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# Scientific Proceedings From Select Sessions at the 2010 Orlando Dermatology Aesthetic & Clinical (ODAC) Conference

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## EDITORIAL



## ORIGINAL ARTICLES



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# Introduction

The 2010 Orlando Dermatology Aesthetic & Clinical (ODAC) conference that took place in January was a resounding success and a truly memorable event. This four-day conference drew 400 dermatologists to learn about the latest advances in medical, surgical and cosmetic dermatology. The faculty included familiar faces and new innovators and comprehensively covered both practical and theoretical topics. The conference itself is unique in its focus on resident education: scholarships to over 150 dermatology residents were provided to attend what has become one of the premier educational events in dermatology.

One of the keys to the success of ODAC is balance. Practical and theoretical issues, and all areas of dermatologic practice, are covered. Practice surveys released by the American Academy of Dermatology[1] reveal the typical dermatologist has a mixed practice with medical, surgical and cosmetic patients. The practice pattern of dermatologists in the U.S. has been stable and mostly unchanged in the 2005, 2007 and 2009 surveys. On average, dermatologists see 129 patients over 34 hours of patient care time in a four-day week. About 67 percent of patient care time is spent on medical dermatology, 25 percent on non-cosmetic surgical dermatology, and eight percent on cosmetic dermatology. While medical dermatology is the overwhelming majority of practice time, I think most dermatologists enjoy learning the latest techniques and innovations in all three areas.

In this issue of *JDD*, we have selected some of the most interesting presentations to serve as a template for the papers herein.

Medical dermatology is covered with two papers on acne by Drs. Fried and Kircik: one is a practical primer on optimizing acne therapy, while the other considers the psychosocial impact that acne may have. Acne is the number one reason for patients to see a dermatologist and therefore an important part of practice. Skin cancer is the focus of surgical dermatology, and a comprehensive article on "Actinic Keratoses: Past, Present and Future" provides information and perspective on this common problem that you may not have considered previously.

Lastly, the practical "how to," as well as the innovative and theoretical, are covered in two papers on cosmetic dermatology. First, Dr. Sachdev advises us on "Cosmeceuticals in Day-to-Day Clinical Practice". Fat melting and laser lipolysis is certainly the hottest topic in cosmetic dermatology right now, and Dr. Taub's presentation on "Laser Lipolysis With the 980 Diode Laser" brings us the latest in this rapidly evolving area.

We hope you enjoy these pearls from the 2010 ODAC conference and look forward to seeing you in Orlando in person next year.

James M. Spencer, MD, MS

[1]AADA Practice Profile Survey, 2009.

# Actinic Keratoses: Past, Present and Future

Neil Alan Fenske MD,[a] James Spencer MD,[b] Adam Friedman MD[c]

[a]University of South Florida College of Medicine, Tampa, FL
[b]Mount Sinai School of Medicine, New York, NY
[c]Division of Dermatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY

## ABSTRACT

Actinic keratoses (AKs) are cutaneous neoplasms composed of proliferations of cytologically aberrant, epidermal keratinocytes caused by prolonged exposure to ultraviolet radiation. Combining the evidence that AKs are the second most common reason for visits to the dermatologist and it is generally believed that they should be treated, it is no surprise that the direct cost of the management of actinic keratoses in the United States (U.S.) is exceedingly high. There are currently numerous treatment modalities with more on the way as there is a demand for formulating newer, cheaper, less painful and less invasive means. The future of AK treatment involves both the continued investigation of current novel therapies, as well as the development of new treatment modalities.

## INTRODUCTION

Actinic keratoses (AKs) are cutaneous neoplasms composed of proliferations of cytologically aberrant, epidermal keratinocytes caused by prolonged exposure to ultraviolet radiation. Although there has been some debate regarding their true nature,[1] it is generally believed that AKs are the initial lesions in a disease continuum that progresses to squamous cell carcinoma. Biologically, multiple mutations and ultimately attenuation of cell-cycle control are the key steps in the transition to malignancy.[2–5] Although multiple mutations are involved, such as in p16 and ras, it is believed that the primary alteration is consistently in the p53 protooncogene. In addition, ultraviolet (UV) damage and resulting immunosuppression collaborates with damaged cell cycle regulators to further facilitate growth and spread of the tumor.[6]

There are two important questions to contemplate when considering and evaluating the AK lesion. First, how frequently does a squamous cell carncinoma (SCC) arise from a pre-existing AK; and second, for a typical patient with several AKs, what is the chance of developing a SCC?

Fortunately, there are numerous investigations that have pursued these very questions. Marks et al. showed that approximately 60% of SCCs arose from AK lesions as well as that each AK has a 0.075% risk of transforming into a SCC per year.[7] In an earlier study, Marks et al. found an annual incidence rate of squamous cell carcinoma occurring in people with multiple actinic keratoses (average 7.7 lesions) to be 0.24% for each keratosis.[8] These findings have been extrapolated to suggest that over a 10-year period, a given individual with an average of approximately eight AKs has a 6–10% risk, respectively, of developing SCC.[8] Therefore the "6–10%" risk refers to a patient with multiple AKs, not the patient with the single lesion.

Overall, two points are evident. First, it is clear that the risk of developing a SCC increases considerably with and proportionally to an increasing number of AKs present on a given person per year.[10] Second and even more importantly, in the average patient with AKs, the very low yearly transformation rate for individual AKs translates into a substantial risk over a lifetime.[9,11] However, it has also been shown that up to 25% of all solar keratoses may remit spontaneously within 12 months and with reduced exposure to sunlight.[8] Putting this all together, the progression to SCC is probably less than commonly stated, but it is not zero. Therefore, these data suggest that therapy for skin cancer prevention is warranted.

### Actinic Keratoses: Conventional Treatment

Combining the evidence that AKs are the second most common reason for visits to the dermatologist, and it is generally believed that they should be treated, it is no surprise that the direct cost of the management of actinic keratoses in the United States (U.S.) is $1.2 billion.[12] The factors influencing how treatment should proceed may be determined by the following: (1) the medical status of the patient; (2) lesion characteristics (e.g., size, location, duration, changes in growth pattern of single, isolated lesions, suspicious lesions and plaques or diffuse lesions); (3) previous treatment; and (4) anatomic location.[13] Therefore, there are multiple treatment modalities as well as a demand for formulating newer, cheaper, less painful and less invasive means. The classic approaches have been based on lesion-targeted modalities. These include cryosurgery, photodynamic therapy (PDT) and electrodessication and curretage (ED&C).

*Cryosurgery*

Cryosurgery with liquid nitrogen is by far the most commonly used treatment.[14] It is fast and cost-effective, and often boasts a "99% cure rate."[15] However, is the touted cure rate accurate? In their 1982 paper, Lubritz et al. reported a 98.8% cure rate. Unfortunately, there are several issues undermining these data. The design was a retrospective follow-up study without any follow-up photographs. The minimum follow-up was at one year, with a maximum monitoring time of 8.5 years. The data were based on 1,018 lesions treated on only 70 patients. Treatments

varied lesionally both in technique and times, ranging form 20- to 45-second thaw times. Lastly, the associated adverse events were not reviewed. More recently, Thai et al.[16] demonstrated an overall cure rate of 67.2% through a prospective multi-center study. Their methods were more stringent, with single timed freeze/thaw cycles with 1–2 mm margin (freeze time defined as time from formation of an ice-ball to the commencement of thawing). They concluded that freezing times ranging from 10–15 seconds provided the optimal risk/benefit balance, the key for success being dependent on duration of freezing. Now, however, hypopigmentation was reported in 29% of the participants (related to freezing time).

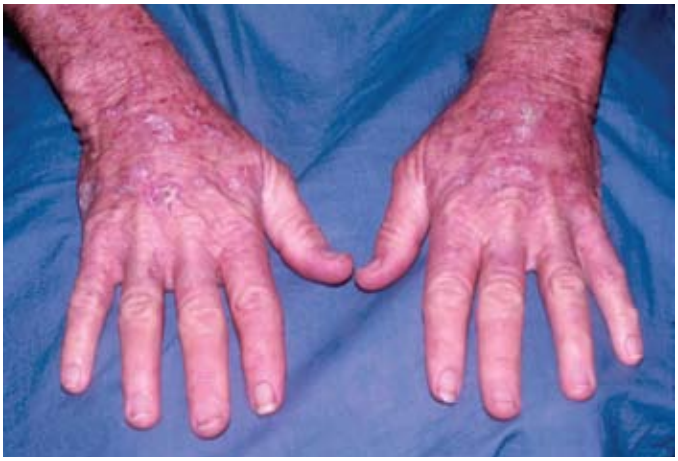
*PDT-Conventional (Levulan Kerastick®)*

PDT is a two-stage process that relies on using an endogenous photosensitizer as a means of destroying pre-cancerous epidermal cells. The photo-sensitizer is introduced in the form of topically applied 20% 5-aminolevulinic acid (ALA), which is absorbed in greater concentrations by highly metabolic, dysplastic cells. Photoactivation via exposure to Blu-U® light (417–432 nm) initiates the generation of destructive reactive oxygen intermediates, ultimately resulting in cell death. In one study, Levulan (5-aminolevulinic acid) 20% solution (Kerastick) was applied to each AK for 14–18 hours. Ten J/cm$^2$ of BLU-U blue light was subsequently delivered at 10 mW/cm$^2$ (1000 sec). Seventy-seven percent of patients completely responded by eight weeks post-treatment, and 89% by week 12.[17] These data have led to an approved indication for the treatment of AKs on the face and scalp.

## Actinic Keratoses: Rationale for "Field Directed" Therapies

Although the above modalities are considered effective treatment options by many dermatologists, disadvantages to ablative therapies have been observed for both AK and BCC (e.g., pain, infection, scarring). Ablative therapies for AKs typically target only individual lesions and do not address multiple subclinical AK lesions within a field of cancerization (i.e., sun-damaged skin) (Figure 1). Topical therapies may potentially reduce the incidence of pain and reduce the risk for infection and scarring as well as provide an opportunity to treat lesions in cosmetically sensitive or difficult-to-treat locations (e.g., face). Topical therapies may also be useful as pre/post treatment adjuncts in order to enhance the cosmetic outcome of invasive procedures as demonstrated with high-risk BCC, high-risk SCC, lentigo maligna, also known as Hutchinson's freckle (10–20% recurrence rate following surgery alone), extramammary Paget's disease (40% recurrence rate following surgery alone) and keloids (50% recurrence rate following surgery alone).[18] Therefore, although a number of physically destructive techniques are currently available, there is an important opportunity for nonablative, field therapy, provided treatment is efficacious and well tolerated.

**FIGURE 1.** "Field Cancerization": Lesions at different stages of evolution (AKs & SCCs) within the "field" of sun damaged skin.



*The Concept of "Field Cancerization"*

The concept of "field cancerization" was conceived by Slaughter et al. in 1944,[19] with the term introduced in 1953[20] as descriptive of histologically altered mucosa surrounding tumors removed from the upper GI tract. The definition changed to include an area which is clinically occult but has multifocal preneoplastic changes, showing genetic mutations, and which precedes the development of second primary tumors and local recurrences (Figure 1). The phenomenon has been described in oropharynx, esophagus, stomach, lung, colon, anus, cervix and bladder, as well as skin.

Several topical nonablative therapies have been investigated in the management of AKs and BCCs: (1) 5-fluorouracil is a chemical agent that inhibits DNA synthesis, prevents cell proliferation, causes necrosis and causes a subsequent inflammatory response at the treatment site; (2) imiquimod 5% cream is an immune response modifier that stimulates the body's own defense system to target diseased tissue. Its efficacy and safety in the treatment of external genital and perianal warts caused by human papillomavirus warranted further investigation of its utility in the management of other dermatologic conditions; and (3) diclofenac 3% gel is a nonsteroidal anti-inflammatory agent that inhibits the upregulation of the arachidonic acid cascade. In the FDA registration studies, patients treated with 5% 5-FU solution demonstrated 86% complete resolution of treated lesions and those treated with 0.5% 5-FU, 58% of patients experienced 100% clearing. With 5% imiquimod cream, 45% of patients demonstrated 100% clearing, and 47% of those treated with 3% diclofenac gel had 100% clearing.

It is clearly difficult to decide which avenue to pursue when choosing on of these therapies. In a head-to-head study comparing 5% imiquimod, 5% 5-FU and cryosurgery, Krawtchenko et al.[19] compared initial and 12-month clinical clearance, histological clearance and cosmetic outcomes

between these three modalities. The subject population included 75 Caucasian patients with 5–10 AKs/50 cm$^2$ on the head and neck. Subjects were randomized into three groups: (1) patients received cryotherapy consisting of a 20–40 sec spray (patients were treated again if lesion still present two weeks following the first treatment); (2) 5% 5-FU applied twice a day for four weeks; and (3) 5% imiquimod cream three times a week for four weeks (with some patients requiring two courses). The investigators concluded that the data suggested that imiquimod has a higher long-term efficacy and better cosmetic outcome. Although the initial clinical outcome pointed towards 5-FU as the more efficacious modality, histologic and sustained clearance rates where more impressive in the imiquimod treatment group. Imiquimod, unlike cryotherapy and 5-FU, stimulates the immune system to clear the cancer field of mutated keratinocytes, to which the results from this investigation can likely be attributed.

*Actinic Keratoses: Innovative Treatment Strategies*

In a world of ever-advancing medical technologies and creative approaches to current modalities, clinical investigators eager to develop new and better means to treat AKs. One such example has been coined "short contact" field therapy PDT.[21] Touma et al. applied 5-ALA to "broad area" for one, two or three hours followed by 10 J/cm$^2$ Blu-U light (as opposed to the FDA approved "spot treatment" with 12–14 hours incubation). Surprisingly, it was demonstrated that clearance rates were similar to those in the pivotal FDA studies (90% resolution target lesions at the one- and five-month follow-ups). They also noted improved cosmesis, and in the authors' opinions, "better tolerance" than with 5-FU.

A second example is termed "sequential therapy," which is based on the long lived principle that two is better then one. The following combinations have been investigated and have demonstrated enhanced efficacy in the treatment of AKs as compared to the use of a sole therapy: 0.5% 5-FU cream followed by cryotherapy;[22–24] cryotherapy followed by diclofenac;[25] and PDT followed by one-month post-treatment with imiquimod.[26]

## Actinic Keratoses: The Future

The future of AK treatment involves both the continued investigation of current novel therapies such as imiquimod and 5-FU as well as the development of new therapeutics.

*Imiquimod: What's Next*

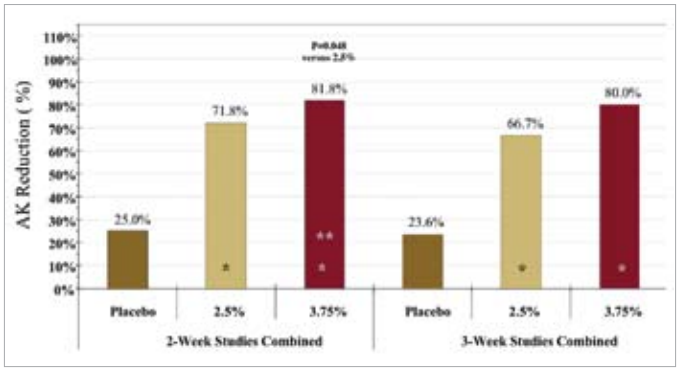
Currently, ongoing research under the heading of the "imiquimod development program" is seeking to optimize the use of imiquimod both with respect to efficacy and cost. Avenues being investigated include large treatments areas (full face or scalp >25 cm$^2$), shorter treatment regimens (four or six weeks), simple dosing regimens (once daily) and decreased concentration to enhance tolerability of daily dosing. There are two pairs of identical studies,[27] each pair evaluating a different treatment regimen and each individual study contains two investigational concentrations (2.5% and 3.75%). The study "rules" included voluntary rest periods of any length during treatment cycles, subjects kept to original study schedule irrespective of rest periods or missed doses, and subjects were to apply study drug in cycle 2 irrespective of clearance in cycle 1. The final evaluation was performed at eight weeks. It was found that imiquimod 2.5% and 3.75% were superior to placebo with respect to complete clearance, partial clearance and median lesion reduction (baseline and new AKs) (Figure 2). Increasing the cycle duration to three weeks did not increase efficacy. For the two-week cycles, imiquimod 3.75% was superior to 2.5% for partial clearance and median reduction in lesions. Imiquimod 3.75% administered daily as a two-week on/off/on regimen displayed the optimal benefit/risk ratio of the treatment regimens tested.

*Ingenol Mebutate Gel*

*Euphorbia peplus* is a common plant found worldwide, including our own yards and gardens. In the early 1800s, its sap was used topically to treat warts, corns and even skin cancers.[28] The active constituent is ingenol-3-angelate (dipertene ester), which has a dual mode of action: rapid removal of tumor via necrosis and prevention of the tumor relapse through immunologic mechanisms. Local necrosis[29] results from disruption of mitochondrial membrane and direct cellular cytotoxicity. Dipertene ester can induce an immune response[30] through several mechanisms such as activation of adhesion molecules (e.g., E-selectin),[31] recruitment of neutrophils via upregulation of IL-8, and the production of tumor-specific antibodies.

There have been several phase 2 and 3 (REGION trials) development trials of the generated product formerly known as PEP005. In one randomized double-blinded, vehicle-control phase 2 study involving various skin sites in 58 patients,[32] 71% lesion reduction and 67% "complete clearance" of four of five target lesions was observed using a concentration of 0.05%.

**FIGURE 2.** AK lesion reduction from baseline (median %).



Adverse events included local skin irritation (red, scaling, crusting). A second randomized, double blinded, vehicle-control study compared short dosing (two to three days) 0.025% and 0.05% gel in order to assess safety and efficacy. Similar results were noted with, once again, minimal side effects.[33]

*MAL PDT + Red Light-emitting Diode (630 nm)*

A new variation of PDT has been introduced. In a randomized, double-blinded, vehicle-control study spanning eight centers in the U.S.,[34] patients were randomized to treatment with two sessions of PDT using either 16.8% methyl-aminolevulinate (MAL) or vehicle cream one week apart. AKs were gently curetted to remove overlying scale/crust. Creams were applied and lesions were occluded for 2.5 to four hours, then washed off. Illumination with red light-emitting diode (LED) light (Aktilite CL 128, PhotoCure ASA) for eight minutes with a total light dose of 37 J/cm$^2$. The results demonstrated that MAL PDT using a red LED light source had response rates similar to double freeze-thaw cryosurgery and 5-FU and complete clearance rates similar to imiquimod 5% cream. Notably, the authors documented that there was an excellent cosmetic outcome. However, there is a need for further evidence in patients with larger numbers of lesions.

## CONCLUSION

Whether you believe actinic keratoses are precursors or variants of SCC, one fact prevails: AKs must be treated. There are numerous treatment modalities, all of which are valuable and have specific roles. Although cryosurgical destruction is still considered the "gold standard" for the treatment of discrete lesions, the concept of "field cancerization" should not be discounted and should continue to be a driving investigational foundation. All patients should be considered for "field treatment" as it can be a useful adjunct to lesion directed modalities like cryosurgery and ED&C.

## DISCLOSURES

Dr. Fenske is a consultant and speaker for Graceway Pharmaceuticals and a speaker for Sanofi-Aventis.

Dr. Spencer is an investigator for, and is on the advisory board for, Graceway Pharmaceuticals and Peplin. He is on the speakers' bureau for Pharmaderm.

Dr. Friedman has no relevant conflicts of disclose.

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## ADDRESS FOR CORRESPONDENCE

**Neil Alan Fenke, MD**
12901 Bruce B Downs Blvd, MDC 79
Tampa, FL 33612

# Psychosocial Sequelae Related to Acne: Looking Beyond the Physical

Richard Fried MD PhD[a] and Adam Friedman MD[b]

[a]Yardley Dermatology Associates, Yardley, PA
[b]Division of Dermatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY

## ABSTRACT

The emotional impact of acne is influenced by numerous factors including age, psychosocial factors, severity of disease, social and familial networks and patient specific personalities. Adolescents are an emotionally vulnerable population, and acne can significantly burden their psychological resources. Looking beyond the physical manifestations of acne can add valuable clinical information aiding clinicians in choosing the most beneficial treatment regimens. Patients at high risk for psychological and/or physical harm can in need of psychiatric referral can also be better recognized.

## INTRODUCTION

The emotional impact of acne is often influenced by numerous factors including age, psychosocial status, severity of disease, social and familial networks, and patient specific personality traits. Today, patients can easily access information, some of it inaccurate, regarding therapy and disease course and these same patients and other consumers are inundated with media messages depicting flawless, often airbrushed or soft-focus images, of beautiful skin. Society's modern preoccupation with blemish-free skin has exponentially intensified the fear and emotional disturbances associated with the burden of acne and skin diseases. Furthermore, the emergence and popularity of over-the-counter and internet-based "miracle cures" often delay access to legitimate and effective therapy. This often leads patients to become confused, angered and distrustful of approved or prescription therapies which require time, patience and compliance.

It is generally accepted that adolescents, who continue to represent the largest population of acne patients, are particularly vulnerable to these influences and ultimately the negative psychological effects. This susceptibility likely stems from the constant emotional and physical stresses associated with the rapid and impressive changes experienced during puberty, making adolescence a highly volatile period in a patient's life. Issues relating to self, beauty, dating, social and academic competence are confronted on a regular basis. Acne, which is both acutely and potentially disfiguring, often initiates or exacerbates feelings of low self-worth which can be perpetuated by hurtful comments and experiences of rejection from both social circles and significant others. These emotional torments can easily serve as the foundation for long-term psychological and functional consequences. Even more recently, this large, vulnerable subgroup has been joined by the quickly growing population of adult women with both continued or new-onset acne. These individuals bring a different dynamic to the potential damaging emotional sequelae as they are dealing with issues of motherhood, sexuality, career demands, and aging. As with the adolescent patient, acne can substantially impact and worsen the enormous stress that burdens women today. Furthermore and conversely, so too can supportive interactions and effective therapy be life altering and saving for these patients.

### Acne: The Many Faces We Treat

The clinical spectrum of acne vulgaris is extraordinarily diverse and requires a patient-specific approach. The term "pimple" so frequently used by patients does not do justice to the various morphologies ranging from comedonal to nodulocytic. Lighter skin phototypes often complain of "red zones," (Figure 1) or residual macular erythema, which often remains long after the acneiform lesion is gone. "Brown zones," or post-inflammatory pigment alteration are often more upsetting to skin of color patients then the acne itself. Scars even range from small indentations that are expected to improve with topical retinoids to disfiguring, large lesions that require procedural intervention (Figure 2). All of these findings can increase levels of anxiety and anger, as well as diminish feelings of self-worth. Often, the degree of anxiety and self-image impairment is directly related to the acne or physical aftermath severity,[1] however the extent to which patients can tolerate their disease varies greatly. It is clear though that degrees of anxiety, depression, anger and damaged self-image are found in all shapes and sizes of acne patients.[2]

### Acne and Emotions

Multiple studies have documented increased frustration and anxiety in acne patients as compared to controls,[3,4] as well as feelings of decreased self-worth.[5] It is clear that patients focus in on their acne as a major source of psychological distress.[6,7] In one study, depression and suicidal ideation was found in 7.2% of acne patients.[8] Interestingly, although stress is often a result of ongoing disease, many patients believe stress to be an etiological factor. Although the data supporting stress as an initiat-

ing feature of acne pathogenesis are somewhat anecdotal,[9] it is clear that there is a significant correlation between stress and ongoing acne severity.[10]

Fortunately, current data suggest that effective treatment of acne can reverse some of the associated emotional and psychological sequelae.[1,11] Not surprisingly, patients who experience the greatest reduction in emotional distress are those who achieve the greatest clinical improvement.[12] Therefore, providing immediate, aggressive and, of course, effective clinical intervention should be considered mandatory in order to improve and maintain psychological well-being. In fact, a new breed of litigators have directed their focus to dermatologists who do not act aggressively enough to prevent the disfiguring changes associated with acne.

## Acne Vulgaris: Psychological Issues Impacting Adolescents

Given that acne causes emotional suffering and emotional suffering causes increased stress (which in turn increases the severity of acne), a negative impact on social and academic is to be expected. One study demonstrated that acne interferes with social interactions such as dating, eating out and participation in sports in both school-age and older patients.[13] A second study documented diminished academic achievement in patients with severe acne.[14] These findings are not surprising seeing that adolescence is a time during which self and body image are forming and constantly being challenged. Modern society has cultivated a sense of immediate gratification, the "fast food" mentality that is easily translated to all areas of life including acne therapy. Combined with the adolescent's poor tolerance of frustration as well as issues with therapy compliance often stemming from the perception that following directions is an affront to autonomy, effective and aggressive acne treatment can be a challenge, although it is absolutely needed.

## Issues Facing Adult Acne Patients

Acne in adults can be divided into three categories: (1) patients who have continued to suffer from acne since adolescents; (2) patients who experienced a remission from their adolescent acne symptoms but have in adulthood recurred; and (3) patients who have never suffered from acne as adolescents and now have new onset acne vulgaris. The final group often has the most difficulty emotionally as these patients never expected that acne would be part of the repertoire to battle in association with aging. All three groups suffer to varying degrees from the various emotional manifestations of acne as experienced by their adolescent counterparts including anger, anguish, depression, introversion and frustration.

Adult acne patients, specifically women, must juggle these feelings in a different forum then adolescents, now having also to deal with the stresses of motherhood, sexuality, career demands and, as mentioned above, aging. Studies have documented that adults with acne demonstrate decreased participation in social activities such as dating and sports, as well as have significantly higher unemployment rates.[15] In light of this documented potential for both psychosocial and even vocational impairment, an understanding of and insistent approach to these patients must be undertaken in order to help the patient achieve and maintain a productive status in society.

## Good Acne Doctors

The "good acne doctor" is one who is not only directed by evidence-based medicine, but appreciates the emotional impact on the patient—one who recognizes the severity of the condition both medically and socially. It must be recognized that patients fear a broad spectrum of potential abandonment from friends, jobs and significant others. Herein lies the urgency to not necessarily correct the disease, but partner with the patient. Over-the-counter product (OTC) advertisements often provide a false sense of security and efficacy, often creating a critical element of time during which the patients believe their clinician must improve them or else the clinician has failed them, like their own bodies have failed them. This expectation can scare many dermatologists, as unrealistic expectations can translate into bad press for the physician when the hopeful but unrealistic patient does not achieve the anticipated result. The key to avoiding disappointment on both fronts is through addressing ownership—ownership of the disease and the responsibility to correct said disease. These patients have come to the derma-

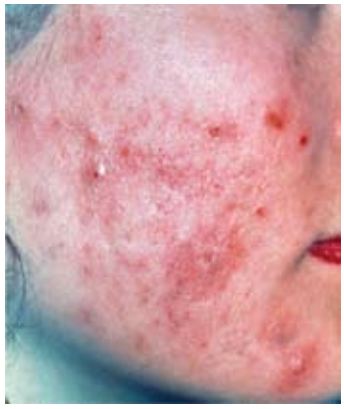

**FIGURE 1.** Patients with lighter skin phototypes complain of "red zones," which often remain long after acneiform lesions are gone.

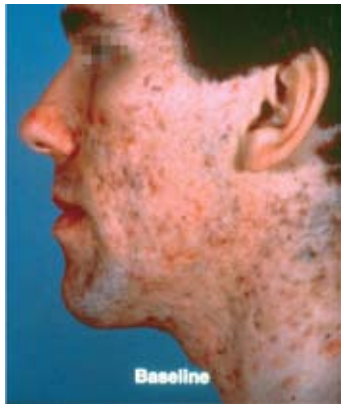


**FIGURE 2.** Acne scarring can range from small indentations to large lesions, and can often be a source of stress, body image issues and decreased self-worth.

tologist to have "us" fix their skin. By transferring ownership to the patient partially, it is not just the dermatologist's fault if and when the patient does not improve. It is rather a partnership, with physician and patient working together to tackle the altered cutaneous biology that initially caused the acne to arrive at satisfactory endpoint.

It is equally as important for the "good acne doctor" to recognize when patients are in danger or appear to be in a downward emotional/psychological spiral. Certain clinical nuances are helpful in uncovering and potentially preventing these potential disasters from the expected response to diseased skin. Once again, the importance of the physician establishing rapport with the patient is paramount. The physician must be observant of affective and behavioral clues during the patient history and exam. The high-risk patient often has impairments in basic communication and interpersonal skills, dysfunctional in family interactions, worsening or new onset of academic difficulties as well as declining social and/or vocational functioning. During the patient interview, manifestations of these features may appear as poor eye contact, limited speech, angry or belligerent remarks/outbursts, poor personal hygiene, damaging compulsive behaviors, verbal self depreciation, noted new or increased drug or alcohol use and recent changes in social networks/circles group.[16] Identification of these high-risk patients is as important as treating the skin disease, or even more so in some respects. Recognition of danger signs should become an integral part of the dermatologist-patient experience. Appropriate interventions can be life-altering and even life-saving in high-risk patients, averting potentially catastrophic emotional, functional and cutaneous damage.

## DISCLOSURES

Drs. Fried and Friedman have no relevant conflicts of interest to diclose.

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## ADDRESS FOR CORRESPONDENCE

**Richard G. Fried, MD, PhD**
903 Floral Vale Boulevard
Yardley PA 19067
E-mail: Dermshrink@gmail.com

# Optimizing Acne Therapy With Unique Vehicles

Leon Kircik MD[a] and Adam Friedman MD[b]

[a]Indiana University, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY
[b]Division of Dermatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY

## ABSTRACT

The science of cutaneous drug delivery is focused on overcoming the major force of resistance to drug penetration and permeation—the stratum corneum. Acne vulgaris is a multifactorial disease of the pilosebaceous unit, resulting from abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation and inflammation. Topical treatment of even mild-moderate acne requires combination topical therapy, yet often systemic therapy is needed to ultimately confer an acceptable clinical endpoint. New delivery systems have emerged in response to the limited routes of entry and therefore efficacy of topical regimens. The unique physical and optical properties of micro/nano encapsulation of known therapeutics such as benzoyl peroxide and tretinoin allow for both improved efficacy while minimizing issues of compliance and adverse events. Vehicles that offer both inherent biological reactivity and permeation enhancement have also been shown improvement over the current armament of topical drug delivery. This current and exciting path of topical drug development will likely be continued with investigative vigor.

## INTRODUCTION

The stratum corneum is arduous impediment to topical drug delivery, making localized therapy a challenge. The hydrophobic barrier of stratum corneum, the "brick and mortar" of the epidermis, places special demands on compounds intended for this unique target. The impenetrability of stratum corneum is in part due to the insoluble nature of corneocytes—a state resulting from extensive cross linking of both the cell envelope and intracellular proteins.[1] Most topical drugs cannot cannot even bypass this outer barrier, let alone pass from one epidermal layer to the next. However, both the active ingredient and/or solvent can be altered to enhance delivery to the target site.[2]

To further understand the complexities of topical drug delivery, several key terms need defining as they are often used interchangeably. First, penetration refers to the entry of into a particular skin layer, whereas permeation refers to a compound moving from one skin layer to another. Absorption, a term often used to describe various avenues of therapeutic uptake, actually is defined by the topically applied drug being taken up by blood vessels in the skin in order to enter systemic circulation.[1] However, systemic absorption is usually not the intended endpoint, rather topical therapy is generally used by the physician to provide high local impact without the potential side effects associated with, for example, an injectable or oral route of administration.

### Structure and Function of the Skin

The skin is an extraordinary organ, serving numerous functions ranging from barrier protection to overseer of fluid/electrolyte homeostasis.[3] The skin is divided into three distinct yet intertwined levels: epidermis, dermis and panniculus. The epidermis is composed of stratified, squamous keratinizing epithelium, which gives rise not only to the outermost protective layer, the stratum corneum, but also is the source of several key cutaneous structures such as the pilosebaceous units, the nails and sweat glands. The stratum corneum can be considered the gatekeeper with respect to permeation of compounds into the body. The stratum corneum consists of the anucleate, fully keratinized corneocytes glued together by various epidermal lipid components, which provides for the "brick and mortar" analogy.[4] With this in mind, it is easy then to appreciate that topical therapy is literally coming up against a brick wall.

With respect to penetration, transport of topically applied materials occurs across the stratum corneum in largely passive diffusion and is reliant on the physiochemical properties of the permeating agent.[5] There are two major routes through which this diffusion across the skin can occur. The first is transappendageal, relying of the natural imperfections in skin integrity associated with hair follicles, and sweat glands. These openings can potentially allow topicals to bypass the low diffusivity of the stratum corneum.[6] Furthermore, this route may aid in the delivery of charged ions and large polar molecules that generally are slow to permeate through the stratum corneum. Ultimately, the choice of vehicle will affect its ability to utilize transfollicular penetration. The second pathway is through the epidermis itself, and is subdivided into two potential avenues, transcellular and intercellular.[4] Hydrophilic compounds are likely to flow through the transcellular route, while lipophilic materials are preferential for the more round about intercellular route. It is believed that the latter pathway is the predominant route of entry for most topical therapies.[7] Unfortunately, this pathway also serves as an impressive impediment for therapeutics intended for topical delivery.

### Topical Acne Therapy: Breaking Through the Wall

Acne vulgaris is a multifactorial disease of the pilosebaceous unit, resulting from abnormalities in sebum production, folli-

cular epithelial desquamation, bacterial proliferation and inflammation. The major classes of therapeutic agents are topical and systemic retinoids, antimicrobial agents and systemic hormonal drugs. Most dermatologists rely on a combination of topical therapies, or topicals with systemic therapies to treat acne, as no single topical acne therapy is effective in addressing all of the etiologic factors. Even with the combination of a retinoid with benzoyl peroxide (BPO), together attacking likely all four of the pathogenic features of acne, penetration of said products can limit efficacy. Strides have been taken to enhance the current armament of topical therapies through novel delivery vehicles.

*Benzoyl Peroxide (BPO)*

BPO is an organic compound in the organic peroxide family. It consists of two benzoyl groups joined by a peroxide group, with a structural formula of $[C_6H_5C(O)]_2O_2$. It is a lipophilic material, which serves as a boon, as it can localize in the lipid rich sebaceous follicles. Current BPO formulations are emulsions, which unfortunately have some limitations. These micronized solid particles, ranging from 5–1000 µm in size, are fairly large particles with poor solubility, ultimately resulting in diminished chemical activity. These formulations lack homogeneity in terms of consistency of the dissolution of particles throughout the formulation, and contain large clusters of BPO, providing for poor penetration and unsightly cosmesis following application. On electron microscopy the surface of the skin after application of a generic current BPO emulsion demonstrated poor penetration and extensive residual product on the skin surface.

*Benzoyl Peroxide (BPO) – New Vehicular Formulations*

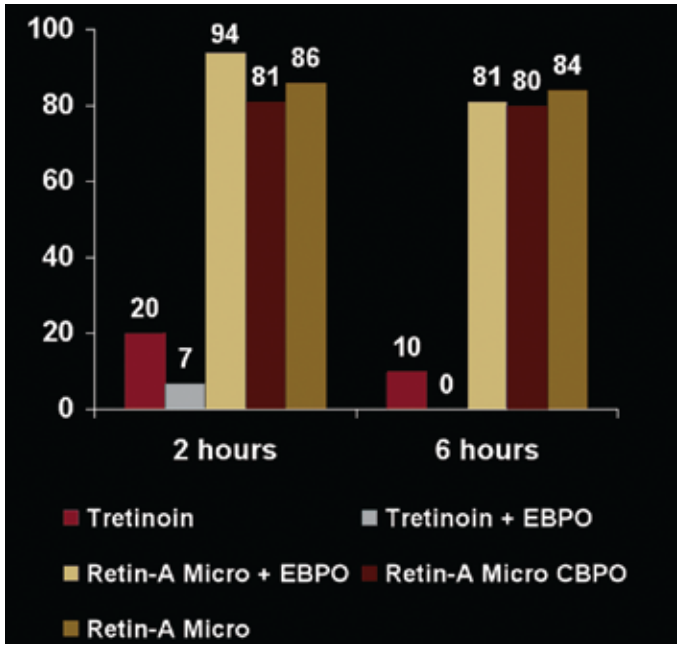
In order to combat this deficiency, solubilized BPO has been formulated, providing solid individual BPO molecules (~$10^{-4}$ µm) in solution. Solubilization is a chemical process which occurs before the BPO is incorporated into final product. This solubilized BPO formulation has both lipophilic and hydrophilic attributes, which aim to enhance penetration into the follicle and dissolve in sebaceous secretions.

A second direction involves encapsulation of BPO in a Microsponge® delivery technology, designed to reduce irritation associated with this active ingredient. Microsponge technology has been used in the past to successfully deliver topical treatments, such as Retin-A Micro® and EpiQuin® Micro. In one study, it was demonstrated that BPO encapsulation in microsponges maximized the amount of time an active ingredient was present on skin surface or within epidermis with minimal penetration of active ingredients through the dermis.[8] This delivery system was also shown to enhance safety profiles by reducing irritancy potential while maintaining efficacy and extending product stability. Improved product aesthetic properties were also noted by the investigators.

Taking this a step further, the success of the applies BPO Microsponge® delivery system was investigated as a "wash-off" rinse. Clearly, a product such as this would only be relevant if the product displays substantivity—meaning it remains on the skin after rinsing. The persistence of effect is determined by the degree of physical and chemical bonding to the surface. Via confocal microscopy imaging, it was shown that wet skin areas treated with microsponge wash for 10–20 seconds then washed and dried had retained product within the follicular ostia. It was also found that this technology lived up to the name "sponge," as the particles absorbed twice their own weight in sebum substrate. Recall in acne, there is an increase in sebum production from the multi-lobular sebaceous follicle. This excess sebum production can be due to a change in the response of the pilosebaceous follicle to androgen stimulation, increased androgen circulation, or to both in combination.[9] One of the interesting features of the microsponge polymeric porous particles is that, as they deliver the active ingredient, they in turn absorb excess surface sebum from the skin. In head-to-head comparisons, microsponge outperformed other conventional cosmetic ingredients used as oil absorbers for sebum.

As mentioned early, combination therapies have been the mainstay of topical therapy in order to address all pathogenic features of acne. So too can combination therapy be pursued to optimize the physical state of active ingredients in the formulation. Lower concentrations of potentially irritating active ingredients can be used when incorporating a compatible moisturizing and drug delivery optimizing agent. For example, combinations of clindamycin and BPO have been inves-

**FIGURE 1.** Tretinoin micro is stable alone and in combination after UV light exposure.



tigated.[10,11] Clindamycin/BPO fixed combination gel formulations were evaluated in a 21-day cumulative irritation study. This single-center, evaluator-blind phase 1 study in 35 healthy human volunteers assessed the cumulative irritation potential of formulations containing clindamycin phosphate 1.2% (CP) in combination with different concentrations of BPO. Test formulations (5% BPO/1% CP, 2.5% BPO/1% CP and 1% BPO/1% CP) were applied under separate occlusive patches on the backs of subjects three times a week for three weeks. Sodium lauryl sulfate 0.3% was used a positive control. Each test application site was observed 48 hours (72 hours on weekends) post-application for signs of irritation or inflammation (a total of nine evaluations). Assessment of skin irritancy was on a scale of 0 (no sign of irritation) to 4 (erythema with edema and blistering). A total irritation score for each subject and formulation was calculated by summing each of the subject's scores on each of the nine evaluation days. The mean cumulative irritation score for each test formulation was calculated as the sum of all subject's total irritation scores for a test formulation divided by 297 (nine evaluations x 33 subjects evaluated).

Based upon the total irritation scores, all of these formulations were classified as slightly irritating under the occlusive test conditions. There was a 33% decrease in mean score the concentration of BPO from 5–2.5%. The benefits of further reducing the BPO concentration to 1% were surprisingly minimal. Overall, cumulative irritation scores increased in a dose-dependent manner with increasing benzoyl peroxide concentration, which is hardly surprising as this was described over 30 years prior.[12] Therefore, it is clear that the development of delivery vehicles aimed at increasing penetration while decreasing irritation will continue to be the focus of novel acne therapies.

*Tretinoin*

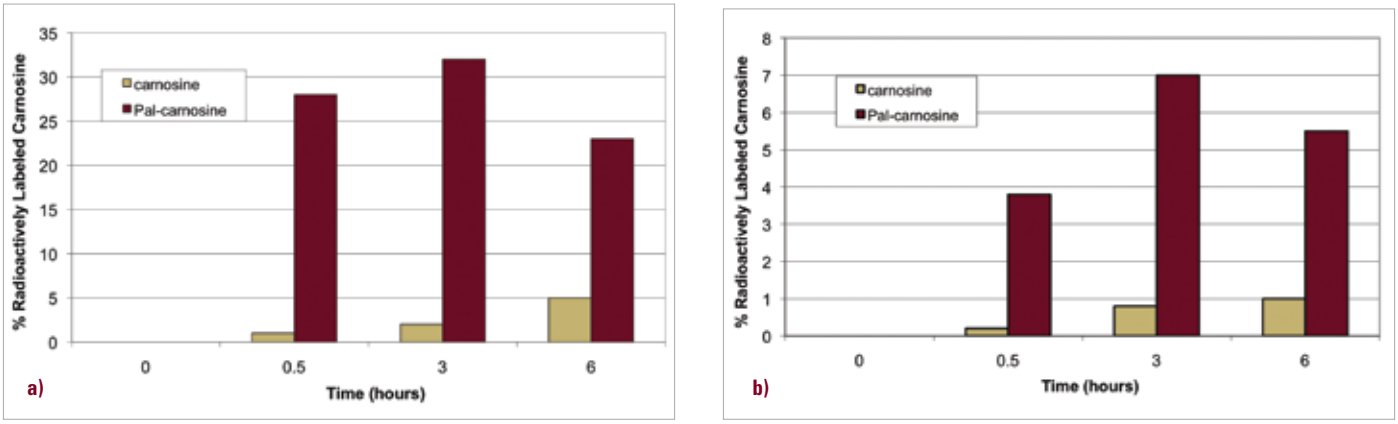
For nearly 30 years, topical vitamin A acid or tretinoin has been the mainstay for condone targeted therapy.[13] Tretinoin efficacy is directly related to its ability to induce comedolysis and normalize the maturation of follicular epithelium in order to prevent future comedone formation.[14] Although extremely efficacious, use can, similarly to BPO, be limited due to skin irritation. In addition, native tretinoin is photolabile and puts constrictions on dosing schedules. Therefore, a means to reduce these limitations has been pursued. A microsphere polymeric technology, allowing for controlled drug delivery onto the skin over time and in response to a trigger[15,16] was developed for topical tretinoin. The system itself consists of porous microspheres that mimic a true sponge in structure and function. Each microsphere is formed by polymeric "ladders" that wrap around one another, forming multiple interconnecting spaces that serve as reservoirs for the drug. These reservoirs open on the surface of the microsphere. The biologically inert polymers used to make microspheres have been shown to be non-allergenic, non-mutangenic, non-irritating, non-toxic and non-biodegradable. Microspheres themselves are too large to permeate the stratum corneum, and, because tretinoin is not available for absorption until it leaves the microsphere, there is a lower accumulation in the epidermis. Furthermore, it was shown that encapsulated tretinoin was less susceptible to degradation following ultraviolet light exposure (Figure 1).[16]

## Vehicle Matters—Current and Future Directions

*Hydrosolubilizing Agents (HSA-3™).*

Metronidazole 0.1% topical gel is a once-daily formulation for treatment of rosacea. Well-controlled studies have shown that it is effective in the treatment of moderate to severe rosacea and well tolerated by varying evaluated subject types. The excellent tolerability is probably due to the gel vehicle, which consists primarily of purified water (92%). Previously, metronidazole was only available as a suspension in a cream formulation. Unfortunately, creams often produce undesirable cosmetic effects such as greasiness, incompatibility with make-up and irritation of the skin for rosacea sufferers, due to emulsifiers and other excipients.

**FIGURE 2.** Biopeptide aids penetration into the skin. **a)** Stratum corneum; **b)** Epidermis.




Carnosine is an amino acid.

Recently, a new gel vehicle capable of solubilizing greater concentrations of metronidazole was developed, making possible the cosmetically desirable attributes of a water-based gel that has the strength, safety and efficacy of 1% metronidazole. This stable aqueous gel formulation containing 1% metronidazole was achieved with the novel combination of hydrosolubilizing agents (HSA-3™).[17] This technology combines niacinamide, which has been shown to improve the appearance of facial skin texture by enhancing skin barrier function, Betadex (beta cyclodextrin), a complexing agent to increase the aqueous solubility of highly water-insoluble and lipophilic drugs, and propylene glycol, a well known humectant and permeation enhancer. The metronidazole 1% gel formulation assumes a unique configuration, with an exterior hydrophilic surface that generates water solubility and enhances moisturization, and an interior hydrophobic cavity than encapsulates the metronidazole molecules and increases drug solubility. The betadex creates a core that enables the solubilization of metronidazole gel 1%.[18]

*Solvent Micro Particulate (SMP™)*

Topical dapsone gel 5% utilizes the advanced Solvent Micro Particulate (SMP™) delivery system, which was specifically designed to deliver dapsone topically. The product is an aqueous gel containing dapsone, diethylene glycol monoethyl ether (DGME), purified water, carbomer 980 neutralized to physiologic pH and methylparaben as a preservative.

The SMP™ delivery system allows dissolved dapsone to permeate the stratum corneum to the epidermis.[19] It was found the properties of the diethylene glycol monoethyl ether (DGME) component helps facilitate permeation into the skin.[20] Transcutol® CG DGME is a hydroscopic liquid that is freely miscible with both polar and non-polar solvents. Transcutol is considered a potential transdermal permeation enhancer due to its non-toxicity, biocompatibility with skin and excellent solubilizing properties.

*Biopeptide Aloe Complex (BAC)*

Biopeptide Aloe Complex (BAC) is a complex combining native collagen fragment chain comprised of three amino acids (Gly-His-Lys) to which palmitoyl is linked, and aloe peptides (Figure 2). The aloe polysaccharide is a pure aloe with a molecular weight range of 50–200 kDa with a mannose:galactose:glucose content of 40:1:1. The linked palmitoyl has both lipid and water solubility, which helps with cutaneous penetration. This material has been shown to increase fibroblast and collagen production as well as have anti-inflammatory and immune activity.[21,22]

## CONCLUSION

The science of cutaneous drug delivery has fought vigorously to overcome the major force of resistance to drug penetration and permeation—the stratum corneum. New delivery systems have emerged in response to the limited routes of entry. Micro/nano encapsulation of known therapeutics and the utilization of delivery vehicles that offer both inherent biological reactivity and permeation enhancement offer patients improved results when using topical therapy. It is clear that this path of development will continue to be pursued with investigative vigor.

## DISCLOSURES

Dr. Kircik is a consultant and investigator, and is on the Advisory Board, for Valeant Pharmaceuticals, Intl., Warner-Chilcott, Intendis, Amgen, Inc., and Galderma Laboratories, LP. He is an investigator, speaker, and is on the Advisory Board for Allergan, Inc. He is a speaker, investigator, consultant, and is on the Advisory Board for OrthoNeutrogena, SkinMedica, Inc., Stiefel Laboratories, Inc., and Connetics Corporation. He is an investigator, consultant and speaker for CollaGenex. He is a consultant and is on the Advisory Board for Colbar. He is a consultant for and stockholder in Johnson & Johnson. He is an investigator and speaker for Leo, PharmaDerm, UCB, and Asteilas Pharma US, Inc. He is an investigator and is on the Advisory Board for Nano Bio and Ferndale Laboratories, Inc. He is a speaker and is on the Advisory Board for Genentech, Inc. He is an investigator for GlaxoSmithKline, PLC, Health Point, LTD, Medicis Pharmaceutical Corp., Navartis AG, Nucryst Pharmaceuticals Corp., Obagi, QLT, Inc., Pfizer, Quatrix, TolerRx, Acambis, Asubio, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biolife, Breckinridge Pharma, Centocor, Inc., Combinatrix, Coria, Dow Sciences and Dusa. He is a speaker for Innovail, 3M, Serono (Merck Serono International SA), Triax, Abbott Laboratories, and Dermik Laboratories. He is on the Advisory Board for Biogen-Idec.

Dr. Friedman has no relevant conflicts of interest to disclose.

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## ADDRESS FOR CORRESPONDENCE

**Leon Kircik, MD**
Physicians Skin Care, PLLC
1169 Eastern Parkway, Suite 2310
Louisville, KY 40217

# Laser Lipolysis With a 980 nm Diode Laser

Amy Forman Taub MD[a] and Adam Friedman MD[b]

[a]Advanced Dermatology, Skinfo, SKINQRI LLCs, Lincolnshire, IL; Northwestern University Medical School, Chicago, IL
[b]Division of Dermatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY

## ABSTRACT

Laser lipolysis is recognized as an effective, non-surgical solution for fat removal and body reshaping. Its appeal lay in the procedure's ability to treat localized fat deposits and correct body asymmetries with apparent decreased risk compared to traditional liposuction. The energy emitted by the laser uses volumetric heating to destroy fat cells, contract skin and stimulate collagenesis. Although devices of five different wavelengths are FDA approved for lipolysis, it has been found that the 980 nm diode laser is consistently successful in inducing the required fat-heat and skin-heat interactions necessary for optimal results. Although laser lipolysis is not intended to replace traditional liposuction, it offers patients a procedure that yields similar benefits with fewer complications and faster recovery.

## INTRODUCTION

Laser lipolysis is designed to provide selective adipose damage, while simultaneously facilitating fat removal, enhancing hemostasis and increasing tissue tightening. The procedure is increasingly gaining recognition as an effective, non-surgical solution for reshaping specific body areas. Laser lipolysis should not be regarded as a replacement for traditional liposuction, nor should it be seen as an alternative to a traditional weight loss regimen. Its role is to treat localized fat deposits (e.g., hips, flanks, etc.) that have shown resistance to diet and exercise. In addition, laser lipolysis can be used to correct body asymmetries (e.g. asymmetry of the knees, male breasts, etc.) or irregular contour (e.g. due to prior liposuction).[1–3] Historically, lasers have been used to target relatively small structures, such as blood vessels and pigment; fat deposits represent a much larger target and require a different focus. Targeting adipose tissue requires one to heat a large volume of tissue; therefore, it is crucial that the wavelength used can propagate adequately into the tissue allowing for enough absorption to maintain sufficient control of the heated area. The heat generated in the fat should transmit to the skin in order to maximize the controlled heating of the skin. The controlled temperature rise in the skin is necessary to achieve optimal skin contraction. Finally, the ideal wavelength should also have the ability to seal small blood vessels which minimized blood loss during the procedure.[4,5]

### The Science of Laser Lipolysis

*Skin-Heat Interaction*

Ever since the introduction of $CO_2$ lasers for skin resurfacing in the early 1990s, the process leading to skin tightening has been further elucidated. Whenever a controlled, reversible thermal injury is created, the body's response is to release mediators responsible for the healing process. In turn, fibroblasts are stimulated to generate and lay a bed of newly formed collagen. As more and more collagen is produced, the skin thickens and becomes more pliable leading to skin contraction.[6] A threshold temperature needs to be reached in order for collagen production to occur. There is a delay of many months after the procedure before the tightening becomes apparent.

*Fat-Heat Interaction*

The extent to which fat is heated and the amount of time the heat is maintained can significantly alter a clinical endpoint. At temperatures below 45°C, any damage done to fat cells is fully reversible and sustained modifications will not be achieved. Between 45°C and 65°C, the cell membrane—though not ruptured—is permanently damaged and will gradually be absorbed by the body through macrophage activity. This process, known as adipocytolysis, is a process that occurs over roughly 90 days, leading to an overall clinical improvement over time. Imparting temperatures above 65°C will rupture cell membranes and cause triglycerides to seep into interstitial spaces, allowing for removal via aspiration or gradual endogenous reabsorption. It is unclear how long the fat needs to be exposed to the appropriate temperature range, but it is believed that the amount of heat exposure can alter the end result. The favored mechanism of action for laser lipolysis is a thermal impact and ideally one should aim to heat the fat to a temperature between approximately 45–65°C to yield optimal results.[7]

*Volumetric Heating*

As previously mentioned, fat often represents a large volume of tissue, requiring the laser to interact with a sizeable target at any given time during therapy. To effectively treat this massive chromophore (more truly represented as hydrated fat, due to the influx of tumescent fluid), the tissue absorption needs to be low enough to have an in-depth effect within the desired target. However, it is equally important to ensure the absorption isn't too low, ultimately requiring excessive power levels to raise the tissue temperature to the appropriate therapeutic levels. Dependency on power levels for an increase in temperature can

result in insufficient control over the laser interaction with the surrounding structures, creating more uncertainty and risk in performing the procedure. This duality of "little, but enough absorption" accurately describes short infrared (IR) wavelengths, particularly 980 nm. Thus far, only near IR wavelengths can achieve controlled volumetric heating in hydrated fat.

However, using IR wavelengths is not straightforward. 1064 nm is poorly absorbed in fat, and can therefore affect large volumes with minimal selectivity posing risk to surrounding structures. At moderate power levels, the volume of tissue involved is so large that the rise in temperature is insufficient. High power levels will cause significant temperature increases, but the lack of selectivity means that this can also affect surrounding structures. In contrast, 1320 and 1440 nm wavelengths are highly absorbed in fat, affecting only a small volume of tissue at any given time. This results in very high temperature gradients being achieved over small volumes creating hot spots in adipose tissue. Though beneficial for targeting fat, the high temperatures generated can potentially damage the fiber tips and overheat the tumescent fluid resulting in skin burns.

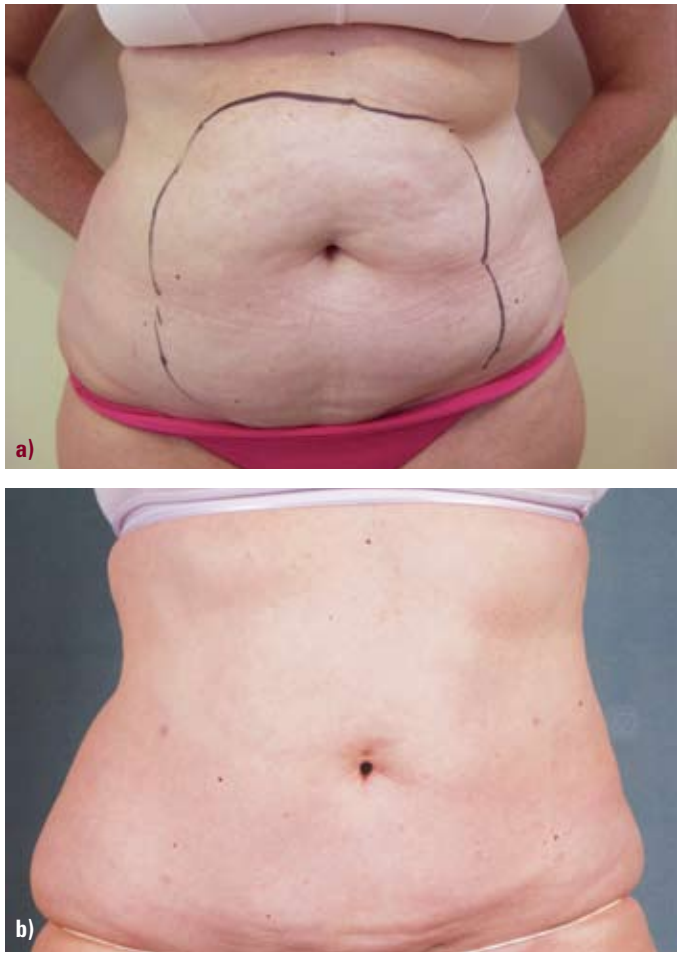
To achieve skin tightening, temperatures of 48–50°C must be reached within the dermis to induce collagen contraction.[8,9] Efficacy is dependent on properly targeting the desired chromophore, and ultimately using the correct energy to induce preferential damage; the dose-dependent relationship between laser energy and thermal damage is well established.[10] Water, as with $CO_2$ and other skin rejuvenation lasers, is the main targets in the case of skin tightening with laser lipolysis. Water has a moderately high absorption peak at 980 nm, whereas at both 920 and 1064 nm, the peak decreases by a factor of 3. Conversely, the peak at 1320 nm is five times higher than that at 980 nm, making 1320 extremely efficient at dermal heating, but also more difficult to control, between these different IR wavelengths. Therefore, accurately targeting water and increasing energy creates not only adipocyte changes, but also dermal collagenesis.[7] Collagen injury from thermal damage promotes collagen remodeling, leading to increases in skin tone and texture.

Putting this together, there appears to be two wavelengths best suited for lysis and lipolysis: 920 and 980 nm. Since 1064 nm is relatively poorly absorbed by adipocytes, it results in poorly controlled interactions with surrounding structures. In contrast, 1320 nm is too highly absorbed in fat, resulting in rapidly elevating temperatures in small volumes potentially creating hot spots. The preferred wavelength may be 980 nm, as there is a greater potential for skin tightening without the increased risk of severe superficial thermal damage. Although the authors prefer the 980 nm laser, many practitioners successfully utilize 1064 and 1320 wavelengths. Combination wavelength devices should also be considered. These devices offer the unique ability to capitalize on the advantages that each wavelength has to offer, as some prove to be superior in absorbing fat, where as others provide better dermal absorption; this is a combination that may optimize the modality's efficacy.

## Laser Lipolysis—Technology

Devices of five wavelengths have been FDA-approved for laser lipolysis: 980 nm (continuous wave), 975, 924, 1064 and 1320 nm and all have been successfully used to performed laser lipolysis.[3] The Lipotherme system, which is a diode laser, emits a continuous wavelength of 980 nm. Diode lasers do not require significant electrical power, relying on 110 V outlets for even high-power systems. Diode lasers are made up of microscopic layers of semi-conductor material alternatively polarized positively and negatively. They emit laser light when their polarity is inverted through electrical stimulation. Because they are excited directly through an electrical current, diode lasers are extremely efficient systems, with a typical efficiency (the ratio of electrical energy required to power the laser versus the light power being emitted) of 30–40%. In contrast,

**FIGURE 1.** Example of laser lipolysis. **a)** Before and **b)** six months after in the upper and lower abdomen with 980 diode laser. Photograph courtesy of Amy Forman Taub, MD.



traditional lasers rely on conversion of electrical power into non-coherent light (a flashlamp) that then excites the laser material. This extra step in the conversion of electrical power into light results in substantial energy losses and accounts for the much lower (5% or less) efficiencies achieved with traditional systems. It also means the box itself must be larger not only for the actual mechanics, but also for adequate cooling.

In one study, Reynaud et al.[5] quantified both, the total energy used in specific areas, as well as patient satisfaction. A total of 534 laser lipolysis procedures were performed on 334 patients. The areas treated included the hips, thighs, abdomen, buttocks, chin, arms and back. Mean cumulative energy was area-dependent, ranging from a minimum of 2200 J (knee) to a maximum of 51,000 J (abdomen). Contour correction and skin retraction were observed almost immediately in most patients. Patient satisfaction was very high. Ultrasound imaging demonstrated collagenous and subdermal bands prior to laser lipolysis, which subsequently dissolved following lipolysis therapy indicating this might be a useful treatment for cellulite. Adverse effects included mild erythema in 17% of cases at one week, three cases of paresthesias at three months, and one report of skin necrosis at prior surgical site near the umbilicus.

## Laser Lipolysis Versus Liposuction: The Battle Continues

Laser lipolysis is an outpatient procedure performed in a standard room under local (tumescent) anesthesia with sterile technique. One to two mm incisions are made to allow for the passage of the laser and aspiration cannula. The laser melts fats more evenly (although good technique allows this to be so), as opposed to making numerous channels as in traditional liposuction. The aspiration process in laser lipolysis requires less effort due to the liquefied fat. This ensures reduced contour irregularities and makes the procedure far less traumatic, leading to minimal bruising and downtime. Laser-induced thrombosis of blood vessels and closure of lymphatic channels may explain the reduction in severity of bruising and swelling after laser lipolysis as well.[5] Less trauma and bruising lead to faster recovery with most patients being able to return to work in two to three days.

Laser lipolysis, as opposed to traditional liposuction, also allows for the induction of new collagen production and subsequent skin contraction.[3] The cutaneous response to the reversible thermal injury from the laser results in an inflammatory response that initiates collagen production. In time, the skin gets increasingly tighter, naturally adjusting to the shape of the body. Liposuction masters argue that "proper" liposuction, i.e. more superficial liposuction, which also damages the dermis, results in tissue tightening as well. A recent study demonstrated convincingly that there was 54% more tightening of the skin with laser than without.[11]

Diode lasers, such as the 980 nm laser lipolysis device, may offer an advantage of increased power and efficiency as compared to other wavelengths.[12] Caution must be taken however, as with higher energy and continuous pulsing comes at an increased risk of damage and subsequent scarring.[12]

*Laser Lipolysis—The Procedure*

The procedure itself is not all different from traditional liposuction, except that an extra step (the laser) has been added between tumescent and aspiration. Patient preparation is similar to that of the tumescent liposuction technique—patients are marked in a standing position as well as are prepped under sterile conditions. Patients are typically given a sedative, and less commonly, some physicians will use spinal or general anesthesia. Note that while the extra step suggests additional time will be required, at least some of that time will be gained back during the aspiration phase as liquefied fat is much easier to extract from the body. Current technology uses 1- to 2-mm optical fibers inserted through small cannulas to transmit the laser into the subcutaneous tissue (Figures 1a and 1b).[3]

*Laser Lipolysis—Potential Pitfalls*

Proper understanding of the laser system is necessary to reduce potential risks. One must be prudent with respect to energy levels, as thermal skin injury can occur if the energy delivered is too highly concentrated.[5] Adverse events include burning the skin with or without skin retraction, uneven skin texture or contour, and the removal of too little fat or too much fat. Some other disadvantages include the cost of the laser and the necessary, but variable, training time. There has also been concern regarding the possible risk of increased circulating triglycerides and free fatty acids as a result of improper aspiration while treating large areas. This could potentially have a negative impact on hepatic and renal function. In response to that concern, two studies established that there is no significant increase in concentrations of free fatty acids following laser lipolysis, concluding there is no potential risk of inducing renal or hepatic toxicity in patients that undergo laser lipolysis.[13] Based on clinical studies conducted thus far, the overall complication rate is low. In a study involving 537 patients who underwent 1064 nm laser lipolysis, there were only 5 reported cases of complications (4 skin burns, 1 local infection) yielding a complication rate of 0.93%.[2] Laser lipolysis is a rapidly expanding field of interest with enormous potential to radically change the paradigm of liposculpture. As experience and technology grow together, safety will likely become less and less operator-dependent.

## Laser Lipolysis—The Future

Techniques, uses and new devices for laser lipolysis will continue to develop as this therapeutic modality evolves. There is an intense interest in using lasers for the treatment of cellulite, a condition for which clinicians can offer very little to patients

and one which continues to be a frustrating aesthetic problem for many women. Even traditional liposuction affords only minimal improvement of cellulite, and can potentially worsen its appearance.[14] In one study, a 1064 nm Nd:YAG system (SmartLipo) was combined with subsequent fat transfer to treat Curri grade III–IV cellulite of the hips, buttocks, thighs and abdomen. Although 84.6% of patients rate their results as good to excellent, it is unclear to what extent the laser played a role in this or whether the laser alone would have been similarly effective.[14] Future, large-scale studies are necessary to determine if laser lipolysis is a reasonable treatment option for cellulite. Additionally, laser lipolysis has had some success in treating uneven contour from previous liposuction.

Within the last three years there has been a rapid increase in new devices on the market. These second-generation models offer more wavelength choices and higher power levels. Larger areas can be treated faster, and these new lasers can be used in conjunction with traditional liposuction as well as can be used for skin tightening/remodeling. As new machines emerge, we may see those with real-time visual feedback of energy delivery, or devices that allow simultaneous suction/laser discharge. Clearly, the future is bright for this effective cosmetic modality.

## DISCLOSURES

Dr. Taub has received honoraria and reduced equipment from Osyris Medical, USA.

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## ADDRESS FOR CORRESPONDENCE

**Amy Forman Taub, MD**
275 Parkway Drive, Suite 521
Lincolnshire, IL 60069
E-mail: drtaub@advdermatology.com

# Cosmeceuticals in Day-to-Day Clinical Practice

Mukta Sachdev MD[a] and Adam Friedman MD[b]

[a]Manipul Hospital, Bangalore, India
[b]Division of Dermatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY

## ABSTRACT

As one of the hottest and fastest growing segments of the natural, personal care industry, Cosmeceuticals are employed to carry out numerous functions, such as preventing UV damage, reducing free radical formation, improving the skin lipid barrier, brightening and unifying skin tone, smoothing texture and reducing pore size. Vitamins and botanicals encompass a large component of the cosmeceutical market, much of which has yet to be clearly defined or regulated. It can be difficult both for the dermatologist and the consumer with respect to choosing the right regimen from the plethora of over the counter choices as well as being informed regarding potential risks and side effects. In fact, dermatologist receive minimal training with respect to this highly tapped and growing genre of topical products. There is clearly a need to research the composite active ingredients of these over-the-counter materials to further characterize their structures, develop means of deriving purified samples from clarified sources, define interactive mechanisms with the skin, and, ultimately, demonstrate efficacy and safety via evidence based means.

## INTRODUCTION

Cosmeceuticals are one of the hottest and fastest growing segments of the natural, personal care industry. They are a category of cosmetic products with biologically active ingredients that offer medicinal benefits.[1] Cosmeceuticals may not be recognized as a separate, legitimate category by the United States (U.S.) Food and Drug Administration (FDA);[2] however they have clearly moved from the sidelines into mainstream medical care. Dermatologists frequently encounter cosmeceuticals as products that can, but more commonly cannot, achieve the promised clinical endpoints listed in their advertisements or packaging. Even with this skepticism, it is of the upmost importance that dermatologists be well-versed in their existence as patients will continue to use them with increasing frequency.

Cosmeceuticals are expected to carry out numerous functions, such as preventing ultraviolet (UV) damage, reducing free-radical formation, improving the skin lipid barrier, brightening and unifying skin tone, smoothing texture and reducing pore size. Although access to these products is limitless and their active ingredients are not regulated by the FDA, cosmeceuticals have the potential to cause unwanted adverse events. Common reactions include skin irritation, contact dermatitis, photosensitivity, comedogenicity, hair and nail damage, pigment alteration, carcinogenicity and potentially even systemic harm. There is clearly a need to research the composite active ingredients of these over-the-counter materials to further characterize their structures, develop means of deriving purified samples from clearly identified sources, define interactive mechanisms with the skin and, ultimately, demonstrate efficacy and safety via evidence-based means.

### Anti-aging and Cosmeceuticals

*Vitamins*

*Vitamin C.* Vitamin C, or L-ascorbic acid, is a highly abundant and easily accessible antioxidant. Humans, unlike most animals or plants, are unable to endogenously generate vitamin C, and therefore it must be obtained from dietary sources.[3] As vitamin C is water soluble, extensive oral supplementation minimally increases skin concentrations, as well as incurs unfortunate gastrointestinal symptoms.[4] Topical application is therefore the only effective means of delivering therapeutic concentrations of vitamin C to the skin. The majority of research in the literature focuses on L-ascorbic acid's functionality as a free radical scavenger through its ability to donate electrons in an aqueous environment, allowing it to quench reactive species and protect intracellular structures from oxidative stress.[5] Even better described is vitamin C's role in collagen biosynthesis and, therefore, wound healing. As a cofactor for prolyl and lysyl hydroxylases, its availability is paramount to stabilizing collagen's triple helical structure. Currently, esterified derivatives of L-ascorbic acid are available in topical preparations, as native L-ascorbic acid is highly unstable.[6] Studies have shown that topically applied vitamin C promotes collagen synthesis and also offers skin lightening, anti-inflammatory and photoprotective properties.[6–8]

*Vitamin E.* Vitamin E is a lipid-soluble antioxidant with eight molecular forms, alpha-tocopherol being the most active and important in providing cellular protection from free radical induced lipid peroxidation. In concert with vitamin C, oxidized alpha-tocopherol can be regenerated back to its reduced form. Vitamin E is highly concentrated in the upper epidermis, where it is released by sebum.[9] It is believed that the physiologic function of epidermal vitamin E is to aid in the quenching of oxidative

stress and physically block ultraviolet radiation (UVR) in order to provide antioxidant defense.[9] Although there is extensive literature discussing the antioxidant effects of vitamin E, along with vitamin C, the data are not always in agreement. Cutaneous delivery of vitamin E for cosmetic purposes in these studies resulted in a range of observations from clinical improvement to no impact. In vitro studies have demonstrated the effects of alpha-tocopherol in reducing the number of epidermal sunburn cells, which are markers of skin damage related to oxidative stress caused by UVB, following exposure to minimal erythemal doses of UVR.[10] It was demonstrated, for example, that vitamin E applied prior to UVR exposure reduces UV-induced erythema and edema. Interestingly, use following sun exposure conferred no protection.[10] Alpha-tocopherol was also shown to act in concert with vitamins A and C in combined products, providing both photoprotection and antioxidant action suggesting a potential synergistc role in photodamage rejuvenation and even skin cancer prevention.[11,12] Unfortunately, topical combinations can be highly unstable, and continued work is required to formulate effectively.[13]

*Niacinamide (Vitamin B3).* Niacinamide, also known as niacinamide, is easily found in our diets in meat, fish, milk, egg and nuts. It is part of the coenzymes nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), molecules that are integral to many cellular metabolic pathways.[14] In its reduced form, NADH or NADPH, it can function as a powerful antioxidant, serving as the impetus for making niacinamide a highly desired component in cosmeceutical products.

The data available are predominantly focused on niacinamide's role as an anti-inflammatory and anti-acne agent.[15] Its anti-inflammatory properties are likely related to its ability to reduce leucocyte peroxidase systems, ultimately preventing localized tissue damage. Furthermore, niacinamide has been shown to improve epidermal structure through its influence on the synthesis of sphingolipids, free fatty acids, cholesterol and ceramides. This physiologic impact results in decreased transepidermal water loss and prevention of the inflammatory cascade, which often ensues as a result of impaired barrier function.[16,17] Clinically, niacinamide has shown to have comparative efficacy to 1% clindamycin gel[18] as well as demonstrate utility in reducing cutaneous erythema is multiple diseases.[16]

Other beneficial features of niacinamide include improving facial dyspigmentation through suppression of melanosome transfer from melanocytes to keratinocytes[19] and improving skin elasticity by increasing collagen production through fibroblast recruitment and stimulation.[20] Together, these physiologic properties, all of which aid in skin rejuvenation and reducing active inflammation, have led to the extensive use of niacinamide in modern cosmeceuticals.

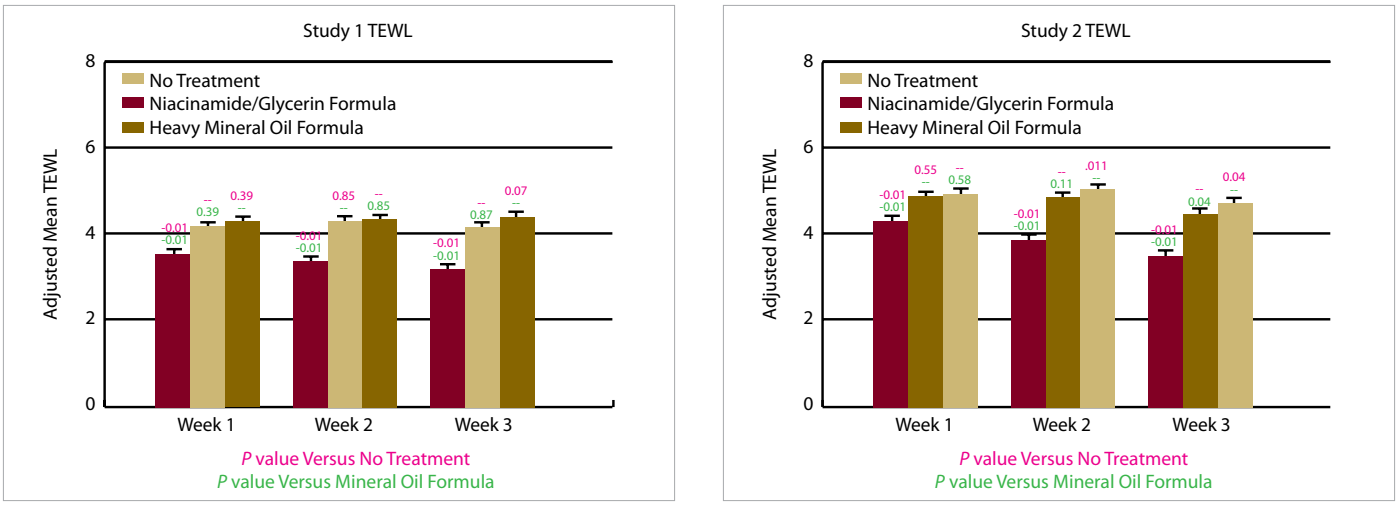
## Botanicals

There are currently over 70 botanicals that are incorporated into everyday cosmeceuticals, but only six have been evaluated via any form of rigorous clinical research. There has been a sharp increase in the use of these agents because the concept of "natural" appeals to patients. For many botanicals, there may be a history of folk and traditional use, however a lack of conventional safety, pharmacokinetic and efficacy data. Also, since botanical extracts may have several (even hundreds of) active constituents, without selection, standardization and study of specific compounds, it can be unclear as to what active compounds are actually present or how they interact with each other. By way of comparison, two well-characterized botanicals are soy and green tea.

### *Soy*

Soy contains a spectrum of non-denatured active components that provide several of the benefits targeted by cosmeceuticals. Soy contains more than 15% unsaturated fatty acids, more

**FIGURE 1.** Niacinamide hand and body (H&B) technology provides barrier repair.



than two thirds of which are essential fatty acids that help provide antioxidant protection. In fact, vitamin E is found in soy, providing its antioxidant properties in addition to soy's innate biological attributes. Soy has numerous clinical applications including skin lightening, enhancing skin elasticity, delaying hair regrowth, controlling oil production, moisturizing the skin and is even thought by some to have the potential to decrease skin aging and prevent skin cancers through the estrogen-type and antioxidative effects of its metabolites.[21]

Small proteins such as soybean trypsin inhibitor (STI) and Bowman-Birk inhibitor (BBI) have been suggested to inhibit skin pigmentation, while large proteins have been found to smooth and soften the skin. STI, BBI and soy milk were shown to not only exhibit depigmenting activity but to also prevent UV-induced pigmentation in vitro and in vivo; specifically, STI and BBI are thought to influence melanosome transfer, and thus pigmentation.[22] Because soy exerts some estrogen-type effects and melasma is somewhat estrogen-mediated, soy use in patients with melasma is not recommended.

In a 12-week, double-blind, randomized clinical study that was conducted to evaluate the properties of skin firmness using a composition of a proprietary soy complex (Total Soy) compared with a composition of retinol/ascorbic acid, soy stimulated in vitro collagen synthesis and in vivo elastin repair, thereby clinically improving skin firmness and reducing facial skin laxity.[23] In an eight-week study conducted to evaluate the overall effectiveness of applying a preparation of Total Soy and a skin conditioner/moisturizer twice daily, shaving twice-weekly, in reducing the appearance of unwanted leg hair, the Total Soy/moisturizing combination was found to improve the appearance of unwanted leg hair by week 4.[24]

*Green Tea*

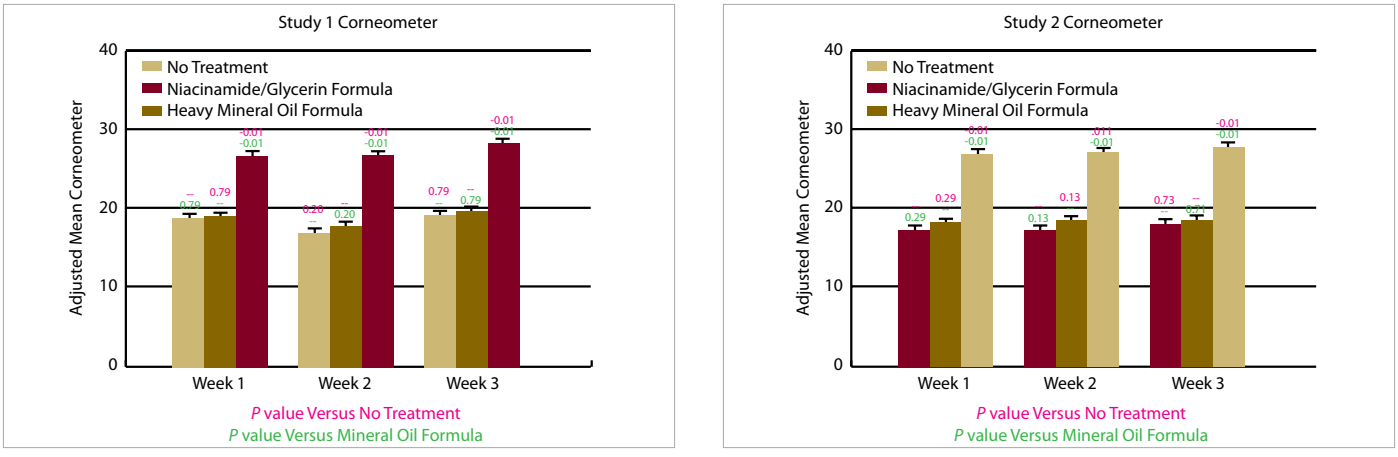
Green tea polyphenols inhibit the activity of collagenase and increase the collagen biosynthesis rate of human fibroblasts. Furthermore, it has been shown to inhibit tyrosinase activity. The most studied of these are: (-)-epigallocatechin-3-gallate (EGCG) and (-)-epicatechin-3-gallate (ECG). First, EGCG inhibits the generation of intracellular hydrogen peroxide, one of the most active DNA-damaging reactive oxygen species, as well as the formation of cyclobutane pyrimidine dimers, a known source of UVR induced DNA damage.[25] Therefore, green tea likely exerts its "anti-aging" properties through its ability to limit inflammation and scavenging free radicals.

## Moisturizers and Cosmeceuticals

The strength of the stratum corneum is derived from its heavy composition of predominantly lipids, but also key proteins/enzymes, and water. Ceramides and its derivatives encompass nearly half of the cornified layer's lipid content, followed closely by cholesterol and free fatty acids. Lipids are synthesized as keratinocytes migrate to the surface of the epidermis, during which time they are packaged in lamellar granules and are ultimately discharged into the junction between the stratum spinosum and corneum to help form the "brick and mortar" water barrier. The barrier is further fortified by the cornified cell envelope (CE), a structure synthesized at late stages of keratinocyte differentiation derived from or composed of loricrin, involucrin, fillagrin and small proline-rich proteins. Lastly, natural moisturizing factor, a breakdown product of fillagrin, is generated in order to tightly hold on to water and hydrate the upper levels of the skin. Perturbation of any of these composites in stratum corneum, whether etiologically endogenous or exogenous, can cause barrier dysfunction and a broad range of clinical pathology—xerosis is likely the most common problem due to defective stratum corneum.

Moisturizers are intended to be agents that can repair the damaged cornified layer by reconstituting the barrier and therefore increase its hydration (Figures 1 and 2). There are several vitamin-/botanical-derived products available that have been investigated. Returning to niacinamide, there have been

**FIGURE 2.** Niacinamide H&B technology provides increased skin hydration.



multiple studies evaluating its ability to repair the epidermis both though increasing barrier lipids[25] and proteins.[26] In one study, a cream containing 2% nicotinamide was tested on atopic dry skin over four or eight weeks as compared to white petrolatum. The nicotinamide-containing cream demonstrated significantly decreased transepidermal water loss as compared to white petrolatum, although both preparations increased stratum corneum hydration.[26] Another study demonstrated that a niacinamide-containing facial moisturizer improved the stratum corneum barrier in patients with rosacea.[27]

Composite replacement has also been a focus of cosmeceutical agents. In one study, a ceramide-dominant physiologic lipid-based emollient demonstrated satisfactory results in the treatment of xerosis in childhood atopic dermatitis.[28] In thinking of dry, flaky skin as an unwanted cosmetic feature, degradation of retained scale has also been a focus of topical agents. Soap-induced xerosis has been shown to be ameliorated by the topical application of exogenous proteases. Morphological and immunologic analysis of bacterial enzyme-treated skin has demonstrated that topical application can induce the degradation of epidermal desmosomes, thereby promoting desquamation and resolving xerosis. [29]

## CONCLUSION

With the current understanding of cosmeceuticals, combination protocols are advisable—it is unlikely that we will be recommending the use of just one active in the near future. Moisturizers are an integral addition to the realm of cosmeceutical recommendations, and there are products that offer both anti-aging and hydration-aiding properties. The combination of cosmeceuticals with cosmetic procedures should also be considered. For example, Alster et al. demonstrated that by using vitamin C cream after resurfacing, post procedure erythema could be reduced. [32]

Cosmeceuticals are currently jamming store shelves and many more are on the way. As physicians, it is of the upmost importance to be aware of these products and the data that are currently available. It is the dermatologist's responsibility to guide patients with these products just as with prescription, FDA-regulated medications, not only to help patients achieve the greatest benefit, but also to help them avoid those agents that can potentially offer more harm then clinical good.

## DISCLOSURES

Drs. Sachdev and Friedman have no relevant conflicts of interest to disclose.

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## ADDRESS FOR CORRESPONDENCE

**Mukta Sachdev, MD**
Consultant Dermatologist
36/1,7th Corss,1st Main,
Cambridge Layout
Bangalore-560008
India

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