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Therapeutic Challenges and New Approaches to the Patient With Acne

The Acne Patient: Quality-of-Life and Clinical Questions

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Approach to the Patient With Acne: Therapeutic Challenges

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New and Emerging Topical Treatments for Acne

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New Approaches to the Patient With Acne

Target Audience

This educational activity has been developed for dermatologists, pediatricians, and other health care professionals who treat patients with acne.

Needs Assessment

Acne vulgaris is a follicular disorder that affects susceptible pilosebaceous follicles, primarily on the face, neck, and upper trunk, and is characterized by both non-inflammatory and inflammatory lesions. Although rarely a serious medical condition, acne is the most common skin disease, with nearly 17 million people in the United States afflicted with the disease. Eighty-five percent of people 12 to 24 years of age develop acne, and nearly 40% of adolescents have acne severe enough to require treatment by a physician. In 2006, approximately 5.1 million patients were diagnosed with acne; of those patients, 50.7% were female.

Emerging therapies and regimens offer clinicians a broader range of options to improve tolerability, sustain positive clinical outcomes, and effectively treat a diverse patient population. Treatment of acne depends on the type, extent, and severity of the condition. Therapies affect acne by reducing sebum production, reducing bacteria, normalizing the keratinization process, and/or reducing inflammation. For patients with moderate to severe and persistent acne, oral and topical antibiotics have been the therapies of choice.

Topical treatments are indicated alone for mild to moderate comedonal lesions, superficial inflammatory (papular or pustular) lesions and nonscarring lesions. Topicals include tretinoin, benzoyl peroxide, adapalene, or salicylic acid. Systemic treatments are indicated for moderate to severe (scarring or non-scarring) lesions and patients with persistent hyperpigmentation and include tetracycline, erythromycin, minocycline, doxycycline, clindamycin, and trimethoprim-sulfamethoxazole. Current guidelines for acne management recommend the use of combination regimens in order to address multiple aspects of acne pathogenesis.

Dermatologists and other health professionals treating patients with acne must have the latest clinical data and knowledge to individualize their patients' care.

Term of Approval: May 2008–May 31, 2009.

Learning Objectives

At the conclusion of the program, the participants should be better able to:

- Discuss the pathophysiology and causes of acne, including the role of diet
- Target acne treatment to the causes of acne
- Identify practical and effective ways to improve tolerability of topical and systemic treatments of acne
- Understand and implement acne maintenance regimens for optimal clinical results

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The Acne Patient: Quality-of-Life and Clinical Questions



Anthony J. Mancini, MD, FAAP, FAAD

Researchers are expanding their work beyond studies on the impact of acne on quality-of-life (QoL) issues and investigating the potential role of diet in managing the care of individuals with acne vulgaris. This article reports on various study findings relating to the impact of acne on the lives of people with this condition, focusing on the implications of a low-glycemic load (LGL) diet in the management of acne.

Impact of Acne on QoL Issues

Research indicates that acne vulgaris imparts a substantial negative impact on QoL of those affected by this condition.¹ QoL factors—such as anxiety, frustration, and perceptions of negative effects on employment and personal relationships—contribute to adverse effects on mood and self-esteem and can contribute to clinical depression and, in extreme cases, suicide.¹ Groups at high risk for compromised QoL include people who do not seek treatment and people whose skin conditions are not optimally managed in the medical setting. Each group has an increased risk for adverse consequences of acne, such as disfigurement, scarring,² and psychologic morbidity.³ Fear of these consequences and the discomfort of acne vulgaris resulted in 4.4 million doctor visits for people seeking treatment during 2006.⁴

Another indicator of the serious consequences of acne is revealed by the Dermatology Life Quality Index (DLQI), a health-related QoL questionnaire that specifically focuses on skin conditions.² To estimate the impact of skin conditions on QoL measures, the DLQI has been administered to various populations suffering from skin diseases. For example, the DLQI instrument asks a series of questions about the effects of the condition on specific situations (such as feeling embarrassed about the condition) and its interference with such activities as playing sports or engaging in social activities. Applying the DLQI scoring measures ranging from zero (indicating no impairment of life quality) to 30 (indicating maximum impairment), the average DLQI score was 8.8 for patients with psoriasis as compared with the average DLQI score of 11.9 for patients with acne.² These findings suggest that patients with acne may feel that their

condition poses a higher threat to their QoL than that of patients with psoriasis.²

Psychological studies have found that patients with acne experience impaired self-worth as well as high levels of anger, anxiety, obsessiveness, and clinical depression.¹ These negative emotions can become severe enough to impair their ability to function.¹ According to a study by Mallon and colleagues, the stress resulting from the impact of acne on an individual's QoL can be disabling,⁵ comparable to the disability resulting from chronic disorders such as diabetes and asthma.³

Psychological studies have found that patients with acne experience impaired self-worth as well as high levels of anger, anxiety, obsessiveness, and clinical depression.

Patients with acne often report that the disease has had negative effects on their social interactions, academic studies, employment, and other aspects of their lives, including a negative impact on participation in sports and activities such as dating or eating out with friends.^{1,6}

For many of these patients, the emotional state of anger is associated with perceptions of QoL deficits and dissatisfaction with medical treatment.⁷ Patients with severe acne had higher scores for trait anger than did patients with less severe acne, suggesting that anger may affect disease severity.⁸

These QoL issues may contribute to clinical depression and suicidal ideation among these patients. Patients with depression often express feelings of low self-worth and unattractiveness.³ Studies have found that clinical depression and suicidal ideation occur in 7.2% of all patients with acne.³

In a secondary analysis of a cross-

sectional survey (known as “Youth 2000”) of 9,567 secondary school students between 12 and 18 years of age, self-reported rates of acne were associated with clinical depression, anxiety, and, to a slightly lesser degree, suicide attempts (odds ratio [OR]: 2.04, 2.3, 1.83, respectively). The strong correlation between suicide attempts and acne remains even after controlling for the other two factors (OR: 1.5).⁹ Acne is not regarded as the only dermatologic condition that increases the risk for suicide. The self-reported prevalence of suicidal ideation among patients with other dermatologic conditions was 8.6%, compared with the 7.1% prevalence of suicidal ideation among patients with acne (See **Table**).¹⁰ Furthermore, researchers have found that the most rapid rise in suicide rates is among males between 15 and 24 years of age.³ This finding is of special concern because acne has its peak occurrence during this age period.

Some Common Beliefs

Although often poorly compliant to medical regimens, patients with acne are often impatient for results¹¹ and often ask their physicians about common beliefs and myths. One question often posed is whether or not acne is caused by diet, particularly chocolate, soda, sweets, and greasy foods.

Recent literature suggests a possible relationship between diet and acne. For example, Cordain and colleagues reported a strikingly different incidence of acne in fully modernized societies compared to that in populations with nonwesternized diets.¹²

These researchers studied acne incidence in two populations: the Aché hunter/gatherers of Paraguay and the Kitavan Islanders of Papua, New Guinea. No papules, pustules, or open comedones were observed during examinations for skin disorders in the entire Kitavan population (n=1,200). Of the 115 subjects in a hunter/gatherer cohort from Aché, no active cases of acne vulgaris were observed, although one 18-year-old male appeared to have acne scars.¹²

The nonwesternized diets of both the Kitavan Islanders and the hunter/gatherers of Aché consist of minimally processed plant/animal foods, which are

devoid of western carbohydrates that may lead to high glycemic loads to elevate insulin levels. These two nonwesternized populations maintain low glucose serum levels and high levels of insulin sensitivity; such levels are believed to be mediated by androgens, insulin-like growth factor 1 (IGF-1), and insulin-like growth factor binding proteins (IGFBPs).¹²

Potential Role of Glycemic Load in Acne Pathogenesis

Building on the work of Cordain and colleagues, other researchers have investigated a possible link between nutrition-related lifestyle factors, hyperinsulinemia, and the incidence of acne. A study conducted by Smith and colleagues involved the use of the glycemic index (GI), exploring the concept that high intakes of refined, high-GI carbohydrates may be a significant contributor to the high incidence of acne in westernized countries.¹³ The GI measures the potential of carbohydrate foods—and various combinations of carbohydrate and non-carbohydrate foods—to cause rapid increases in blood glucose. These blood glucose spikes are known as the glycemic load (GL). Accumulating evidence suggests that LGL diets may have a role in the prevention of hyperinsulinemia by improving insulin sensitivity and lowering postprandial insulin levels.¹³

To study the effects of a LGL diet, the trial conducted by Smith and colleagues was a parallel-design, investigator-blinded controlled trial using a 12-week randomized dietary intervention for 50 males (15 to 25 years of age) with acne.¹³ A total of 43 subjects completed the study; 7 subjects did not complete the study (5 males in the control group and 2 males in the LGL group), and 4 subjects were removed from the data set (2 males because of noncompliance and 2 males who began medications known to affect acne).

Study participants in the control group were allowed to eat carbohydrate-dense (high-glycemic) foods. The intervention group followed a LGL diet that pro-

vided 25% of its energy from protein and 45% from low-GI carbohydrates. Before the intervention began, acne counts were made for each participant. After adjusting for variables, the reduction in total lesion counts was significantly greater ($P=0.02$) in the LGL group than in the control group. The researchers also noted a greater reduction in total weight, body mass index, and free androgen index measurements.¹³

A study published in 2007 by Kaymak and colleagues reported on their findings when comparing 49 college students with acne at 42 colleges to students without acne (the control group).¹⁴ Measures for fasting glucose, insulin, IGF-1, IGFBP, GI, and overall dietary GL levels were recorded before the study and re-measured at study end. However, no differences between patients with acne and patients without acne were found.¹⁴

Milk is an LGL food, according to the GI.¹⁵ Data from the Nurses' Health Study II showed that milk intake was associated with a self-reported history of teenage acne, with a stronger effect for those who drank skim milk.¹⁶ One study published in 2005 by Adebamowo and colleagues found a positive association with acne for intake of total milk and skim milk, based on data from 47,355 women who completed questionnaires on their diet during high school.¹⁶

Adebamowo and colleagues also conducted a prospective cohort study of 6,094 females, 9 to 15 years of age. Their dietary intake was reported via questionnaires at three points in the study from 1996 to 1998. Data on the recalled presence/severity of acne were also compiled and analyzed. These researchers concluded that the data showed an association between milk intake and increased risk of acne in teenaged girls. Based on their multivariate analysis, they calculated the following prevalence ratios (listed highest to lowest intake): 1.20 (total milk), 1.19 (whole milk), 1.17 (low fat milk), and 1.19 (skim milk).¹⁷

The hypothesis in both of these studies by Adebamowo and colleagues was that the hormonal content of milk

affects acne. Previous articles have reported that 75% to 90% of the milk brought to market is derived from pregnant cows.¹⁸ Some researchers have suggested that ingestion of dairy products from pregnant cows exposes humans to various hormones, including progesterone, other dihydrotestosterone precursors, prolactin, somatostatin growth hormone-releasing factor, gonadotropin-releasing hormone, insulin, IGF-1, and IGF-2, as well as many others.¹⁸

The Dietary Link to Acne

In response to the findings of these studies and others, some researchers have posed questions about whether other dietary factors might also be involved. Researchers have observed that nonwesternized populations eat more fish than do westernized populations; one study found that the primary signs of acne were substantially lower among teenagers who consumed a diet high in saltwater fish and seafood.¹⁹ This study also showed that fish oil is rich in polyunsaturated fats, containing anti-inflammatory omega-3 fatty acids. Furthermore, omega-3 fatty acids are well documented to have leukotriene B₄ inhibiting properties in humans.²⁰ Data have indicated that people in nonwesternized cultures ingest 30% more fiber than do people in westernized cultures; this finding also may have a therapeutic effect on various skin conditions.²¹

Katzman and Logan have hypothesized that certain nutritional factors, combined with a weakened antioxidant defense system and altered intestinal microflora, have overlapping effects on both acne and depressive/anxious mood states.²² These authors have pointed out that zinc/selenium levels are lower in patients who suffer from both depression and acne than in people who do not have these conditions. Furthermore, they also hypothesize that other nutrients that might have beneficial effects against acne include folic acid, chromium, and nicotinamide. Further study is needed on the role of antioxidants and oxidative stress, the role of intestinal microflora, and the potential benefits (if any) of probiotic supplementation.²²

Summary

Acne vulgaris presents a challenge to the QoL of patients with this condition and may even contribute to clinical depression and suicidal ideation. For years, clinicians have discounted the influence that western diets may influence the incidence and severity of acne. However, recent epidemiologic research has presented some evidence that a link

TABLE. Suicidal Ideation and Acne

- Prevalence of suicidal ideation (SI) among patients with dermatologic conditions
- Outpatients (294), inpatients (172)
- Patients completed self-report instruments
- 40/466 (8.6%): SI in last 2 weeks
- Prevalence of SI among patients with acne: 7.1%

Adapted from: Picardi A et al.¹⁰

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Approach to the Patient With Acne: Therapeutic Challenges



Magdalene A. Dohil, MD

Today's existing and emerging therapies and combination regimens for acne offer patients and clinicians an increasingly broader range of options for effective treatment, improved tolerability, and sustained clinical benefits. However, when choosing the appropriate treatment, clinicians must consider and address the potential barriers to patient compliance: patient misperceptions regarding the condition, the fact that treatments for acne usually must be continued daily for a prolonged period, and that regimens often are complex and tedious to sustain and may lead to potentially irritating treatment side effects. Another major challenge in acne therapy is the increasing prevalence of antibiotic resistance with the inherent risk for treatment failure.

Pathophysiology and Treatment Approaches

The treatment goals in managing acne vulgaris are based on what is currently known about the pathophysiology of this multifactorial disease. Thus, therapy involves normalizing the keratinization process, lysing comedones, reducing sebum overproduction, eradicating bacteria, and stopping inflammation, with the long-term goals of preventing dyspigmentation in patients with skin of color and scarring in patients of all skin types.

The options for therapy are familiar to clinicians and are summarized in Table 1. A stepwise method for using these treatments offers a logical approach to pathophysiologic target areas. Agents are chosen according to how well they address each of the underlying causes (Table 2) and are matched to the individual patient's skin type and degree of acne. Patients who have an understanding of this strategy are more likely to cooperate with complex therapy recommendations.

The first step is often the use of topical benzoyl peroxide to address inflammatory lesions, with retinoids added when microcomedones (noninflammatory lesions) are present. To further control inflammation, a topical antibiotic can be added as the second step; if the degree or extent of inflammation is severe, oral antibiotics may be additionally needed. In this context, combination topical products may be helpful in simplifying

regimens by combining several treatment steps in one. The third step, in female patients, is the use of oral contraceptives or spironolactone to control androgenic stimulation of the sebaceous glands. Oral isotretinoin is reserved for carefully selected patients with severe, recalcitrant inflammatory acne.

Within the past several years, laser therapy has become an option,¹⁻³ sometimes as monotherapy but more frequently as adjunctive treatment for patients on standard topical and oral acne medication regimens. These modalities include high-intensity, narrow-band blue light (405-420 nm) to reduce inflammatory lesions; a broad-spectrum (430-1200 nm) flashlamp, which targets endogenous porphyrins produced by *Propionibacterium acnes*; a 1450-nm diode laser, which works by thermal destruction of the sebaceous glands; and the pulsed, nonablative erbium:YAG laser, which reduces the appearance of scars by stimulating neocollagenesis. More recently, a combination of various light sources with photodynamic treatment has been advocated as an adjunctive treatment modality.

Overcoming Antibiotic Resistance

In acne, both topical and oral antibiotics work by reducing the viable number of *P. acnes* organisms and, therefore, decreasing the production of inflammatory stimuli.⁴ Antibiotic therapy has been a mainstay of acne treatment for more than 45 years; however, beginning in the 1970s, *P. acnes* began to show decreased sensitivity to antimicrobial agents.^{5,6} Analyses of global data on antibiotic-resistant *P. acnes* showed that the worldwide prevalence of resistant strains of this organism increased from 20% in 1978 to 62% in 1996.⁷ Today, tetracycline-resistant strains are found in up to 20% of patients, and erythromycin-resistant organisms are seen in up to 50% of patients.⁷

Several factors have been associated with this trend. These include antibiotic monotherapy, the use of low-dose antibiotics, long treatment duration, sequential and/or simultaneous treatment with different classes of antibiotics, and poor patient compliance. In addition, it has been found that the clinical efficacy of oral antibiotics is compromised by pre-existing *P. acnes* resistance to tetracyclines.

The underlying mechanisms of *P. acnes* antibiotic resistance are still being explored, but more than 2 decades ago, Lee and colleagues⁸ speculated that after the organism adheres to the dermal follicle, it synthesizes and secretes a protective extracellular polysaccharide biofilm. It is known that bacteria in a protected biofilm environment are between 50 and 500 times more resistant to antibiotic therapy than are free-floating bacteria.⁹ In 2003, Burkhart and Gottwald¹⁰ proposed that the presence of a *P. acnes* biofilm would explain why antimicrobial therapy often must be prolonged to be effective. Furthermore, in a recent study, Coenye and colleagues¹¹ found that multiple *P. acnes* strains, including acne isolates, can form biofilms in vitro.

The results of investigations involving the topical treatment of acne with benzoyl peroxide combined with several different antibiotics have been published, demonstrating that the combinations are more effective than is antimicrobial monotherapy.¹²⁻¹⁴ The addition of benzoyl peroxide increases antibiotic efficacy in

TABLE 1. Treatment Options for Acne: A Summary

- **TOPICAL**
 - Benzoyl peroxide
 - Retinoids
 - Antibiotics
 - Azelaic acid
 - Glycolic acid
 - Salicylic acid
 - Sodium sulfacetamide
 - Nicotinamide
 - Zinc
- **SYSTEMIC**
 - Antibiotics
 - Contraceptives (female patients)
 - Isotretinoin
 - Spironolactone (female patients)
 - Oral corticosteroids (rarely)
- **OTHERS**
 - Laser
 - Photodynamic treatment

at least two ways: (1) by reducing the proliferation of resistant strains of *P. acnes* that were present prior to the start of therapy and (2) by decreasing the emergence of antibiotic-resistant strains during therapy. In the presence of antibiotics, highly active benzoyl peroxide radicals form, resulting in damage to the biofilm, which in turn enhances penetration of the antibiotic.

Clinicians can take a number of steps to avoid contributing to the further emergence and proliferation of antibiotic-resistant strains of *P. acnes*. In general, of course, the use of any antibiotics should be limited to proven indications. With regard to acne vulgaris, specifically, topical retinoids should be tried for initial treatment. Antibiotic monotherapy for acne—either topical or oral—should be avoided. If antibiotic treatment is indicated, the duration of the initial course should be limited to the time it takes to bring the inflammatory process under control, most commonly seen within 12 weeks of treatment. Topical therapy should be initiated at the same time and continued for maintenance beyond the use of oral antibiotics. Combination products may facilitate continued long-term treatment with a retinoid and benzoyl peroxide or a topical antibiotic and a benzoyl peroxide.

Acne in Skin of Color: Special Considerations

The ethnic population in the United States has been increasing for several decades, and further significant increases are predicted for the near future. Thus, clinicians will be treating larger numbers of patients of color for common skin conditions such as acne, and it will be necessary for clinicians to refine treatments to prevent the unique challenge of postinflammatory hyperpigmentation seen in these patients.

In darker skin, comedones seem to have a stronger inflammatory component,

and a hyperreactivity of melanocytes also exists that increases the risk for dyschromia. In fact, postinflammatory hyperpigmentation often is the primary reason for patients of color to consult a dermatologist.^{15,16}

The main challenge in successful therapy for acne in this patient population is to start anti-inflammatory therapy early and to treat aggressively. However, it is also extremely important to select topical agents carefully to prevent excessive irritation of the skin, which may itself cause pigment changes. Lower concentrations of benzoyl peroxide and retinoids in cream vehicles may be considered.^{15,16}

Enhancing Compliance: Practical Tips for Clinicians

In addition to educating patients about the causes of acne and the types of medications that can be considered in individual cases, some other specific messages should be stressed. Some of these may seem obvious to clinicians, but they are usually not obvious to patients.

Patients must be realistic about their expectations about treatment. The most rational approach to acne therapy is “slow and steady,” and there are no quick or easy remedies to solve the problem. They should understand that there is no “cure” for acne. The goal is effective symptom control, and to achieve it, patients must participate in the process and recognize that it takes work to manage their condition. Toward that end, compliance over the long term can be enhanced if the initial treatment focus is on prompt and effective anti-inflammatory control before introducing other, more complex treatment goals.

Many patients are aware that some oral medications are used to treat acne, and it may seem like an attractive option compared to complicated topical regimens. For this reason, the option of oral medication should be addressed, and an

FIGURE. Range of Acne Lesions



Inflammatory lesions (top) should be treated early and aggressively to prevent hyperpigmentation and scarring. Patients with noninflammatory, mild acne (bottom) may be managed with nonprescription benzoyl peroxide products.

explanation should be offered regarding the suitability of such medications in an individual patient’s case. For those cases in which oral antibiotics are indicated, it is important for the patient to know from the outset that the course of therapy will be limited and why. It is not unusual for patients who respond well to the anti-inflammatory action of oral antibiotics to want to continue taking the medication indefinitely.

Patients should also be advised that the initial therapeutic response may be slow but that they must adhere to the treatment plan over the long term for best results. This may be particularly difficult if an initial flare occurs when topical retinoid therapy is initiated. Education about gradual retinization and the reason why a flare may occur is essential to prevent premature disuse of the medication because a patient concluded that the retinoid not only did not help the condition but made the acne “worse.” Patients should be told to anticipate the possibility of this and other common often-transient side effects associated with retinoids, benzoyl peroxide, and other topical medications.

Along with stressing compliance with a medication and a proper topical treatment regimen, clinicians must explain why sun protection and moisturization are important for all patients, but especially for those using a retinoid.

TABLE 2. Pathophysiologic Targets of Acne Medications

	Comedones	<i>Propionibacterium acnes</i>	Inflammation	Sebum Production
Benzoyl peroxide	+ / ++	++	++	–
Topical retinoids	++++	–	++	–
Topical antibiotics	+	++	++	–
Benzoyl peroxide/antibiotics	+ / ++	+++	+++	–
Topical antibiotics/retinoids	++++	+++	++++	–
Oral antibiotics	+	++++	+++	–
Oral contraceptives	+	+	++	++

+ = positive effect on the pathophysiologic target; – = no effect on the pathophysiologic target.

Source: Courtesy of Magdalene A. Dohil, MD.

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New and Emerging Topical Treatments for Acne



David M. Pariser, MD

The armamentarium of topical treatment options for acne vulgaris continues to grow, and these developments are welcome additions as clinicians seek to optimize therapy for individual patients. Several of the latest options include new combinations of currently approved agents, fixed combination products, and a new molecular entity. Among the new fixed combination products is clindamycin 1.2% plus tretinoin 0.025% in a gel vehicle, which provides the benefits of both established acne therapies in a single product; it is the only antibiotic-retinoid fixed combination approved to date by the US Food and Drug Administration (FDA). Another fixed combination product is the retinoid adapalene 0.3% plus benzoyl peroxide 2.5%; although this product has not yet been approved by the FDA, a phase III clinical study has been completed.

This article discusses the evidence concerning the efficacy and safety of these two important combination products and other selected new and emerging products.

New Formulations

Adapalene 0.3% Gel

A randomized, investigator-blind, multicenter, vehicle-controlled, phase II trial of adapalene 0.3% gel demonstrated the efficacy and safety of this formulation against the 0.1% concentration of this agent and against the corresponding gel vehicle.¹

In addition, a phase III study (also a randomized, placebo-controlled, 12-week trial) was conducted with a total of 653 study participants and involved comparisons between adapalene 0.3% gel, adapalene 0.1% gel, and gel vehicle only.² In this study, women who were pregnant, planning a pregnancy, or nursing were excluded, as were any subjects with underlying diseases that required the use of topical or systemic therapy that would have interfered with the results.

After undergoing a washout period, the subjects were treated once daily for 12 weeks, and evaluations were performed at baseline and at weeks 1, 2, 4, 8, and 12. The primary efficacy end points were total facial, noninflammatory, and inflammatory lesion counts—and a rating of clear or almost clear on an

investigator's global assessment of acne severity.

At week 12, 23.3% of the patients in the adapalene 0.3% gel group had ratings of clear or almost clear ($P=0.005$) compared to baseline. In contrast, 16.9% of the patients in the adapalene 0.1% gel group were clear or almost clear, and 10.0% of those in the vehicle group were clear or almost clear ($P=0.005$ compared to the group treated with adapalene 0.3% gel).

The Consensus Guidelines for acne management suggest that enhanced therapeutic benefits may be obtained by combining therapeutic agents with different but complementary mechanisms of action.

The most frequent treatment-related adverse events—most of which were mild or moderate—were dryness (14% of those receiving adapalene 0.3% gel vs 6.9% receiving adapalene 0.1% gel) and skin discomfort (5.8% of those receiving adapalene 0.3% gel vs 4.6% of those receiving adapalene 0.1% gel). Eight patients discontinued the study due to adverse events; 6 of these patients (3 patients receiving adapalene 0.3% gel, 2 patients receiving adapalene 0.1% gel, and 1 patient receiving gel vehicle) did so because of events related to treatment.

Clindamycin Phosphate 1% Foam

A 12-week, randomized, investigator-blind, vehicle-controlled, multicenter phase III study compared clindamycin phosphate foam 1% with clindamycin phosphate 1% gel and foam and gel vehicles in 1,026 patients with mild to moderate acne vulgaris.³

The active drug with foam vehicle was superior to both vehicles in the mean percentage reduction of total lesions ($P<0.0001$). In addition, at week 12, clindamycin foam was comparable in mean

total lesion count to that of clindamycin in the gel vehicle—42.8% versus 35.7% over baseline, respectively. Clindamycin foam also was statistically superior to the vehicles in mean percent reductions in both inflammatory and noninflammatory lesions and was comparable to the efficacy seen with clindamycin gel.

A primary efficacy end point was treatment success defined as the proportion of subjects with an Investigator's Static Global Assessment score of 0 or 1 (clear or almost clear) at week 12. In the clindamycin foam group, 31% of the patients achieved these scores as compared with 27% of those in the clindamycin gel group, 18% of those in the foam vehicle group ($P=0.0025$), and 20% of those in the gel vehicle group.

Overall, the data demonstrated that clindamycin phosphate 1% foam also is well tolerated: 8% (29 of 386) had treatment-related adverse effects as compared with 3% (10 of 385 patients) in the clindamycin gel group. The four most common treatment-related adverse effects in the active treatment groups were application site burning, desquamation, dryness, and pruritus. Two patients discontinued participation in the study because of adverse effects.

Solubilized 5% Benzoyl Peroxide Lotion

A new system, formulated for use in patients with normal or dry skin, is available containing 5% benzoyl peroxide lotion, a therapeutic moisturizer containing 2% glycerin and 20% dimethicone, and a proprietary cleanser. Other benzoyl peroxide products typically contain insoluble macrocrystals that may be too large to enter the follicles. In contrast, the benzoyl peroxide in the new three-step-system formulation is solubilized, which may enhance follicular penetration of this agent and improve clinical efficacy.

To test the tolerability of the new system, 50 female volunteers between 18 and 45 years of age with clear facial skin participated in a split-face, investigator-blind, randomized study.⁴ Once each day for 3 weeks, the subjects applied the three-step system to one side of the face and a clindamycin/benzoyl peroxide combination prescription product (tube gel formulation) in an optimized vehicle containing two emollients. Study monitors supervised the applications on week-

days. An expert grader evaluated erythema and dryness on both facial sides; the subjects reported their assessments of burning or stinging and comfort.

Throughout the study period, the mean levels of comfort were greater than “comfortable,” the levels of dryness and burning or stinging were below “slight,” and the mean levels of erythema were below “mild” with both regimens. However, with both regimens, some subjects had clinically relevant levels of dryness, burning, or stinging. Compared to the prescription combination product, the solubilized benzoyl peroxide system showed lower mean levels of dryness ($P < 0.05$ at day 14), comparable mean levels of erythema, and higher mean levels of burning or stinging ($P < 0.05$ at days 7, 14, and 21). However, the facial side treated with the solubilized benzoyl peroxide system was rated as significantly more comfortable overall than the clindamycin/benzoyl peroxide-treated side ($P < 0.01$); this may be due to the fact that burning or stinging is usually mild and transient, but dryness may be longer-lasting.

New Combinations

The Consensus Guidelines for acne management suggest that enhanced therapeutic benefits may be obtained by combining therapeutic agents with different but complementary mechanisms of action.⁵ In addition to enhanced efficacy, combination therapy in single products are more convenient for patients and encourage compliance.

Adapalene/Benzoyl Peroxide

An emerging treatment not yet marketed is adapalene 0.3% gel and benzoyl peroxide 2.5% as a fixed combination.

In a phase II study of 517 subjects, 149 participants received the active adapalene 0.1%/benzoyl peroxide 2.5% combination; 148 others received adapalene 0.1% alone, 149 participants received benzoyl peroxide alone, and 71 participants received the vehicle only.⁶ The primary end point was the percentage of patients who achieved evaluations of clear or almost clear on the Global Evaluation Scale [GES] (Table) at week 12; the secondary end point was the lesion count reduction.

By week 12, most patients were clear or almost clear (Figure 1 on page 10). There were statistically significant and clinically meaningful results for more patients on the combination adapalene/BP treatment compared to the two active ingredients or to the vehicle individually.

Because acne lesions have been shown to return after discontinuation of a combination treatment, many patients require long-term therapy. The phase II study described above was continued after week 12 for an additional 9 months.⁷ Safety and efficacy evaluations were performed at baseline, at weeks 1 and 2, and at months 1, 2, 4, 6, 8, 10, and 12. These evaluations demonstrated a significant clinical benefit of continued treatment with adapalene 0.1%/benzoyl peroxide 2.5%. In the combination treatment group, 27% of the patients achieved this score, as compared to 15% of those in the group who received adapalene alone, 13% of those in the benzoyl peroxide group alone, and 10% of those in the vehicle only group.

Clindamycin 1.2%/Tretinoin 0.025%

A combination topical therapy of

clindamycin 1.2% and tretinoin 0.025% in an aqueous polymer gel was studied in three phase III clinical trials.⁸ Two of these studies, which will be discussed here, involved a total of 2,538 subjects with mild, moderate, or severe acne (1,250 subjects in the first study and 1,288 in the second). The results of the third study were similar. In all three studies, the subjects were between 12 and 18 years of age.

Enrollment eligibility was based on lesion counts, 20 to 100 noninflammatory lesions, 20 to 50 inflammatory lesions; and no more than two nodules (defined as inflammatory lesions of 5 mm or greater in diameter). The goal of these phase III trials was to demonstrate the superior efficacy of the combination topical therapy of clindamycin phosphate 1.2% and tretinoin 0.025% gel over the individual ingredients used as monotherapy.

In the combined analysis of these two studies, all end points at week 12 achieved statistical significance in both the intent-to-treat population and per protocol populations.⁸ At week 12, the reductions in inflammatory, noninflammatory, and total lesion counts in the clindamycin/tretinoin gel group were significantly better than those seen in the groups that used individual active ingredients and vehicle alone ($P < 0.0008$). Treatment with the combination gel also produced significant improvement in GES and appearance (Figure 2 on page 10).

Furthermore, patient improvement increased over time, with longer use of the combination product. In a long-term, open-label study, 57% of patients using the clindamycin-tretinoin gel had clear or almost clear skin at 12 months, compared to 48% of study participants at 12 weeks. In this long-term study, the majority of patients (78%) were treated with the combination gel only; 22% were receiving one or more additional agents (oral antibiotics, 12%; other topical therapy, 9%; and isotretinoin, <1%).

The incidence of reported adverse events ranged from 1% to 5%. The most frequently reported adverse effect was nasopharyngitis (5%) for clindamycin. Approximately 35% of the subjects reported erythema at the beginning of the study, but that incidence dropped to 26% by the end of the treatment period. Other local skin reactions included scaling, itching, burning, and stinging. The aqueous gel formation vehicle was used in all four treatment arms, which may explain the uniformly low incidence of dry skin. The low incidence of erythema at the end of the treatment period may be due to the fact that patients used sunscreen and emollients during the study.⁸

TABLE. Global Evaluation Scale*†

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost Clear	Rare noninflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Noninflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules; there may or may not be one small nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules, and many nodulocystic lesions

*The US Food and Drug Administration uses improvements on this scale as an indicator of efficacy in studies of acne treatments. The Global Evaluation Scale (GES) focuses on inflammatory changes that reflect a real-world measure of efficacy, including improvements in appearance.

†The GES was used to evaluate efficacy in the studies of adapalene 0.3%/benzoyl peroxide 0.5% gel and clindamycin 1.2%/tretinoin 0.025% gel.

Source: http://www.fda.gov/ohrms/dockets/ac/02/slides/3904S1_03_Carr/index.htm

The vehicle base of the clindamycin/tretinoin combination is an aqueous polymer gel containing no alcohol. In the gel vehicle, crystalline tretinoin, dissolved tretinoin, and solubilized clindamycin are in equilibrium; as the product penetrates the skin, the equilibrium is upset, causing the crystalline component to dissolve. The “phased release” of tretinoin means that less unbound retinoid is present in the skin, reducing irritation. Tolerability may be further enhanced by the anti-inflammatory effects of clindamycin.

New Molecule

The pooled data from two phase III clinical trials demonstrated the efficacy and safety of a new molecule called dapsone gel, 5%.⁹ The combined total of 3,010 study participants had mild to severe acne (most of the subjects—approximately 60%—had moderate acne).

More than 40% of the patients treated in these trials achieved scores of

clear or nearly clear. In the subset of patients with severe acne, approximately 50% improved to at least mild acne. The difference between the active treatment group and the vehicle-only group was statistically significant.

A total of five dermal safety studies showed no phototoxicity, irritation, photoallergic response, sensitization, or contact hypersensitivity. Reported local adverse effects for the active drug compared to vehicle alone were oiliness, peeling, dryness, erythema, burning, and rash. The most commonly reported systemic adverse effects for the active drug were nasopharyngitis (4.8%), upper respiratory infection (3.2%), headache (3.1%), pharyngitis (2.5%), cough, (2.1%), sinusitis (1.9%), and dysmenorrhea (0.5%).

Conclusion

The evidence reviewed here demonstrates the efficacy and safety of promising newly available and emerging topical

therapies that clinicians should consider as new options in the treatment of patients with acne vulgaris. These therapies include two combination products: clindamycin 1.2%/tretinoin 0.025% gel and adapalene 0.3%/benzoyl peroxide 0.25%. In addition, new formulations of adapalene (0.3% strength) and clindamycin (in a foam vehicle) have been developed, as has a topical dapsone 5% gel.

The evidence available to date on these fixed combination products further confirms and extends the concept that combination drugs affect multiple areas of pathophysiology. All of the products discussed in this article are among advances that offer clinicians more treatment options in providing care for their patients with acne vulgaris.

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FIGURE 1. 12-Week Results on GES of Adapalene/Benzoyl Peroxide (BPO) Fixed Combination

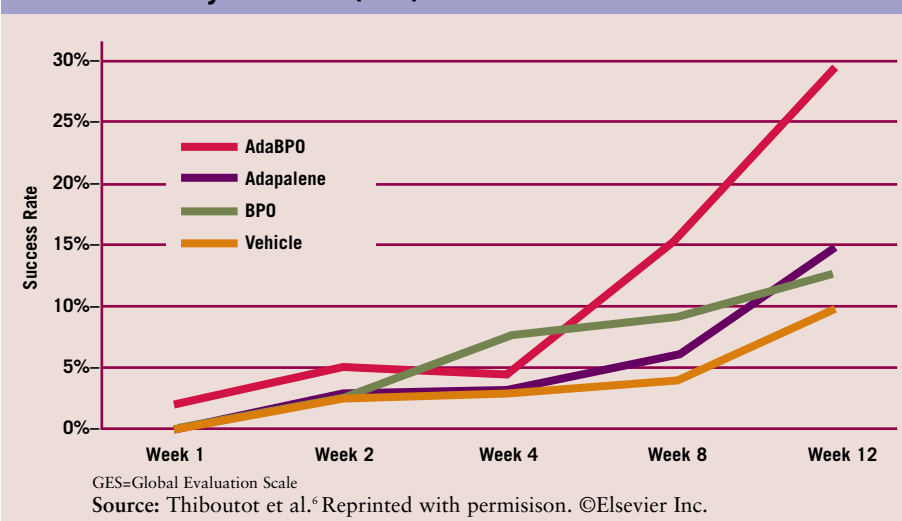
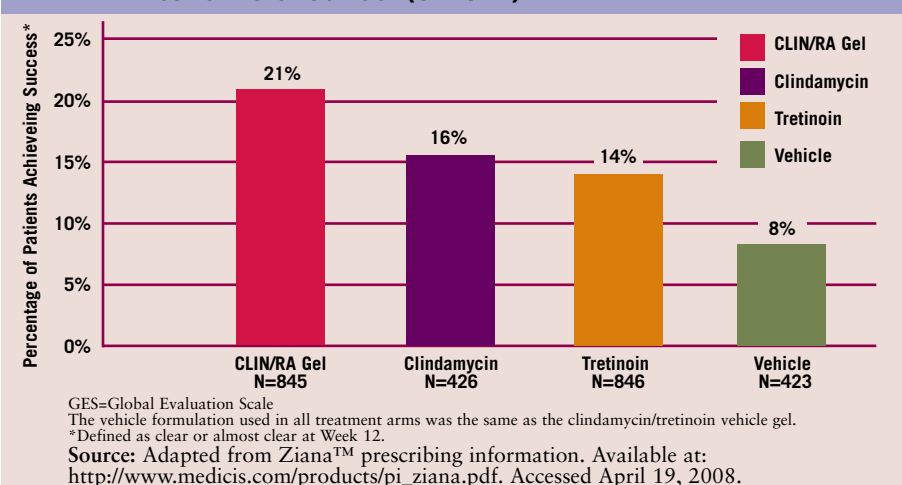


FIGURE 2. 12-Week Results on GES of Clindamycin 1.2%/Tretinoin 0.025% Gel (CLIN/RA)



continued from page 5

between diet and acne may exist. More research is needed to increase our understanding about the relationship between diet and acne, which includes the possibility that LGL diets may have therapeutic potential in reducing symptoms of acne.

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Approach to the Patient With Acne: Therapeutic Challenges

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Conclusion

The options for treating acne have greatly expanded over prior decades, and a wide range of acne treatments are available to target one or more of the known mechanisms involved in the pathogenesis of the disease. An individualized yet simplified regimen is likely to be the most effective and most acceptable approach to patients. In choosing the elements of the treatment plan, the multiple causes of acne must be evaluated, antibiotic-resistant organisms must be considered, and postinflammatory hyperpigmentation should be evaluated early and aggressively, particularly in skin of color. Combination treatments may offer some advantages for effective long-term control of acne by targeting several components in the pathophysiology of acne with one agent, simplifying treatment regimens, and, as such, facilitating patient compliance with prescribed treatment plans.

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CME Post-Test Answer Sheet and Evaluation Form

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INSTRUCTIONS: For each question or incomplete statement, choose the answer or completion that is correct.
Six of eight correct responses are required for credit.

- Acne incidence in males begins to peak starting at ____ years of age.
 - 11
 - 13
 - 15
 - 17
- A prospective cohort study of girls from 9 to 15 years of age by Adebamowo and colleagues showed that an increased risk for acne was correlated with the subjects' intake of _____.
 - Caffeine
 - Chocolate
 - Fish
 - Milk
- It has been found that the clinical efficacy of oral antibiotics have been compromised by preexisting resistance of *Propionibacterium acnes* to:
 - Clarithromycin
 - Clindamycin
 - Erythromycin
 - Tetracycline
- Application of benzoyl peroxide enhances the efficacy of topical antibiotics by:
 - Altering the pH of the skin
 - Damaging the protective biofilm surrounding *P. acnes*
 - Normalizing keratinization
 - Reducing inflammation
- Acne-related inflammation in skin of color must be treated early and aggressively to reduce the risk for:
 - Bacterial resistance
 - Cystic acne
 - Dyschromia
 - Nodular acne
- The US Food and Drug Administration (FDA) uses improvements on this scale as an indicator of efficacy in studies of acne treatments.
 - Acne Global Severity Scale (AGSS)
 - Global Acne Assessment Score (GAAS)
 - Global Evaluation Scale (GES)
 - Investigators' Global Assessment Scale (IGAS)
- In phase III trials of the clindamycin-tretinoin combination agent discussed in this article, the incidence of dryness was:
 - Significantly lowest in the clindamycin-only comparison group
 - Significantly lowest in the tretinoin-only comparison group
 - Uniformly high in all treatment arms
 - Uniformly low in all treatment arms
- In a long-term, open-label extension study of subjects from the phase III clinical trials of clindamycin 1.2%/tretinoin 0.025% combination agent, the improvement seen at 12 weeks:
 - Declined rapidly over the subsequent 9 months
 - Declined slowly over the subsequent 9 months
 - Increased over the subsequent 9 months
 - Was virtually unchanged by month 12

EVALUATION FORM: We would appreciate your answering the following questions in order to help us plan for other activities of this type.

Please Print (All information is confidential.)

Name: _____ Specialty: _____

Degree: MD DO PharmD RPh NP RN BS PA Other

Affiliation: _____

Address: _____

City, State, ZIP: _____

Telephone: _____ Fax: _____ E-mail: _____

Signature: _____

CME CREDIT VERIFICATION: I verify that I have spent ____ hour(s)/____ minutes of actual time working on this CME activity. No more than 1 CME credit(s) will be issued for this activity.

PRETEST ASSESSMENT: Please rate your current knowledge of "Therapeutic Challenges and New Approaches to the Patient With Acne" on a scale of 1 to 5, with 1 being the lowest and 5 the highest. 1 2 3 4 5

POST-TEST ASSESSMENT: Please rate your current knowledge of "Therapeutic Challenges and New Approaches to the Patient With Acne" on a scale of 1 to 5, with 1 being the lowest and 5 the highest. 1 2 3 4 5

COURSE EVALUATION: Please evaluate the effectiveness of this activity by circling your choice on a scale of 1 to 5, with 1 being the lowest and 5 the highest.

Objective #1. Discuss the pathophysiology and causes of acne, including the role of diet 1 2 3 4 5

Objective #2. Target acne treatment to the causes of acne 1 2 3 4 5

Objective #3. Identify practical and effective ways to improve tolerability of topical and systemic treatments of acne 1 2 3 4 5

Objective #4. Understand and implement acne maintenance regimens for optimal clinical results 1 2 3 4 5

How do you rate the overall quality of the activity? 1 2 3 4 5

How do you rate the educational content of the activity? 1 2 3 4 5

After participation in this activity, have you decided to change one or more aspects in the treatment of your patients? ____ Yes ____ No

If yes, what change(s) will you make? _____

If no, why not? _____

Was the presented information fair, objective, balanced, and free of bias in the discussion of any commercial product or service? ____ Yes ____ No

If no, please comment: _____

Suggested topics for future activities: _____

Suggested authors for future activities: _____

Would you be willing to participate in postactivity follow-up surveys? ____ Yes ____ No

Would you be willing to participate in a phone, e-mail, or in-person discussion exploring ways to improve our CME activities? ____ Yes ____ No