D. Tazarotene

7. On which of the following areas of the face are hypertrophic scars most likely to occur?

A. Cheeks
B. Forehead
C. Lower mandible
D. Temples

8. Scarring can occur in which of the following circumstances?

A. Inflammatory acne, even if not severe
B. Severe inflammatory acne
C. Severe, nodular acne
D. Severe acne with or without nodules

9. Of the following factors, quality of life in adult patients with acne has been shown to be most affected by:

A. A clinician's assessment of the extent of disease
B. A patient's subjective opinion about his or her disease severity
C. Severity of the disease according to lesion counts
D. Sites affected—facial versus trunk

10. To help promote adherence with a treatment regimen, clinicians should guide patients' expectations. Some studies suggest that most patients expect to see significant improvement in:

A. 1 week
B. 2-4 weeks
C. 4-6 weeks
D. 3 months

Challenges in the Treatment of Acne in the United States Evaluation Form

FOR NOTES PURPOSES ONLY. MUST BE COMPLETED ONLINE.

Original Release Date: September 2015 • **Most Recent Review Date:** September 2015
Expiration Date: September 30, 2017 • **Estimated Time to Complete Activity:** 2.5 hours; 3.0 contact hours

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. CME/CE credit letters and long-term credit retention information will only be issued upon completion of the post-test and evaluation online at: **http://tinyurl.com/acne2015**.

Please indicate your profession/background:

☐ MD/DO ☐ MSN/BSN/RN ☐ PA ☐ APN/NP ☐ PharmD/RPh ☐ Resident/Fellow Researcher ☐ Administrator ☐ Student
☐ Other; specify _____

LEARNING OBJECTIVES: *Having completed this activity, you are better able to:*	Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
Discuss the safety and efficacy of the various classes of agents used for treating acne	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Explain the mechanisms of action of systemic and topical agents used to treat acne	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Diagnose and determine appropriate systemic and topical treatment options for patients with mild to severe acne	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Describe the appropriate candidates for isotretinoin therapy, and incorporate improved protocols for the optimum use of this agent	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Discuss strategies for minimizing the risk of acne scarring	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Recognize the urgency of prompt treatment of acne to prevent physical and psychological scarring	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Advise patients regarding the nature and management of their diseases and suggest practical psychosocial coping techniques	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Implement educational strategies to improve adherence with treatment plans, including ways to help reduce relapse rates in adolescent patients	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

_____

_____

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? *(check one)*

☐ Implement a change in my practice/workplace.
☐ Seek additional information on this topic.
☐ Do nothing differently. Current practice/job responsibilities reflect activity recommendations.
☐ Do nothing differently as the content was not convincing.
☐ Do nothing differently. System barriers prevent me from changing my practice/workplace.

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

_____

_____

If you plan to change your practice/workplace, may we contact you in 2 months to see how you are progressing?

☐ Yes. *E-mail address:* _____
☐ No. ☐ I don't plan to make a change.

If you are not able to effectively implement what you learned in this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc)?

_____

_____

OVERALL EVALUATION		Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
The information presented increased my awareness/understanding of the subject.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The information presented will influence how I practice/do my job.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The information presented will help me improve patient care/my job performance.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
The program was educationally sound and scientifically balanced.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Overall, the program met my expectations.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
I would recommend this program to my colleagues.		☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Hilary E. Baldwin, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
James J. Leyden, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Guy F. Webster, MD, PhD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Andrea L. Zaenglein, MD	Author demonstrated current knowledge of the topic.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Author was organized in the written materials.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

What topics do you want to hear more about, and what issue(s) regarding your practice/professional responsibilities will they address?

_____

_____

Please provide additional comments pertaining to this activity and any suggestions for improvement.

_____

_____

The University of Louisville thanks you for your participation in the is CME/CE activity. All information provided improves the scope and purpose of our programs and your patient care.