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Optimizing Patient Adherence: Update on Combination Acne Therapy—Teens and Beyond

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Optimizing Patient Adherence: Update on Combination Acne Therapy—Teens and Beyond

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Statement of Need

According to the American Academy of Dermatology (AAD), a dermatologist is a physician who specializes in skin care. A dermatologist is singularly qualified to prevent, diagnose and treat a wide variety of benign and malignant skin conditions, including acne vulgaris.

Acne is a skin disease that is most commonly seen by dermatologists. The optimal treatment of acne requires dermatologists to apply both new scientific knowledge and skills learned in the everyday clinical practice.

Educational Objectives

At the conclusion of this CME activity, attendees will be able to:

- Identify the various topical agents and vehicles that target different aspects of acne pathogenesis.
- Compare the various topical agents and vehicles with patient compliance and long-term treatment efficacy, tolerability, and safety.
- Understand the clinical pharmacology including method of action for new topical fixed-dose combination therapies for the treatment of acne vulgaris.
- Recognize patient-centered approaches in acne therapy and their application in individual patient treatment outcomes.

Target Audience

This CME enduring material has been designed to meet the educational needs of Dermatology Physicians and Dermatology Residents.

Accreditation Statement

This activity has been planned and implemented in accordance with the essential areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the National Association for Continuing Education and the *Journal of Drugs in Dermatology*. The National Association for Continuing Education is accredited by the ACCME to provide Continuing Medical Education (CME) for physicians.

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DISCLOSURES

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Any real or apparent conflicts of interest have been addressed through a peer-review process, as required by ACCME.

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Optimizing Patient Adherence: Update on Combination Acne Therapy—Teens and Beyond

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ABSTRACT

Acne vulgaris can cause both physical and emotional scarring. Effective treatment requires an understanding of acne pathogenesis and the key elements of keratinocyte differentiation and comedone formation, sebum production, colonization with *Propionibacterium acnes* (*P. acnes*) and subsequent inflammation. Addressing issues of compliance is critical for good outcomes, and newer combination therapies help improve adherence to daily therapy.

INTRODUCTION

Acne vulgaris is a common and chronic skin condition that brings with it significant psychological and emotional distress.[1] While acne affects at least 80 percent of teenagers, it can occur at any age and negatively impact many aspects of one's life.[2] Topical retinoids are the foundation of successful acne vulgaris therapy, and newer formulations and products with multiple active ingredients are helping to increase treatment efficacy. Not only do these combination agents target more than one pathway in the acne pathophysiology, but they also help increase patient adherence to topical regimens—a critical component of successful management. In this review, the authors discuss the pathogenic targets of acne therapy, the benefits of newer agents available and tips for improving clinical outcomes and patient satisfaction.

Pathogenesis of Acne

Successful treatment of acne vulgaris begins with a good understanding of its pathogenesis. There are four primary factors that drive the formation and propagation of acne vulgaris: (1) aberrant keratinization and comedo formation; (2) androgens and sebum production; (3) colonization and proliferation of *Propionibacterium acnes* (*P. acnes*); and (4) the body's immune response. Effective medical therapy of this chronic skin disease should target as many factors as possible.

Abnormal proliferation and differentiation of keratinocytes promote the formation of comedones, which, in turn, stimulate inflammation. Eventually, these comedones may evolve into inflammatory papules and pustules. Topical retinoids are a mainstay in acne treatment and a first-choice for mild-to-moderate acne as well as an adjunct for moderate-to-severe acne or as maintenance. Retinoids and retinoid-containing combination agents target keratinocytes proliferation, thus halting the formation of comedones. Additionally, retinoids have anti-inflammatory effects that help to suppress the immune response in acne.

Another essential component of acne pathogenesis is sebum production. Around the time of puberty, circulating androgens begin to influence the composition and production of sebum. Sebum, which naturally inhibits some dermatophytes, acts as a food source for other organisms such as *P. acnes*. *P. acnes* break down the triglycerides in sebum to form glycerol and free fatty acids (FFA). The FFA, along with other cytokines, stimulate inflammation. Chemotactic factors that are byproducts of *P. acnes* metabolism of sebum attract neutrophils, which release lysosomal products that cause local tissue destruction and further inflammation. By targeting *P. acnes* via antimicrobial products, such as benzoyl peroxide, less sebum will be converted to glycerol and FFA, resulting in less inflammation.

It was commonly thought that the level of circulating androgens or amount of *P. acnes* colonizing the skin correlated directly with acne severity. While the *P. acnes* population in the skin is proportional to sebum production, it is not directly proportional to acne severity. The severity of a patient's acne appears to be related to how sensitive they are to the *P. acnes* rather than the quantity of colonizing bacteria, and that an immune hypersensitivity to *P. acnes* may be the cause of inflammatory acne.

Some patients may wonder if a particular food or diet is the cause of their acne. While foods do not cause acne, there is some evidence that a high glycemic and low protein diet may worsen existing acne. There is no evidence, however, that a particular food—such as chocolate—stimulates acne. While little evidence between food and acne exists, a well-balanced diet may do more for a patient's overall health and should continue to be encouraged.

Antibiotics in Acne Vulgaris

Antibiotics improve acne through two separate mechanisms. First, they can reduce the population of *P. acnes* in the skin, thereby decreasing a primary stimulant of acne pathogenesis. Second, some antibiotics function via direct anti-inflammatory pathways. They can inhibit the migration of neutrophils into the skin, inhibit proteases and inhibit the formation of granulomas. The best evidence for these anti-inflammatory actions has been demonstrated using tetracycline antibiotics.

In the treatment of acne, minocycline appears to be the most potent of the tetracyclines, followed by doxycycline and tetratcycline trailing by a distant third. Macrolides are less useful in acne treatment due to the increasing prevalence of resistance in *P. acnes* populations. To help reduce antibiotic resistance, all patients that are placed on antibiotics should also be given a benzoyl peroxide leave-ons or wash. If a topical antibiotic is chosen, it should be used in conjunction with a topical retinoid. The combination has synergistic effects by both increasing penetration of the antibiotic as well as having direct beneficial actions of the retinoid.[3]

Patient Adherence and Patient-centered Care

Acne treatments are only as effective as the amount by which a patient uses them. Noncompliance or nonadherence to treatment regimens can manifest in at least four different ways: (1) The patients do not fill the prescription. (2) The patients fill the prescription, but then do not use it. (3) They attempt to use the medication, but do not use it very well. If a patient never fills the prescription, he or she will not get the benefits from the medication. Even if a patient fills the prescription, they may not use it or use it properly. (4) Some patients get several prescriptions, then pick and choose one or two, either for convenience or because they believe one works better than another. Prescribing combination agents can increase compliance by reducing ability to pick and choose.

Standard methods for assessing adherence to medications include self-report diaries and blood levels. Unfortunately, these are inadequate at reporting accurate adherence levels. While physicians may like to believe what their patients tell them, many patients either do not tell the truth about their medication use or simply forget how much they actually used. While a blood level may tell us if the patient took the drug within the past day or two, it provides no information about whether or not they regularly took the drug between office visits.

A more accurate means of detecting adherence is electronic medication event monitors (or MEMS caps).[3,4] These monitors tell the physician the exact date and times that a patient opened his or her medication. While the application of electronic monitors may not be feasible in every clinical practice, their use in clinical trials has provided insight into possible ways to increase adherence in our patients with acne. When used in a clinic population, these monitors have illustrated just how poorly patients use medications in the "real world."[3] Furthermore, adherence to topical medication is particularly poor compared to oral medications.[5]

Many physicians have heard parents say, "Doc, I don't understand it. You always catch it on a 'good day.'" The reason acne is caught when it is less severe than normal is due to the patient's increased use of the medication the day or two before the office visit. Physicians now know that office visits help to drive compliance with medication, a term called "white-coat compliance." Doctors can enhance compliance and thus promote better outcomes by using judicious scheduling of return visits.

Patients' perceptions of medication efficacy likely impact their use of the medication. To provide a "proof of efficacy," physicians should focus on getting good adherence early in the course of treatment. By showing patients that the medication does in fact work if they use it, the patient will be more likely to trust their doctor and be more motivated to use the medication regularly over the long-term.

Some believe that patients are already motivated to use their medications regularly because of the psychologically distressing nature of acne. However, it has been learned from other diseases, including gonorrhea and psoriasis—both psychologically bothersome diseases—that patients do not necessarily use their medications.[6,7] One cannot assume that the patient will use the medication, and use it regularly, simply because they are bothered by their skin disease.

To help provide additional motivation, physicians may enlist the help of parents to remind their children to use the medications. However, this may be counterproductive. A recent study that randomized teenagers with acne to four intervention groups, including the use of "frequent office visits," "daily phone calls" or "daily parental reminders" versus no reminders. The group with the best adherence was the "frequent office visits" group. Interestingly, the "parental reminders" group had the worst adherence—even worse than having no additional reminder. Teens may see daily reminders from parents as "nagging," which may trigger them to do the opposite of whatever the parents say. This type of oppositional-defiant behavior is common in teenagers, a group particularly prone to poor medication adherence. At the initial office visit, it is important to identify who is more concerned about the acne—the patient or the parent. If it is the latter, poor adherence in the patient can be expected.

Establishing a good relationship with the patient is essential to having good outcomes. A prospective study showed that better

patient satisfaction at three days post visit predicted better outcomes at one month.[8] As part of a study on qualities of an office visit that influence patient satisfaction, communication, access, interpersonal skills and care coordination were all identified as critical components of the visit.[9]

If patients perceived that the physician was caring and took the time to listen to their problems, they were more likely to give a better score for the visit. One way to convey to patients that you are a caring physician is though education. Discussing different aspects of their disease in a way that the patient can understand will not only help with compliance, but also with your relationship with that patient. Clinical studies in atopic dermatitis (AD) patients have demonstrated that AD "school" helps improve patients' adherence and clinical outcomes.[10,11] The same is likely to be true for acne patients.

The use of written action plans has proven to be helpful at increasing medication compliance in a variety of diseases, and should also be employed in the management of acne.[12,13] Simply telling the patient to put the medication on his or her face each day may not be enough. A written hand-out that provides information about the patient's skin disease, what to expect from the medication and what to do if adverse effects occur may help patients better understand their disease as well as remember what the doctor explained in the office. Many times patients leave the office and simply forget what physicians told them. Some form of written brochure or action plan can serve as another form of reminder. Additionally, physicians can refer patients to support groups and websites to explore on their own in the event that a question arises down the road.

In creating a plan of action, physicians need to set realistic goals and time frames for patients so that they know what to expect. Every patient wants the instant fix. Unfortunately, acne vulgaris is a chronic condition that requires long-term therapy. Patients may be discouraged by the thought of never getting better or otherwise being on medication for the rest of their lives.

By setting milestones and using judiciously scheduled return visits, physicians can help create a "treatment horizon." The phrase "the light at the end of the tunnel" is frequently quoted in society, and clinicians need to create that light for their patients. If they believe or feel that the treatment is only temporary, they will be more inclined to use it. The shorter the duration of treatment, the better the compliance.

Simplifying treatment regimens can also help to increase patient adherence to the medication. As doses per day increase, compliance rapidly decreases.[14,15] In order to optimize efficacy of a topical treatment, while keeping the frequency of applications to a minimum, one should use combination therapies. New topical formulations that contain multiple active ingredients can help achieve this goal.

A topical antibiotic plus a topical retinoid is more efficacious than either alone. Phase 3 clinical trials demonstrate that a single application per day of clindamycin 1.2% plus tretinoin 0.025% in an aqueous gel is more efficacious than application of either component alone.[16] It is believed that a synergistic[3] action occurs due to increased penetration of the clindamycin into the follicle. However, benefits of using these two ingredients together in one product also include enhanced compliance with one versus two applications per day.[16]

Other combination topical products have hit the market, including benzoyl peroxide (BPO) plus clindamycin and benzoyl peroxide plus adapalene. With antibiotic resistance on the rise, the implementation of a BPO-containing product has become essential. The addition of the BPO helps to decrease selection for antibiotic resistance in *P. acnes*, and is more effective at eradicating *P. acnes* from the skin than clindamycin monotherapy.[17] Again, synergistic effects are seen in clinical trials that demonstrate greater efficacy of these combination products over either component alone.[18–20] By using BPO plus adapalene, one can eliminate the use of topical antibiotics all together and thus minimize the risk of antibiotic resistance.

Safety and the Benefit of Side Effects

Any medication given to patients can have potential adverse effects. Topical retinoids, the first choice for all types of acne, are not exceptions to this rule.[21] It is important to educate patients about the potential adverse effect of topical retinoids, which include local skin irritation, erythema, peeling, dryness and burning.[22] To help combat local irritation, a daily facial moisturizer can be used.[23] If minor adverse effects do occur, they can be used to the clinicians' advantage. Tell the patient that some mild skin discomfort is "a sign of the medication working." By giving a favorable way of looking at the adverse effects, patients may be less likely to discontinue the medication. Furthermore, patients may actually be encouraged to continue use of the medication because they can "feel it working," thus providing more proof of efficacy. It should also be mentioned to the patients, however, that anything other than local skin irritation should not be simply ignored.

Not all topical retinoids are created equal, and if a patient becomes too bothered by the adverse effects, switching to a more gentle formula would be prudent. The cumulative irritation of a retinoid depends on the concentration and formulation of the product. A study compared the tolerability of different formulations of topical retinoids and reported three groups of descending order of irritancy: 0.1% tretinoin cream and 0.05% tretinoin cream; 0.025% tretinoin gel, 0.01% tretinoin gel, and 0.025% tretinoin cream; and 0.1% adapalene gel and petrolatum (control).[22,24]

While concentration and vehicles play a role in skin irritation, a patient's skin type is not likely to be a major factor. A meta-analysis was performed using data from 468 patients who used tazarotene 0.1% gel or cream once daily for 12 weeks. No differences in skin irritation were found among different skin types, ethnicity or gender.[25] The topical retinoid appeared to be equally effective and well tolerated regardless of demographics. However, this does not mean that one drug should be prescribed for every patient.

A patient's preference for vehicle type is important when choosing a medication. Some patients prefer creams, while others like gels. Studies reveal a preference for less messy vehicles such as foams.[26] If a patient likes the way a medication feels, better adherence and outcomes are apt to follow.

Treatment Regimens for Various Levels of Severity

Case Report 1

A 12-year-old Caucasian male presents to the clinic with his mother complaining of greasy facial skin and bumps on his nose. He had never been treated by a physician for his acne and does not currently use any over the counter products. When the patient and his mother were asked how concerned they were about his acne, the boy replied 2 out of 10 (little concern), while his mother stated 10 out of 10 (very concerned).

Treatment options for this patient include a topical retinoid or a topical retinoid + benzoyl peroxide. Topical and oral antibiotics have not been shown to impact comedogenesis, and would not be the best choice in the absence of inflammatory lesions—the primary targets of antibiotics.

One could also suggest not treating the boy at this time. Given his disinterest in acne treatment, it is unlikely that he will bother to use the medications. Furthermore, given that the mother is very concerned over such a mild case of acne, one can imagine that she may attempt to frequently remind the boy to use these medications. As seen before from clinical trials, this frequent parental reminder may be counterproductive. Simply educating both the parent and patient about treatment options and the benign nature of mild acne would be a reasonable approach. When the boy is more interested in treating his acne, he could return to the clinic at that time.

Case Report 2

A 40-year-old African American woman presented seeking treatment for her acne. She had primarily comedonal lesions with some ice-pick scars. No inflammatory lesions were evident on exam. The patient was previously prescribed a topical retinoid, which she discontinued on her own claiming "it didn't work."

While a topical retinoid should be used for every acne patient who is not currently taking oral isotretinoin, this patient may require a bit more than a topical retinoid as monotherapy. The ice-pick scars indicate that either she had inflammatory lesions in the past and may get them again, or that she has subclinical inflammation that is causing scarring. With a background of inflammation or otherwise a tendency to scar, one should be more aggressive in treatment. Increasing the concentration of the retinoid in a stepwise fashion (i.e., from 0.1–0.3% for adapalene) as well as adding benzoyl peroxide would be prudent. Both have comedolytic activity needed for this patient, and also contain anti-inflammatory properties. One may also want to prescribe a topical antibiotic to maximize the anti-inflammatory potential of the regimen. To help minimize noncompliance with a multidrug regimen, one could use combination products such as adapalene + BPO or clindamycin + BPO.

Case Report 3

A 14-year-old girl with multiple papules, erythema and some scars on the face presented very distressed. She stated that she does not want to go to school because she was ashamed of her appearance. The girl reports that the acne began shortly after her first menstrual period a year and a half ago, and that she gets "flares" around the time of menstruation.

While the patient's acne appears to only be moderate in severity, the psychological impact may prompt a physician to be more aggressive and begin isotretinoin therapy. However, given that the acne appears to flare around the time of menstruation, an oral contraceptive (OCP) may prove effective. Along with a topical retinoid + BPO + antibiotic, the OCP may be enough to control her acne. Furthermore, if the time comes that the patient needs to go on isotretinoin, she will already be taking one form of birth control, fulfilling part of the federal requirements for isotretinoin therapy.

In addition to aggressive medical management, one should keep in mind the potential for body dysmorphic disorder in this patient. While dermatologists can readily treat acne and prevent physical scarring, emotional scarring may prompt a referral to a psychologist. It is important when evaluating any acne patient to inquire about mood and how much the skin disease is affecting his or her emotional status.

Case Report 4

A 15-year-old boy has had severe acne for a few years that has been unresponsive to oral minocycline. On exam, he had multiple inflammatory lesions, including several nodules on the face. His chest and back were clear. The patient stated that his acne was painful and he was willing to try anything.

This is a classic case of severe nodulocystic acne in which oral isotretinoin would be the treatment of choice. Attempting topicals alone would be inappropriate. Furthermore, given that he is still forming painful nodules during treatment with mi-

nocycline, it is unlikely that another oral antibiotic would be of much use. To help provide immediate pain relief, one could inject a few of the tender nodules with triamcinolone to help decrease the inflammation.

The length of treatment with oral isotretinoin is based on a cumulative target dose of 150 mg/kg, and is typically spread out over four to seven months. Approximately one third of patients treated with a course of isotretinoin will require a second course. There is no defined limit to the number of courses of isotretinoin therapy that a patient is able to get. However, one should wait at least four months in between courses, as the full effects of the isotretinoin may not be apparent until a few months after the final dose. Furthermore, residual or recurrent acne tends to be more responsive to both topical and other oral agents after a course of isotretinoin.

Since a course of isotretinoin lasts several months, it is not uncommon for some patients to have a surgical procedure for an unrelated medical condition at some point during their course of acne treatment. Currently, there is no evidence for isotretinoin causing delayed wound healing, and as such, it is unnecessary to stop the isotretinoin. If a patient needs surgery, do not delay it due to the patient being on isotretinoin.

CONCLUSION

Acne vulgaris is a chronic skin disease that can cause both physical and emotional scarring. Treatment should be tailored according to a patient's disease severity, vehicle preference and ability to comply with the regimen. Every patient with acne should be treated with a retinoid (either topical or oral isotretinoin). Unfortunately, adherence to topical therapy is very poor, and dermatologists need to address issues of adherence to ensure a good outcome. Simplifying treatment regimens via combination drugs (retinoid + BPO), using adverse effects of medication "as a sign the medication is working," and creating a treatment horizon through shorter-interval return visits will all help to increase adherence to therapy and promote better clinical results.

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ADDRESS FOR CORRESPONDENCE

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CME Post-Test: Please select your best answer for each of the following questions and insert into the Answer Grid found on the Evaluation/Certificate Request Form on the next page and **return along with your completed Evaluation/Certificate Request Form** to *JDD* by fax to (212) 213-5435, mail to 377 Park Avenue South, 6th Floor, New York, NY 10016, or to complete this activity online, please visit www.JDDonline.com in the Medical Education Library. Successful completion of the Post-Test is required to earn *AMA PRA Category 1 Credit*™.

1. Effective treatment of acne vulgaris requires an understanding of acne pathogenesis and:

   a. The key elements of keratinocyte differentiation.
   b. Comedone formation.
   c. Sebum production.
   d. Colonization with *Propionibacterium acnes* (*P. acnes*) and subsequent inflammation.
   e. All of the above.
   f. None of the above.

2. Noncompliance or nonadherence to acne vulgaris treatment regimens can manifest in the following way or ways:

   a. The patients do not fill the prescription.
   b. The patients fill the prescription but do not use it.
   c. The patients start or try to use the prescription but do not use it properly.
   d. All of the above.
   e. None of the above.

3. In the treatment of acne what medication appears to be the most potent of the tetracyclines?

   a. Doxycycline.
   b. Minocycline.
   c. Tetracycline.
   d. All of the above.
   e. None of the above.

4. A method (or methods) to assess adherence to acne medication is (or are):

   a. Self-report diaries.
   b. Blood levels.
   c. Electronic medication event monitors (MEMs).
   d. All of the above.
   e. None of the above.

5. To improve compliance with acne medications, a written hand-out should be provided that provides:

   a. Information about the patient's skin disease.
   b. What to expect from the medication.
   c. What to do if adverse events occur.
   d. All of the above.
   e. None of the above.

6. The main combination product(s) available for acne is (or are):

   a. Clindamycin 1.2% plus tretinoin 0.025%.
   b. Benzoyl peroxide (BPO) plus clindamycin.
   c. BPO plus adapalene.
   d. All of the above.
   e. None of the above.

7. The potential side effect(s) of topical retinoids for acne is (or are):

   a. Local skin irritation.
   b. Erythema.
   c. Peeling.
   d. Dryness.
   e. Burning.
   f. All of the above
   g. None of the above.

Evaluation/Certificate Request Form

Update on Combination Acne Therapy—Teens and Beyond

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this Evaluation/Certificate Form and return to *JDD* by fax to (212) 213-5435, mail to 377 Park Avenue South, 6th Floor, NY, NY 10016, or complete online at JDDonline.com in the Medical Education Library. ***You must complete and submit this form or complete the CME activity online to receive credit for completing this activity.***

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The content presented:

Was timely and will influence how I practice
1 2 3 4 5

Enhanced my current knowledge base
1 2 3 4 5

Addressed my most pressing questions
1 2 3 4 5

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1 2 3 4 5

Addressed competencies identified by my specialty
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Avoided commercial bias or influence
1 2 3 4 5

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Name one new strategy you learned as a result of completing this activity:

_____

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Please list any topics you would like to see addressed in future educational activities:

_____

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Additional comments about this activity:

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Name one thing you intend to change in your practice as a result of completing this activity:

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Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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