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Real World Strategies for Customizing Acne Regimens for Improved Outcomes

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EDITORIAL

ORIGINAL ARTICLES

REAL WORLD STRATEGIES FOR CUSTOMIZING ACNE REGIMENS FOR IMPROVED OUTCOMES

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Statement of Need

Acne affects most of the population at some point in their lives and is not subject to a specific age group, gender, or demographic. Adolescents continue to be the most widely affected by acne; however, almost 30% of all patients treated for acne are over 24 years of age. Over fifty-percent of adult women have experienced acne within their adult years. Providing optimal patient outcomes continues to be a challenge in the treatment and management of acne vulgaris. The availability of multiple treatment options for acne vulgaris increases the probability of effective therapy. It is important for clinicians to know what treatment options are effective in treating various levels of severity. The lack of extensive education on combination acne therapy in residency programs, coupled with the vast etiologic nature of acne and the changing role of antibiotics, creates a need to increase clinician knowledge in optimal acne management.

Educational Objectives

This activity is a multi-specialty, evidence-based initiative designed to increase the knowledge and competence of aesthetic practitioners by providing them with the simultaneous integration of knowledge, skills, and judgment from thought-leader testimonials, science-based research, and evidence-based data to address the difference between present patient outcomes and those considered achievable in the field of aesthetic medicine.

Upon completion of this activity, participants should be able to:

- Identify combination treatment options for various levels of acne severity, including severe as it relates to new, evidence-based research.
- Develop a customized treatment plan for various skin types and sequela.
- Define strategies for limiting antibiotic resistance in acne therapy.
- List evidence-based strategies for improving patient adherence and improved patient outcomes.

Target Audience

This activity is intended for dermatology physicians, residents, nurse practitioners, and physician assistants who treat patients with acne vulgaris.

Accreditation Statement

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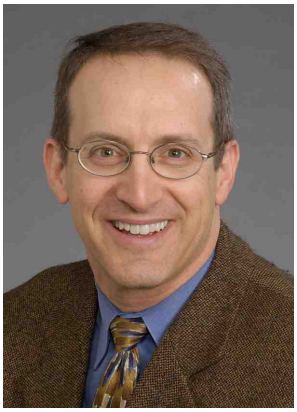
Customizing Acne Regimens for Optimal Outcomes



Steven R. Feldman MD PhD

Acne is the single most common disorder cared for in the dermatology clinic. A typical dermatologist will see hundreds of patients with acne every year, several every day. And yet, treating acne rarely seems rote, rarely cookie-cutter medicine. Developing a facility in tailoring acne treatment regimens is a critical aspect of medical dermatology.

Why isn't treating acne more like serving a standard burger at a fast food joint? Perhaps it is because of the multiple pathophysiologic elements—follicular hyperkeratinization, excess sebum, bacteria, and inflammation—involved in the disease. It may also be because patient co-morbidities need to be assessed and addressed. The very broad array of available treatments surely contributes. And, no doubt, patients' personalities and behaviors make acne treatment a rich, varied, and sometimes entertaining endeavor.

This supplement covers practical, real world strategies for customizing acne regimens to the patients' specific needs. To start, Dr. Linda Stein Gold presents information on topical retinoids and antibiotics and discusses the role of benzoyl peroxide. She presents data on the effectiveness of combination products, and the use of such products to maintain control of acne after initial treatment with oral antibiotics.

Dr. Joshua Zeichner describes the issues of acne treatment in specific populations. He begins with acne in pre-pubertal patients. The population of patients with pre-teen acne is growing. Dr. Zeichner presents data on the safety and effectiveness of topical acne treatments that have been tested in this population. He also describes the thorny issue of the relationship between treatments for acne and development of inflammatory bowel disease; he also provides specific advice on the management of acne in patients who already have inflammatory bowel disease.

What I find most fascinating about acne treatments is how poorly patients with acne use their topical medications, even when the acne bothers them. Teenagers are a trip! To get the most out of our treatments for acne, the psychology of the teenage mind needs to be considered. Both parent/patient and physician/patient relationships need to be considered. Simplifying treatment and encouraging use through the timing of office visits can be helpful. An intriguing use of surveys over the Internet also seem to provide a powerful means of enhancing teenagers' medication use.

Dermatology offers many opportunities for satisfaction, both for our patients and us. When we help teenagers control their acne, we can have a major impact on their self-esteem, an impact on their skin and psyche that may last a lifetime. Customizing acne treatments for our patients may not be cookie cutter medicine, but it is our bread and butter.

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Current Issues in the Topical Treatment of Acne

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ABSTRACT

Effective acne therapy involves targeting the pathogenic pathways. Most patients with mild to moderate acne can be managed with topical therapy. The key to successful therapy is to use combination treatments with complementary mechanisms of action. Steps to minimize bacterial resistance are important for long term therapy. Formulating an effective treatment plan focuses on efficacy, tolerability and ease of use.

J Drugs Dermatol. 2012;11(6)(suppl):s7-s9.

INTRODUCTION

The pathogenesis of acne vulgaris depends on four key processes, including abnormal epithelial desquamation in the follicle, excess sebum, the presence and activity of *Propionibacterium acnes*, and inflammation; these pathogenic processes are therapeutic targets.[1] Topical treatment options target all of these pathogenic pathways except for excess sebum production. Recent research into the pathogenesis of acne now suggests that inflammation is the initial step in the formation of the acne lesion.[2] Increased sebum levels lead to a relative decrease in linoleic acid levels. IL-1 levels are up-regulated and a subsequent increase in CD4+ lymphocytes and macrophages and the release of pro-inflammatory cytokines. This new information may explain why anti-inflammatory treatments have a beneficial effect on non-inflammatory acne lesions.

> "This new information may explain why anti-inflammatory treatments have a beneficial effect on non-inflammatory acne lesions."

Multiple options exist for the topical treatment of acne including retinoids, antibiotics and benzoyl peroxide. Topical retinoids have such as tretinoin, adapalene and tazarotene have both comedolytic and anti-inflammatory effects.[3] They have no direct effect on *P. acnes* but have been shown to potentiate follicular penetration when used with topical antibiotics. Topical retinoids also play a central role in the maintenance of remission.[4] Topical tretinoin was the first of the topical retinoids. Original vehicles had been associated with a flare in acne in the initial treatment stage.[5] Newer formulations are better tolerated and have improved stability with UV exposure or benzoyl peroxide.[6,7] Adapalene is stable with both light and benzoyl peroxide. The efficacy of the 0.1% gel is similar to tretinoin 0.025% gel with better tolerability compared to the 0.4% tretinoin microsphere and tazarotene 0.05% gel.[8-11] Adapalene 0.3% gel has been shown to have better efficacy than the 0.1% gel with tolerability comparable to tazarotene 0.05% cream.[12-13] Tazarotene 0.1% gel has been shown to be more effective than tretinoin 0.1% microsponge gel with similar tolerability.[14]

Clindamycin and erythromycin are the most commonly used topical antibiotics. They have antibacterial activity against *P. acnes* and some studies suggest that they also have anti-inflammatory properties.[5,15] They have been shown to have mild comedolytic activity as well. A growing problem with the use of antibiotics, including topical antibiotics, is the development of resistance. We have seen the efficacy of topical erythromycin decrease with time.[16] The Global Alliance on acne treatment has formulated guidelines to limit antibiotic resistance. They recommend that topical antibiotics be used in mild to moderate acne as long as they are combined with benzoyl peroxide. It is recommended that antibiotic use be limited and assess the response and continuing need at 6 and 12 weeks. Benzoyl peroxide, when used with topical antibiotics, reduces the development of antibacterial resistance.[1]

Benzoyl peroxide itself has antibacterial activity with the lack of *P. acnes* resistance.[17] It is effective against *P. acnes* that are resistant to other antibiotics. This has been shown for both the gel and the cleanser formulations.[18] In clinical trials it has demonstrated good efficacy in both inflammatory and non-inflammatory acne lesions.[17] Local skin irritation is the main side effect. Studies have shown that benzoyl peroxide has a similar efficacy in lower concentrations while providing better tolerability.[19] Formulating BPO as a microsponge delivery system and liposomal gel also reduces irritation. Controlled-release BPO also reduces skin irritation by reducing the rate of drug release and minimizing transdermal penetration.[15,20]

Topical dapsone is the newest of the topical agents. Clinical trials with the 5% gel show a significant reduction in inflammatory, non-inflammatory and total lesions in a 12-week trial.[21]

Topical dapsone 5% gel was shown to be safe and efficacious in a 12-month open label study.[22] It has also been shown to be safe in glucose-6-phosphate dehydrogenase-deficient and in sulfonamide allergic patients.[23]

Combination therapy increases the efficacy in acne treatment. Fixed combination products provide the convenience of duel therapy with a single application of drug. Clinical trials require the combinations drug to show statistically significant efficacy against not only the placebo, but also the individual active ingredients. Three fixed combinations of clindamycin and benzoyl peroxide currently are on the market. The first two utilized a 5% benzoyl peroxide with clindamycin phosphate 1%. Both of these products showed statically significant improvement in inflammatory lesion reduction and total lesion reduction as compared with 5% benzoyl peroxide, 1% clindamycin or vehicle.[24,25] In the clindamycin 1%/BPO 5% BID gel the reduction in comedos and the global improvements were similar between the combination agent and BPO.[24] The newest combination, clindamycin phosphate 1.2%/benzoyl peroxide 2.5% did show superior efficacy in the inflammatory, non-inflammatory and total number of acne lesions.[26]

Two combination products with clindamycin phosphate 1.2%/0.025% tretinoin gel have also been approved. The first of this combination showed superior efficacy in treating moderate to severe acne for all efficacy parameters measured.[27] The second similar combination utilizes a solubilizing water based gel vehicle.[28] This clindamycin phosphate 1.2%/0.025% tretinoin gel also was significantly more effective in the percentage of patients who achieved either clear or almost clear skin as well as a 2 grade improvement compared with tretinoin gel, clindamycin gel, and vehicle gel. Incorporating a benzoyl peroxide into the treatment regimen would minimize the risk of antibiotic resistance occurring.

Adapalene 0.1%/benzoyl peroxide 2.5% gel is the first fixed combination utilizing a retinoid and benzoyl peroxide. This combination also showed statistical significance in decreasing inflammatory and non-inflammatory acne lesions at 12 weeks.[29] A 12-month safety and efficacy study was also done.[30] Efficacy was seen as early as one week and continued through month 4. No decrease in efficacy was seen over the 12-month study period. Local skin irritation in these trials peaked at two weeks.

A combination study looked at patients with more severe acne who required oral antibiotics in addition to topical therapy.[31] Two consecutive randomized, double-blind controlled studies were undertaken lasting 12 and 24 weeks, respectively. In the initial study all patients were treated with oral doxycycline and either A/BPO or vehicle. Subjects who had at least a 50% improvement at 12 weeks were subsequently randomized to topical therapy alone with either A/BPO or vehicle as maintenance therapy for an additional 24 weeks. The patients treated with A/BPO and doxycycline as initial therapy followed by A/BPO as maintenance resulted in the highest efficacy and patient satisfaction compared to the other regimens. This regimen study provides evidence that effective control for severe, non-nodulocystic acne is possible with limited oral antibiotic use.

CONCLUSION

Topical therapy provides effective acne treatment for mild to moderate acne patients and is effective when used with oral antibiotics in patients with more severe acne. Treatment success depends upon tailoring the treatment regimen to the specific needs of the patient. Setting realistic expectations is essential in creating a trusting partnership between physician and patient.

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Acne Vulgaris: More Than Just a Cookie Cutter Treatment

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ABSTRACT

Certain populations of patients with acne are unique and should be given special consideration. Pre-pubertal patients and those with inflammatory bowel disease are two such groups. An appreciation of what sets these patients apart from the average acne patient can help optimize outcomes when treating them.

J Drugs Dermatol. 2012;11(6)(suppl):s10-s13.

INTRODUCTION

Acne vulgaris is one of the most common skin conditions seen by dermatologists, as over 40 million Americans are treated for acne each year.[1] The majority of patients can be treated effectively using combination therapy addressing multiple pathogenic factors. However, the treatment of acne is more than just a cookie-cutter algorithm. Certain populations of patients with acne are unique and should be given special consideration. Pre-pubertal patients and those with inflammatory bowel disease are two such groups. An appreciation of what sets these patients apart from the average acne patient can help optimize outcomes when treating them.

Acne Pre-Pubertal Patients

Pre-pubertal acne is defined as the development of acne in patients between 7–11 years old. Facial acne may be the presenting sign of puberty, as acne onset has been shown to correlate with adrenarche.[2] When the adrenal cortex matures during puberty, it begins to secrete androgens, such as DHEAS, which exert an effect on the skin. During this time, sebaceous glands enlarge and increase the production of sebum. Higher sebum levels support *P. acnes* colonization in the pilosebaceous unit.[3] The typical clinical presentation of pre-pubertal acne patients is with comedonal disease predominantly in the midface, such as the nose and forehead.[3]

Recognition of acne in pre-teens may help prevent severe disease later in life. A five-year, longitudinal study following over 800 girls showed that comedonal acne occurring before the teenage years was a reliable marker for the development of acne when the patients entered their teens.[4] Similar predictors, however, have not been found in studies of pre-teen boys. Treatment of acne early in its course can improve outcomes and minimize acne sequelae, such as permanent scarring.

Data suggests that patients are developing acne at a younger age than they did 30 years ago. The National Ambulatory Medical Care Survey is a nationally conducted survey of physicians in the United States. It is a large dataset that provides a broad representation of the U.S. population. Investigators tracked patients between 6 and 18 years old from 1979–2007 and reported trends in acne with respect to patient age, sex, and race.[5] Overall, the mean age of children presenting for acne treatment decreased from 15.8 years in 1979 to 15.0 years in 2007. There was no statistical difference in this age decrease with respect to sex of the patient. In terms of race, the age of Caucasian children presenting with acne decreased, while there was no decrease of age in African American children presenting for acne treatment. The patient population with the lowest mean age of acne treatment was African American girls at 14.37 years old, and highest mean age occurred in Caucasian boys at 15.6 years old.[5]

The development of acne earlier in life in adolescent girls has been shown to be associated with an earlier onset of puberty as well. A recent study evaluated 1239 girls, ages 6–8 years, in three large U.S. cities: New York City, Cincinnati, and San Francisco. Investigators evaluated patients for puberty onset, defined as Tanner Stage II breast development. Compared to data from 30 years ago, a higher percentage of Caucasian girls are entering puberty at 7–8 years old. On the other hand, no change was observed in African American girls. Earlier onset of puberty was also associated with a higher body mass index.[6]

The treatment of acne in pre-teens should be dictated by severity, as it should be in other age groups. Early intervention, especially in treating inflammatory lesions, is important to limit scarring potential. Both patients and parents should be educated that acne is a chronic disease and may require months to years of treatment. Moreover, treatment is important, as acne early in life may be a predictor for more severe disease in the future.[7,8]

As most cases of pre-teen acne are comedonal, topical treatments can be used as first line therapy. For mild acne, with few comedones clinically, topical benzoyl peroxide (BPO) alone may suffice. In cases of moderate to severe acne, where patients suffer from many comedone with occasional inflammatory lesions, topical BPO should be combined with a topical retinoid.[9]

The majority of topical acne medications are indicated for patients 12 years or older, however, most are used off-label for patients younger than the labeled indication. Micronized tretinoin 0.05% gel is labeled for treatment of acne vulgaris in patients 10 years of age or older.[10] In this medication, micronized tretinoin molecules are solubilized in an aqueous hydrogel vehicle, which contains moisturizing agents such as hyaluronic acid, collagen, and glycerin.

The safety and efficacy of two topical acne medications have been demonstrated in pre-teen acne patients. Adapalene (ADA) 0.1% / BPO 2.5% fixed dose combination gel has been investigated in pediatric patients. Boys and girls, ages 9–11 years old, with moderate facial acne applied ADA/BPO gel once daily in the evening. Two hundred and eighty five subjects were enrolled and randomized 1:1 to receive ADA/BPO or vehicle gel. The success rate (defined as >2 grades improvement of investigator global assessment score) after 12 weeks was 47.2% of patients using active medication compared to 15.4 % in the vehicle group ($P< 0.001$). Total lesion count reduction at week 12 was also statistically superior in the ADA/BPO group compared to vehicle ($P< 0.001$). The most common adverse event reported was skin burning, which was mild in most cases.[11] ADA/BPO is currently FDA approved for patients 12 years and older.[12]

The second medication evaluated in the pre-teen age group is tretinoin microsphere gel (TMG) 0.04%, which was studied in 40 boys and girls, ages 8–12 years old with mild to moderate facial acne. Patients applied the medication nightly for 12 weeks. TMG was found to be effective, safe, and well tolerated.[13] TMG is FDA approved for topical treatment of acne in patients 12 years and older.[14]

Systemic medications are not commonly needed in pre-pubertal acne patients, as disease is usually comedonal. Oral antibiotics should be prescribed in combination with topical therapies. In addition, as in any age group, antibiotic use should be limited to prevent the risk of bacterial resistance.[7,15] One special consideration for pre-teen patients is the risk associated with tetracycline antibiotics in young patients. Tetracyclines should not be given to patients under 8 years old because of the known risk for tooth and bone abnormalities.[7]

In cases where patients fail treatment after 3–4 months of therapy combining oral antibiotics with topicals, alternative systemic medications may be used. There are currently four oral contraceptives pills (OCPs) with FDA approval for the treatment of acne. While these pills are indicated for girls over 14 or 15 years old, they have been used off label in younger girls. Expert opinions recommend waiting to prescribe OCPs until at least one year after menarche. If the patient is not sexually active, a gynecological exam and Pap smear is not necessary.[9] Finally, the use of isotretinoin has not been studied in patients under 12 years old, however it has been used off-label in recalcitrant cases.[9]

Acne in Patients with Inflammatory Bowel Disease

There has been much recent media and legal attention on the association between acne treatments and inflammatory bowel disease (IBD). Special considerations should be taken when treating these patients because of possible associations of commonly used acne therapies with IBD.

"Special considerations should be taken when treating these patients because of possible associations of commonly used acne therapies with IBD."

Two large scale studies have evaluated the association of isotretinoin and IBD. The first of these is a 2009 study using the Canadian population epidemiology database that found no association between isotretinoin use and development of IBD.[16] Evaluating data from a universal healthcare system, investigators had access to a comprehensive database of cases and matched controls. All cases of isotretinoin use before an IBD diagnosis were included, without temporal constraints. The investigators found no statistical associations between cases who used isotretinoin before the IBD diagnosis, cases who used isotretinoin after the IBD diagnosis, or between the cases and control group (patients who used isotretinoin but did not have IBD). Finally, there was no statistical difference between patients who used isotretinoin before a Crohn's disease (CD) diagnosis compared to an ulcerative colitis (UC) diagnosis. In summary, no causal relationship was established between the diagnosis of IBD and isotretinoin use.[16]

A second large study found an association between the use of isotretinoin and the development of UC. This case-control study evaluated patients in a large U.S. insurance claims database. Approximately 8000 cases of IBD and 21,000 matched controls were included. Cases were limited to patients who took isotretinoin in the 12 months prior to their IBD diagnosis. In this study, investigators also looked at exposure and dose of isotretinoin.[17] UC was strongly associated with isotretinoin exposure. This risk was increased in patients on higher doses and longer exposure (>2 months) to isotretinoin. CD, on the hand, was not found to be associated with isotretinoin. While the absolute risk was found to be extremely small, in this study, UC but not CD was associated with previous isotretinoin exposure.[17]

While two large case-control studies offer different data, a small but real association between isotretinoin and UC may exist. Despite this relationship, there are several case reports in the literature documenting use of isotretinoin in IBD patients. Isotretinoin has been used successfully for the treatment of pyoderma faciale in patients with both CD[18] and UC.[19] Moreover, isotretinoin has been used to treat severe acne in patients with known IBD.

One case series of four patients reported two patients with no adverse events, one patient who developed rectal bleeding from hemorrhoids, and one patient who developed a CD flare while on treatment.[20] The relationship of the CD flare to isotretinoin is questionable as neither large scale study showed a relationship between isotretinoin and CD.

In November 2010, the American Academy of Dermatology published a position statement on the possible association of isotretinoin and IBD:[21]

"Current evidence is insufficient to prove either an association or a causal relationship between isotretinoin use and inflammatory bowel disease (IBD) in the general population. While some recent studies have suggested such a relationship further studies are required to conclusively determine if the association or causal relationship exists and/or whether IBD risk may be linked to the presence of severe acne itself."

"The Association concludes that the prescription of isotretinoin for severe nodular acne continues to be appropriate as long as prescribing physicians are aware of the issues related to isotretinoin use, including IBD or psychiatric disturbance, and educate their patients about these and other potential risks. Physicians also should monitor their patients for any indication of IBD and depressive symptoms."

Almost all patients who have taken isotretinoin have previously been prescribed oral antibiotics. So the question is raised whether there is also a link between oral antibiotics and IBD. Three retrospective, case-control studies have been performed outside the U.S. evaluating the use of oral antibiotics patients who have IBD. Possible associations have been made between several antibiotics with Crohn's disease, but not UC. It is important to note that these studies were not performed in patients treated for acne.[22]

One retrospective analysis of approximately 95,000 patients in the United Kingdom recently assessed antibiotic use in acne patients and its association with IBD. The investigators did find an association between the use of tetracycline class antibiotics and developing IBD; tetracycline and doxycycline, but not minocycline, were found to be associated with CD. However, none of the tetracycline class antibiotics were associated with UC. The study was limited by the fact that that no adjustments were made for acne severity, total amount of antibiotic administered, or patient adherence to medication regimens.[23]

While acne treatments such as isotretinoin and oral antibiotics have been associated with the development of IBD, these relationships remain unclear. One confounder is the fact that both acne and IBD are inflammatory conditions that frequently develop in the same population of patients and in the same age group. Severe forms of acne have been reported to be associated with IBD, independent of any therapy.[24] The question of whether these two inflammatory diseases are related remains to be answered.

Pseudomembranous colitis (PMC) is a rare, but well-documented complication of use of clindamycin. This adverse event may be especially problematic in patients with IBD. While PMC is usually associated with oral clindamycin, there are rare case reports of development of PMC after topical clindamycin application. Most of these cases have been associated with the use of clindamycin hydrochloride, which is absorbed to a greater extent than clindamycin phosphate.[25] Clindamycin phosphate is the form of clindamycin used in the currently FDA approved topical medications used to treat acne.

When treating acne patients with IBD, it is important to consider not only the disease itself, but also the society in which we live. It is impossible eliminate the television commercials advertising lawsuits against dermatologists because of adverse events from acne therapy. We live in a litigious society, so familiarity with current data and patient education are the key to treating these patients and protecting ourselves. If patients develop gastrointestinal symptoms during or after treatment, these symptoms must be taken seriously, and patients should be referred for evaluation by gastroenterologists. Moreover, while the risk is likely extremely low, regimens that avoid topical clindamycin may be appropriate for patients with IBD.

CONCLUSION

Not all patients with acne can be treated according to cookie-cutter algorithms. Two populations that deserve particular attention are pre-teen patients and patients with inflammatory bowel disease. Both acne and puberty are occurring earlier in life than they did 30 years ago. Pre-pubertal acne may be a predictor for teen acne in girls, and early intervention can minimize sequelae later in life. Acne therapy for pre-teens should be chosen based on severity, and clinical trial data exist for treating these patients. With respect to inflammatory bowel disease, isotretinoin may have an association with ulcerative colitis, but not Crohn's disease. This absolute risk, however, is low. In addition, oral antibiotics themselves may be associated with Crohn's disease. Finally, topical clindamycin has been reported to be rarely associated with pseudomembranous colitis. Familiarity with what sets these populations apart from other acne patients will allow practitioners to select appropriate treatment regimens and ultimately maximize outcomes.

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A Novel Approach to Increasing Patient Outcomes and Adherence

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ABSTRACT

Extensive research has led to greater understanding of the complex pathogenesis of acne. Based on our understanding of this pathogenesis, further research has led to the development of many individual treatments for acne, often used in combination in order to best address the multifactorial nature of the disease. The effectiveness of these treatments, however, is critically dependent on how well patients use the medicines. This presentation will first describe the typical ways patients use their treatments and then describe concrete approaches dermatologists can undertake to enhance patients' adherence behavior.

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INTRODUCTION

Extensive research has led to greater understanding of the complex pathogenesis of acne. Based on our understanding of this pathogenesis, further research has led to the development of many individual treatments for acne, often used in combination in order to best address the multifactorial nature of the disease. The effectiveness of these treatments, however, is critically dependent on how well patients use the medicines. This presentation will first describe the typical ways patients use their treatments and then describe concrete approaches dermatologists can undertake to enhance patients' adherence behavior.

Patients' Adherence Behaviors

The concept of adherence encompasses a complex array of processes.[1] First, patients have to procure the prescribed medicine. Getting the medication can be a hurdle for some patients. Patients may not start medication when expected. When patients do start treatment, they may use the medicine well or poorly during the period which they use the medicine. Moreover, they may stop using the medicine entirely before the end of the prescribed duration of the treatment.

One study done in Denmark used national pharmacy data to assess the first component of adherence to dermatologic treatments, whether patients obtain the drug from the pharmacy.[2] The study used the pharmacy database to determine how many days elapsed between the day the prescription was given to the patient until the prescription was filled. Of prescriptions for acne or infectious conditions, half the prescriptions were filled within a day of prescription, 80% within a week, and roughly 90% within two weeks of the office visit; about 10% of the prescriptions were not filled within four weeks of the day they were given to the patient. Prescriptions for atopic dermatitis were less likely to be filled with only about 60% to 70% of prescriptions filled within a month. Psoriasis prescriptions were the least likely to be filled with only about 20% filled within the day of the visit and only half of the prescriptions filled within one month.

Even when patients get a prescribed medication, they may not use the medication well. A feasibility study was done to assess the use of electronic monitors to determine the use of topical therapy in patients with psoriasis.[3] As part of a study of topical tacrolimus for psoriasis, patients were given 6% salicylic acid gel to increase penetration. The 6% salicylic acid was supplied in medication bottles fitted with caps containing electronic monitors; the monitors recorded each time the bottle was opened or closed. Subjects were told to apply the 6% salicylic acid gel twice a day, they were told they would be monitored, they were asked to complete a daily treatment diary, and they were asked to bring the bottles in to be weighed; the patients were not specifically told there were electronic devices in the caps recording the use of the medicine. Of the initial 10 patients in this feasibility study, only one used the medication exactly as described in the treatment diary. Two of the patients reported using the medicine about 80% of the time in their diaries but actually used the medication only about 20% or less of the time according to the computer chips in the medication bottle caps. Other patients showed varying degrees of adherence to treatment varying from 50% to 100%.

Further data from the 6% salicylic study showed that while patients generally reported using their medicine each day of the study in their treatment diaries, the actual use of the medication steadily declined over the eight-week study.[4] There were intermittent increases in use every two weeks during the study, coinciding with the days of the study visits.[5] This phenomenon of greater use around the time of visits has been termed "white coat compliance" or more colorfully as the "dental floss effect" (in recognition of how people tend to floss more frequently before they see the dentist). The timing of the office visit may be a powerful tool to encourage patients to use their medication.

In a similar study, electronic monitors were used to record the use of topical triamcinolone ointment in patients with atopic dermatitis.[6] Unlike the previous study, this study investigated

real life patients who were not told they were in a study nor were they told they were being monitored. Their use of the triamcinolone dropped by approximately 60% to 70% over just the first three days of the study. I believe that it is likely that apparent failure of topical corticosteroids in patients with atopic dermatitis is nearly always, if not universally, due to poor adherence to topical treatment.

A study investigating the use of a return visit to boost adherence in patients with atopic dermatitis looked at the use of 0.1% tacrolimus ointment twice daily in children with atopic dermatitis.[7] One group was told to apply the medicine twice daily and return in one month. The other group was told to use the medicine twice daily and to return in one month but also to return in one week during follow-up. Patients who were in the standard of care, one month return group used the medication at 54% of the recommended applications. Patients who were also given a one-week return visit used the medication at 77% of recommended doses. The return visit is a powerful inducer of patients' adherence behavior.

Adherence in Patients With Acne

It is perhaps not unexpected that teenagers with acne are not fully adherent to recommended topical acne regimens. A study using electronic monitors examined use of once daily benzoyl peroxide in teenagers with acne.[8] The average adherence over a six-week period ranged from 15% to just below 80%. None of the subjects in the trial achieved the 80% adherence level that is generally considered good adherence behavior. Subjects in the study generally used the medicine well for the first few days with adherence in the 70% to 90% range, but by the end of six weeks only about 3 in 10 subjects applied the medication on any given day.

The once a day adherence seen in the benzoyl peroxide study may overestimate acne patients' adherence because the multifactorial pathogenesis of acne requires using multiple treatments. The use of multiple treatments adds to the complexity of therapy and may contribute to poor adherence. A study investigated this by comparing patients' adherence with a once daily topical combination clindamycin/retinol product to separate application of a topical clindamycin product plus a separate topical tretinoin product.[9] There was a dramatic difference in the adherence behavior. Median adherence for the group using the combination product was over 80% after three months of treatment, while median adherence to the two separate products used in combination dropped below 20% at three months. Simplifying treatment regimens, including use of combination products, may be helpful in encouraging better adherence behavior.

Another study investigated ways of improving adherence in teenagers with acne. In this study, four groups of teenagers with acne were given adapalene 0.1% gel to apply once daily.[10] The product was provided in containers that included electronic monitors in the container caps. The first of the four groups was given return appointments at 6 and 12 weeks, consistent with usual practices of acne management. The medication use in this group dropped from 80% the first week down to 40% after three months of treatment. A second group received the same medicine but was also given return appointments at weeks 1, 2, 4, 6, 8, and 12. Better adherence was seen in this group, with adherence in the first week at 90%, dropping only to 60% by the end of three months. The third group of teenagers was called each day to remind them to use the medicine; adherence in this group differed little from the standard of care group that had just visits at weeks 6 and 12 without reminder calls; reminder calls seemed to have little impact on the teenagers' adherence behavior. In a fourth group, the teenagers parents were called on a daily basis and the parents were told to remind their child to use the medication; that group of teenagers used the medication *less* than all the other groups, with only 70% adherence at the first week, dropping to below 30% at week 12. Involving parents may not always be the best strategy for enhancing the adherence behavior in teenagers.

Tips for Enhancing Better Adherence

The fact of poor adherence should not make physicians throw their hands up in disgust or resignation. Doctors have considerable control over patients' adherence behavior. One of the most important things a physician can do in this regard is to establish a strong patient/physician relationship,[11,12] gaining patients' trust in their physicians and in their physician's recommendations. Establishing this trust reduces patients' fear of side effects and may make the patient more apt to use their medication in order to please their physicians. Involving patients in the choice of treatment is important as well. Patients have difference preferences.[13] Those preferences may differ considerably from physicians' preferences. Using treatments that the patient wants to use is more likely to result in use of the medicine than choosing treatments that the patient does not want to use.

Another way to encourage adherence is to give treatments that are fast acting. Patients who see treatment working initially are less likely to get frustrated and discontinue their treatment. An early return visit can also be used to make patients use their medicine well when they first start using the treatment. Getting them to use the medicine well in the early period results in better improvement in the disease than would otherwise occur, further encouraging the patient to continue to use the medication. Moreover, regular initial use of the medication may help the patient develop a routine, a regular pattern of use of the medication that will continue over the long run.[14]

Giving written instructions is also critical to treatment success. Patients have a propensity to forget the instructions given at the office visit. Things that are old news and simple for doctors to remember are new and can be quite complicated for patients to remember. While the patient may feel that they will remember what the doctor told them to do, by the time they get to the pharmacy or grocery

store, patients may have completely forgotten the doctor's instructions, or worse, remembered the opposite of what the doctor said.

A Novel Survey/Contest to Improve Adherence

Many of these suggestions for improving adherence require time and dedication from physicians. It would be helpful if there were ways of using technology to encourage better use of treatment. As described earlier, simple reminders may not be a particularly effective as a means to promote better adherence behaviors. If a technology could mimic some of the key physician interventions that result in better adherence—such as improving the physician/patient relationship, engendering trust, "the dental floss phenomenon," or other factors that encourage better use of medication—perhaps better adherence could be achieved. A study that was done investigating whether having patients participate in a survey of the progress of their acne would improve their use of medication.[15] This was a small, investigator blind, prospective, controlled trial of an Internet-based survey to improve adherence in adolescents with acne. The study enrolled teenagers aged 13–18 with mild to moderate acne. Patients were instructed to apply 5% benzoyl peroxide gel once daily. They were randomized to one of two groups. The control group was not surveyed, they were just told to return in 6 and 12 weeks; the intervention group was also told to return in 6 and 12 weeks but in addition were sent a link to a survey once a week to be performed over the internet. The survey consisted of just a single page and queried patients on factors that included frequency and ease of use, effectiveness and safety.

> "If a technology could mimic some of the key physician interventions that result in better adherence—such as improving the physician/patient relationship, engendering trust, 'the dental floss phenomenon,' or other factors that encourage better use of medication—perhaps better adherence could be achieved."

In order to encourage participation in the survey, subjects were entered in a contest to win an iPod Nano. If they completed 5 of 6 surveys, they received a $5 iTunes gift card. Prizes were awarded whether the patient used the medication or not. Use of the medication was assessed with electronic monitors in the medication caps. Acne severity was also graded using an acne global assessment scale and inflammatory and non-inflammatory lesion counts. Twenty-two subjects enrolled in this study, of whom 15 completed the trial, 8 in the control group, and 7 in the Internet survey group. Median adherence was 74% in the Internet group versus only 32% in the control group ($P<0.01$). In the control group there was a median of 66 days that the teenagers did not apply their medication with only 30 of those days in the Internet survey group ($P<0.01$). While the medication use was very good in the first week in both groups, adherence quickly dropped off in the control group: adherence was only 40% at week 6 and 20% at week 12. In the Internet survey group, adherence was a robust 90% at week 6, and still nearly 80% at week 12. Acne improved in both groups and while the absolute level of improvement was greater in the internet survey group, the difference was not statistically significant in this small study.

CONCLUSION

Adherence to treatments is one of the pillars—along with accurate diagnosis and correct treatment—successful dermatologic therapy.[14] Non-adherence is pervasive. Physicians need practical, cost effective and easily implemented means of improving adherence in order to obtain optimal treatment outcomes. Physicians have a great degree of control over their patients' adherence behavior. Establishing a strong physician/patient relationship, involving the patient in the choice of treatment, simplifying the treatment, addressing potential side effects, and shortening the time horizon to the next follow up visit are powerful tools to enhance patients' adherence to treatment. The Internet contest results are intriguing and suggest that perhaps other technological means can be developed that could prove to be practical, cost effective ways of improving treatment outcomes. This may be particularly true for our teenage patients with acne.

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1. Adapalene is inactivated by which of the following:
   a. Benzoyl peroxide
   b. UV light
   c. *P. acnes*
   d. None of the above

2. Which of the following statements about benzoyl peroxide is true?
   a. Effective against non-inflammatory lesions but not inflammatory lesions
   b. A preferred treatment for nodular acne
   c. Shown to prevent bacterial resistance to antibiotics when used in combination
   d. Treatment should be limited to 8-12 weeks

3. Which of the following statements about topical retinoids is true?
   a. Should not be used initially in acne due to possible flare
   b. Appropriate for treatment and maintenance acne therapy
   c. Effective as monotherapy for severe acne
   d. All of the above

4. Effective ways to minimize bacterial resistance include:
   a. Limiting monotherapy of topical antibiotics to 12 months
   b. Adding a topical antibiotic to oral antibiotic therapy
   c. Using Benzoyl peroxide in combination with antibiotics
   d. None of the above

5. The parents of acne patients often exclaim, "Doctor, it is so frustrating! You always catch the acne on a good day and don't get to see what it is usually like." Doctors tend to catch the acne on a good day because:
   a. The lighting is better in the doctor's office
   b. The severity of the acne is tied to the patient's menstrual cycle (in the case of male patients, to the sister's menstrual cycle)
   c. Patients tend to use their medications better before office visits
   d. The parents are confused and just think the acne is better

6. One of the best ways to encourage teenagers to use their acne medications is:
   a. Call them up every day to remind them
   b. Ask their parents to remind the patient every day
   c. Simplify the treatment regimen
   d. Add multiple medications to enhance penetration

7. A proven effective way to use the Internet to enhance adherence to acne treatment is to:
   a. Send the patient daily email reminders to use the medication
   b. Survey the patient once a week on how many times the medication was used, how well the medication is working, and any side effects that have occurred.
   c. Send the patient educational information showing how frequently teenagers don't use their medication
   d. Encourage parents to remind their child to use the medicine with daily email reminders

8. Pre-pubertal acne is characterized by all of the following except:
   a. Comedones on the forehead, nose, and chin
   b. Onset correlating the menarche
   c. A correlation between pre-pubertal acne and more severe acne in girls later in life
   d. Onset correlating with adrenarche

9. Recent epidemiologic studies on pre-pubertal acne suggest that:
   a. Acne is developing in children at a younger age than 30 years ago
   b. African-American children in particular are developing acne at a younger age
   c. Caucasian children in particular are developing acne at a younger age
   d. Both a & b
   e. Both a & c

10. In treating pre-pubertal patients with acne:
   a. Topical BPO plus a retinoid should be first line therapy
   b. Topical BPO plus a topical antibiotic should be first line therapy
   c. Combination therapy with topical BPO plus a retinoid along with oral antibiotics should be first line therapy
   d. Patients under 8 years old should not be prescribed oral tetracycline class antibiotics
   e. Both a & d

11. Two large, case-controlled studies have evaluated the correlation between isotretinoin and inflammatory bowel disease. Which of the following best summarizes their findings?
   a. A possible association between isotretinoin use and Crohn's disease but not ulcerative colitis in one study, and no as sociation in the other study
   b. A possible association between isotretinoin use and ulcerative colitis but not Crohn's disease in one study, and no association in the other study A possible association between isotretinoin use and both Crohn's disease and ulcerative colitis
   c. A possible association between isotretinoin use and ulcerative colitis but not Crohn's disease in both studies
   e. No association between isotretinoin use and ulcerative colitis or Crohn's disease in both studies

Evaluation Form

Real World Strategies for Customizing Acne Regimens for Improved Outcomes

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. There is no fee for this CME activity.*** You must earn a passing score of at least 70% and complete the activity evaluation form in order to complete the course and receive a certificate for *AMA PRA Category 1 Credits™*.

Request for Credit

Name		Degree	
Organization		Specialty	
Address			
City, State, ZIP			
Telephone		Fax	
Email			

Signature		Date		
I am registered on JDDonline.com	☐ Yes ☐ No	If yes:	User Name Password	

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10	11

☐ I certify my actual time spent to complete this educational activity to be: _____

☐ I participated in the entire activity and claim 1 *AMA PRA Category 1 Credits™*.

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree	2 = Disagree	3 = Neutral	4 = Agree	5 = Strongly Agree

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

Provided new ideas or information I expect to use
1 2 3 4 5

Addressed competencies identified by my specialty
1 2 3 4 5

Avoided commercial bias or influence
1 2 3 4 5

Impact of the Activity

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

_____

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

_____

Additional comments about this activity:

_____

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

_____

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