Topical interventions are appropriate for the majority of acne presentations, yet some individuals experience suboptimal treatment response. Patient non-adherence with topical therapy is one significant cause of poor therapeutic response. Until relatively recently, contributing factors to non-adherence had not been well-studied, although intuitively prescribers have recognized that poor tolerability of therapy, high prescription costs, and inconvenience have all influenced non-adherence. Patient surveys and clinical studies now document evidence regarding adherence. In response to these findings, new topical formulations are being designed with the goal of improving adherence and, as a result, therapeutic outcomes. Clinicians must be aware of new therapeutic advancements as well as emerging data on existing treatments in order to devise the best topical regimen for each patient with mild to moderate acne vulgaris.

The Problem of Adherence
Acne is a near-ubiquitous condition, yet data suggest that a significant proportion of affected adolescents do not seek medical care for the disease. According to responses to anonymous surveys administered to 1,214 public middle and high schools students (age 10–19 years-old) in New Jersey, 83 percent of those with acne had not seen a physician. Respondents varied in gender, race, and ethnicity. The frequency and severity of acne was shown to increase with age and was higher in white than non-white individuals. The

Take-Home Tips. Research documents clinically evident complexities of patient adherence in topical acne therapy. Prescribing topical therapies with good tolerability within simplified regimens encourages therapeutic adherence. Clinicians must be familiar with research on patient non-adherence as well as formulation developments in order to individualize successful topical regimens for each patient with mild to moderate acne.

By Joseph Bikowski, MD
responses suggest that blacks with acne of mild or moderate severity are more likely to see a health professional compared to white respondents with acne of the same severity. By contrast, Hispanic respondents with mild or moderate acne are less likely to see a health professional compared to whites with the same acne severity.² While the study does not provide clear explanations of the low rate at which patients seek medical care, one might assume that, in addition to financial or logistical barriers to physician access, patients may be influenced by a belief that OTC therapy is sufficient, prescription therapy is of limited benefit, or therapy is otherwise not worth pursuing.

Another study—an analysis of healthcare utilization records—also shows an under-representation of adolescents among those seeking medical treatment for acne. Teenagers (ages 12-17 years) comprised only 36.5 percent of patients with acne, while the majority of patients (61.9 percent) were 18 years or older. This same analysis also showed that female patients seeing physicians for acne treatment outnumber male patients nearly three to one (65.2 percent versus 34.8 percent). At 10.6 percent, rates of depression were higher in females with acne in the analyzed population.³ A recent European study has also suggested that female patients may be more psychologically affected by acne. In that analysis, female patients scored worse on the baseline Dermatology Life Quality Index (DLQI) than did male patients, though scores did not correlate to the clinical grading of acne nor to the choice of therapy (a likely indicator of severity). Quality of life scores improved after treatment at a group level; following six months of therapy, the DLQI correlated with clinical outcome.⁴

The patient’s quality of life (QoL) can impact therapeutic adherence. While numerous other factors, including age, gender, duration of illness, and third-party drug coverage did not correlate with adherence in one study, health-related QoL did. Adherence was found to improve in relationship to the patient’s QoL.⁵

Finally, a recent worldwide survey of 3,339 acne patients from the Americas, Europe, and Asia found a poor adherence rate of 50 percent overall.⁶ The rate of poor adherence was highest (60 percent) among patients prescribed a combination of systemic and topical therapy. Usually, patients were non-adherent with the oral component. The rate of poor adherence was 40 percent among those prescribed topical therapy only. Adherence was lowest among those less than 15 years of age. Based on analysis of the full cohort, factors that correlated with poor adherence among these patients were age, the occurrence of side effects, lack of improvement as evaluated by a dermatologist, previous systemic therapy, lack of knowledge about acne treatment, consultation with a primary care physician, and lack of patient satisfaction with treatment.

The same study uncovered factors that correlated positively with adherence. These include use of skincare (moisturizers, cleansers), use of either topical therapy alone or isotretinoin, good clinical improvement as evaluated by the dermatologist, patient satisfaction, and knowledge of treatment.

### The Role of Treatment Selection

These various findings help the dermatologist recognize that there is no “typical” acne patient, although there may be some commonalities among affected individuals. Importantly, clinicians should recognize the importance of effective therapy to improve the patient’s quality of life—and by extension long-term adherence. If, as these findings suggest, patients are not confident that medical therapy can improve acne, then clinicians must pursue treatments most likely to provide results and thus engender confidence in the prescriber. Of course, the establishment of realistic treatment expectations is crucial. Finally, simplified regimens built upon formulations with good tolerability are expected to improve adherence.

Data confirm the clinically-evident notion that formulation tolerability will influence patient adherence.³ For example, a recent study found that self-reported dryness and irritation associated with clindamycin-BPO (5%) fixed combination acne treatment often led to non-adherence among patients.⁶ It’s worth noting that this Internet survey of acne patients also revealed some of the ways patients modify their prescribed regimens in response to treatment-induced irritation. One-third of patients said they applied the fixed combination formulation on individual lesions rather than to the whole face, and nearly as many (28
percent) only applied medication when breakouts seemed worse. Subjects also reduced their use of medication without physician direction: Some used medication less frequently than recommended (32 percent), some stopped use for brief periods (32 percent), and others (10 percent) stopping use altogether. Any one of these “strategies,” the clinician quickly recognizes, is counter to our knowledge of the pathophysiology of acne and its treatment.

The same survey also showed that, due to the experience of side effects, a proportion of patients switched therapies. Sixteen percent of subjects reported switching to another prescription product, while 13 percent switched to a non-prescription product.9

Options and Data to Consider

Recognizing the role of tolerability in promoting adherence, formulators have focused on developing new products with enhanced tolerability and convenient, simplified regimens. Following is a review of some of the newest topical acne therapies with an emphasis on features intended to support adherence.

Benzoyl peroxide foam. One of the oldest and most widely-used agents in topical acne management, benzoyl peroxide now is available in a novel 9.8% foam formulation that is shown to be effective as a short-contact therapy (BenzEFoam Ultra, Onset/PreCision) and is especially suitable for management of truncal acne. Recently presented results of a two-week open-label, single center study of short contact therapy in 20 healthy subjects (>18 years old) confirmed its benefit. (Leyden, J. Fall Clinical Dermatology Conference, November 2010.) Subjects were all confirmed to be colonized with P. acnes on their backs (>10,000 colonies per cm²). Once daily for two weeks each subject applied BPO (9.8%) foam to the dry back and left it in place for two minutes before rinsing if off with water and wiping the area with a cloth. This protocol was performed under supervision at the study center during the week and unsupervised at home on the weekends.

Mean reduction of P. acnes counts on the back was 0.91 log per cm² after one week of treatment, and 1.66 log per cm² after two weeks of treatment with BPO (9.8%) foam (p<0.0001); this is equivalent to a 98.3 percent reduction in P. acnes counts. The two-minute contact time is expected to be longer than with a BPO wash applied to the back and rinsed off immediately, as is done conventionally. Emollient characteristics of the foam coupled with short duration of contact are expected to minimize BPO irritation while providing adequate antimicrobial effect.

The original BenzEFoam 5.3% BPO foam formulation has demonstrated significant reduction in P. acnes on the back when used either as a leave-on or as short-contact therapy for five minutes. In addition to convenience and tolerability, short-contact therapy may minimize the risk of benzoyl peroxide bleaching of clothing in truncal acne patients.10

BPO plus clindamycin fixed combination. With a BPO concentration of 2.5%, a relatively new benzoyl peroxide/clindamycin fixed combination formulation (Acanya Gel, Coria Laboratories) also features emollient ingredients intended to reduce local cutaneous irritation. A 21-day cumulative irritation study of higher (5%) and lower (2.5%) concentration BPO plus clindamycin with the same vehicle base showed that the 2.5% concentration formulation reduced irritation by 33 percent.11 An in vitro percutaneous absorption study showed comparable bioavailability of the 2.5% BPO/clindamycin formulation to other marketed fixed-combination formulations with BPO 5%.11

BPO plus adapalene fixed combination. Also relatively new to the market is the fixed-dose combination gel containing adapalene 0.1% and benzoyl peroxide 2.5% (EpiDuo, Galderma). Recent data confirm the safety and efficacy of the combination gel in patients as young as 12 years old. A subgroup analysis looked at 2,453 patients aged 12-17 years, selected from three randomized, controlled trials. After 12 weeks of treatment, significantly more patients in the adapalene-BPO group were “clear” or “almost clear” (30.9 percent, p<0.001) compared to either monotherapy or vehicle. Subjects receiving the combination therapy had mean percentage reductions from baseline of 56, 63 and 54.5 percent, respectively, in total, inflammatory, and non-inflammatory lesions. These reductions were significantly higher than in the monotherapy groups and vehicle group (all p<0.001). Onset of effect from the combination gel was...
observed at week 1. Mean scores for dryness, erythema, scaling and stinging/burning for the combination treatment were less than 1 (mild) at all study visits.12

Another subgroup analysis of results from three randomized, double-blind, vehicle-controlled, clinical trials of adapalene/benzoyl peroxide assessed safety and efficacy in patients with darker skin tones. Researchers compared reports of erythema, scaling, dryness, and stinging/burning at week 1 in subjects with Fitzpatrick skin types I to III compared to reports in subjects with Fitzpatrick skin types IV to VI. Week 1 was the point at which cutaneous irritation scores were highest in all three trials.

There were no statistically significant differences in dryness, scaling, and stinging/burning with adapalene/benzoyl peroxide treatment between the two patient groups. Erythema assessments were statistically significantly lower for subjects with Fitzpatrick skin types IV to VI (rated as having "none" more often than those with Fitzpatrick skin types I to III (p<0.001)). Researchers suspect that assessment of erythema may have been more difficult in darker skin tones.13

The once-daily combination retinoid/BPO product is expected to improve adherence by simplifying the patient’s daily regimen; dermatologists had been prescribing combination therapy for some time, and a recent trial has confirmed the synergy of the two drugs. In the study, adapalene/BPO gel was significantly more efficacious than either monotherapy in decreasing lesion counts as early as week 1 and throughout the study (p<0.05).14

Clindamycin phosphate 1.2% and tretinoin 0.025% gel. The newest topical acne therapy on the market, clindamycin phosphate 1.2% and tretinoin 0.025% gel (Veltin, Stiefel, a GSK company) was approved late last year for the topical treatment of acne vulgaris in patients 12 years and older. The fixed combination water-based gel formulation is indicated for once-daily treatment. The two active ingredients are solubilized within the gel. In a phase 3 clinical trial including 1,649 patients, a significantly higher percentage of patients treated with clindamycin 1.2% and tretinoin 0.025% gel achieved a 2-grade improvement in the Investigator Static Global Assessment compared with tretinoin gel alone, clindamycin gel alone, and vehicle gel. The percentage of subjects who were assessed as “clear” or “almost clear” and had a 2-grade improvement was significantly higher in subjects receiving the combination gel compared with tretinoin gel, clindamycin gel, and vehicle gel.

Combination clindamycin/tretinoin gel was significantly more effective than tretinoin gel, clindamycin gel, and vehicle gel at reducing total acne lesions. It was also significantly more effective than tretinoin gel and vehicle gel at reducing the number of inflammatory acne lesions and was significantly more effective than clindamycin gel and vehicle gel at reducing the number of non-inflammatory acne lesions at 12 weeks.

Of note, combination gel treatment was no more effective than clindamycin gel alone at reducing the number of inflammatory acne lesions and no more effective than tretinoin gel alone at reducing the number of non-inflammatory acne lesions at 12 weeks.

Tretinoin microsphere gel. The tretinoin microsphere pump dispenser (Retin-A Micro Pump, 0.04%, 0.1%, Ortho Dermatologics) was designed to control dosing to minimize over-use of tretinoin and potential irritation. Studies show a high level of patient satisfaction with the dispenser since its debut a few years ago. The majority of adolescent patients (82.3 percent) in a trial rated the pump dispenser as an "excellent" or "very good" means of dispensing medication; 86 percent were "very" or "extremely satisfied" overall with the pump application.15

Recent data support the safety and efficacy of tretinoin microsphere 0.04% gel therapy in patients as young as eight. An analysis of data for patients age eight to 12 shows the efficacy of 12-weeks of tretinoin 0.04% microsphere gel therapy. The mean Evaluator’s Global Severity Score for treated patients decreased significantly from baseline to week 12 (2.6 vs 2.1; p<0.001). Three-quarters (75 percent) of subjects were graded as almost clear or mild. Treatment-associated adverse events were minimal.16

New data also suggest that patients may be able to apply topical tretinoin microsphere gel immediately following use of a BPO cleanser.17 Use of tretinoin at the same time as or in temporal proximity to benzoyl peroxide had been avoided historically due to concerns that BPO degrades tretinoin. It now appears
that microsphere encapsulation protects and stabilizes tretinoin, permitting a convenient, once-daily regimen of BPO cleanser plus tretinoin.

The randomized, investigator-blinded, 12-week, phase 4 trial assessed the non-inferiority of an once-daily morning combination regimen of 5% BPO wash plus tretinoin microsphere 0.04% gel pump compared to a sequential regimen (BPO in the morning/tretinoin in the evening) in patients 12 years of age or older with moderate facial acne. A total of 247 subjects (mean age: 18.5 years) were randomized to either regimen, which were found to have comparable tolerability. There was no statistically significant difference in therapeutic response between the two regimens.

**Tretinoin 0.05% gel.** A recently-published combined analysis of data from two clinical trials of a newer low-concentration formulation of tretinoin (Atralin Gel 0.05%, Coria Laboratories) in a hydrogel vehicle included a comparison of the 0.05% gel to 0.1% microsphere gel. While the efficacy rate of tretinoin gel 0.05% was approximately 12 percent less than tretinoin gel microsphere 0.1%, tolerability was markedly improved. Incidence of skin-related AEs in the tretinoin gel 0.05% group (31 percent) was significantly lower compared with the tretinoin gel microsphere 0.1% group (52 percent, p<0.001).

Adverse events in both groups were generally mild to moderate and rarely resulted in participant discontinuation.

**Topical dapsone 5% gel.** Now on the market for two years, topical dapsone gel 5% is primarily anti-inflammatory, notably decreasing inflammatory lesions as early as two weeks into therapy in clinical trials; a statistically significant reduction in inflammatory lesions versus placebo was evident at week 4.

Findings confirm that topical application of dapsone 5% is safe and effective in acne vulgaris. A review of pharmacokinetic and safety data in acne patients found that topical dapsone gel has a favorable short- and long-term safety profile and has been shown to have no risk of hemolytic anemia, including in G6PD deficient patients.

Some prescribers have questioned the safety of dapsone in patients with sulfonamide allergies because dapsone is structurally similar to sulfonamides. Dapsone is not a sulfonamide and no cross-reaction with sulfonamides has been demonstrated.

**Toward Individualized Regimens**

A growing body of research supports the clinically evident complexities of patient adherence in topical acne therapy. Prescribing topical therapies with good tolerability within simplified regimens is one way to encourage therapeutic adherence. Clinicians must keep up with the latest research on patient adherence as well as formulation developments and product data in order to individualize a successful topical regimen for each patient with mild to moderate acne.

Dr. Bikowski has served on the speaker’s bureau or advisory board or is a shareholder or consultant to Allergan, Coria, Galderma, Stiefel/GlaxoSmithKline, Intendis, M edics, Promius, Quinnova, Ranbaxy, and Warner-Chilcott.