New knowledge of the pathogenesis of vitiligo has given rise to new treatments and new hope for sufferers of this condition, says Pearl E. Grimes, M.D. She is director of the Vitiligo and Pigmentation Institute of Southern California and clinical professor of dermatology at The University of California Los Angeles David Geffen School of Medicine.

Thanks to genetic research over the past decade, she says that "We now know that probably 90% of the genes that have been identified in vitiligo are immune-susceptibility genes; 10% are pigment-related genes." Such a genetic predisposition can lead to "sick melanocytes," she says. "Melanocytes from people with vitiligo do not grow as well in culture. There are probably some inherent defects in these melanocytes that may tie back to the genetics of the disease."

Oxidative stress might be the primary event that initiates the immune dysfunction that leads to vitiligo, Dr. Grimes says. "In vitiligo, we know that hydrogen peroxide is up, [while] catalase—a major oxidative stress fighting molecule—is down. Alterations in the body’s innate ability to protect against oxidative damage may play a role in releasing autoantigens and neo-antigens, she says. This leads to a major influx of CD8 lymphocytes—the major players in mediating the destruction of melanocytes proven that adipose tissue is a rich source of stem cells, and this likely explains the sustained benefit seen with fat transfer for volume replacement. Blood or plasma are also sources of stem cells leading to potential benefit of [platelet-rich plasma] PRP in cosmetic dermatology for rejuvenation and healing, although well-controlled studies are needed to establish efficacy. Data on the use of stem cells

Behind the hype in stem cell therapy

Lisette Hilton | Senior Staff Correspondent

True therapeutic application of stem cells in dermatology is a tapestry of hope, promising early studies and false claims. While stem cells are showing promise in areas such as wound healing and in the treatment of skin fragility from epidermolysis bullosa, their use in heavily promoted topical antiaging preparations is, by our experts’ accounts, nowhere near ready for prime time.

Roy G. Geronemus, M.D., chairman of the board of the New York Stem Cell Foundation, the largest stem cell research program in the country, says he strongly believes in the present and future of the clinical use of stem cells.

“I do, however, urge caution and restraint in reference to the commercial claims regarding the potential efficacy of stem cells in dermatology at this point in time,” he says. “As for cosmetic dermatology, it has been well

SOARING DRUG COSTS: DEFINING A DILEMMA

The costs of popular drugs—even generics—in dermatology are soaring, leaving patients scrambling for coverage or financial assistance and dermatologists spending precious hours on prior authorizations, drug appeals and reviews. Over the course of the next few months we’ll explore a systemic problem, the challenges that each member of the system faces, and whether there is a solution that can balance affordability, access and innovation. Here, experts and patients begin by attempting to define the problem from the cost of free samples to payer policies to the intricacies of research and development. There are no heroes and no villains here, just a complex problem hungry for a fix.

BUSINESS READ THE FULL STORY, page 60

New hope for patients with vitiligo

Cutting-edge therapies combined with old-fashioned TLC

John Jesitus | Senior Staff Correspondent

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The seachange in attitudes and methods for removing tats

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Largest ever study for vismodegib posts results, learn details here
FROM DRY, CRACKED SKIN TO MINOR WOUND CARE, WE’VE GOT IT COVERED.¹

Aquaphor Healing Ointment repairs the barrier and helps protect compromised skin.¹

Reference: ¹ Data on file, Beiersdorf, Inc.

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Dermatology Times is the only clinical news resource serving a readership of more than 14,000 dermatologists and other professionals focused on skincare. Through unbiased reporting, we strive to help practitioners put into perspective developments that affect their business. Our goal is to provide practical information that will help them to better understand clinical, regulatory and financial issues, as well as chart business growth.

Our Mission

Let your voice be heard, contact us: editor@dermatologytimes.com
INDICATION AND USAGE
SERNIVO Spray is indicated for the treatment of mild-to-moderate plaque psoriasis in patients 18 years of age or older.

IMPORTANT SAFETY INFORMATION
SERNIVO Spray can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. Systemic effects of topical corticosteroids may also manifest as Cushing’s syndrome, hyperglycemia or unmasking of latent diabetes mellitus, and glucosuria. These events are rare and generally occur after prolonged exposure to larger than recommended doses, particularly with high-potency topical corticosteroids. Do not use if atrophy is present at the treatment site. Do not use with occlusive dressings. Avoid use on the face, scalp, axilla, groin or other intertriginous areas. Use of SERNIVO Spray is not recommended in pediatric patients as they are more susceptible to systemic toxicity. Allergic contact dermatitis may occur.
The most common adverse reactions (≥ 1%) were application site pruritus, burning and/or stinging, pain, and atrophy. Local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use, or use of higher potency corticosteroids. These are not all the possible side effects of SERNIVO Spray.

Please see brief summary of the Full Prescribing Information on the reverse side.

To report SUSPECTED SIDE EFFECTS, call Promius Pharma at 1-888-966-8766 or contact the FDA at 1-800-FDA-1088.

Reference: 1. Sernivo Prescribing Information. Promius Pharma, LLC. Princeton, NJ. February 2016. Sernivo™ is a trademark of Promius Pharma, LLC. ©2016 Promius Pharma, LLC. All rights reserved.
MINIMIZE THE UNWANTED RISKS FROM ENDOCRINE EFFECTS BY MITIGATING THE RISK FACTORS FAVORING INCREASED SYSTEMIC BIOAVAILABILITY AND BY USING THE PRODUCT AS RECOMMENDED [SEE DOSAGE AND ADMINISTRATION].

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. Use of SERNIVO Spray is not recommended in pediatric patients [see Use in Specific Populations].

Allergic Contact Dermatitis

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Corroborate such an observation with appropriate diagnostic patch testing. If irritation develops, discontinue the topical corticosteroid and institute appropriate therapy.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In two randomized, multicenter, prospective vehicle-controlled clinical trials, subjects with moderate plaque psoriasis of the body applied SERNIVO Spray or vehicle spray twice daily for 4 weeks. A total of 352 subjects applied SERNIVO Spray and 180 subjects applied vehicle spray.

Adverse reactions that occurred in at least 1% of subjects treated with SERNIVO Spray for up to 28 days are presented in Table I.

Table 1: Adverse Reactions Occurring in ≥2% of Subjects Treated with SERNIVO Spray for up to Four Weeks

<table>
<thead>
<tr>
<th></th>
<th>SERNIVO Spray b.i.d. (N=352)</th>
<th>Vehicle Spray b.i.d. (N=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site pruritus</td>
<td>6.0%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Application site burning and/or stinging</td>
<td>4.5%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Application site pain</td>
<td>2.3%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Application site atrophy</td>
<td>1.1%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Less common adverse reactions (with occurrence lower than 1% but higher than 0.1%) in subjects treated with SERNIVO spray were application site reactions including telangiectasia, dermatitis, discoloration, folliculitis and skin rash, in addition to dysgeusia and hyperglycemia. These adverse reactions were not observed in subjects treated with vehicle.

Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing reports for local adverse reactions to topical corticosteroids have also included striae, irritation, dryness, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, hypertrichosis, and milia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. SERNIVO Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. The abnormalities observed included umbilical hernias, cephalocele, and cleft palate.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids can result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when SERNIVO Spray is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of SERNIVO Spray in patients younger than 18 years of age have not been studied; therefore use in pediatric patients is not recommended. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk of systemic toxicity, including HPA axis suppression and adrenal insufficiency, when treated with topical drugs. [See Warnings and Precautions]

Rare systemic effects such as Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids. Local adverse reactions including skin atrophy have also been reported with use of topical corticosteroids in pediatric patients.

Geriatric Use

Clinical studies of SERNIVO Spray did not include sufficient numbers of subjects who were 65 years of age or older to determine whether they respond differently from younger subjects.

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Distributed by: Promius Pharma, LLC., Princeton, NJ 08540
Sernivo is a trademark of Promius Pharma, LLC.
Issued: 02/2016
WHAT’S YOUR DIAGNOSIS?

AT HER REGULAR OB APPOINTMENT, a 31-year-old woman pregnant with her first child expressed concern about a nodule that had appeared on her lip in the past two weeks. Currently in her third trimester, she had only been taking prenatal vitamins since the beginning of her pregnancy. The red, friable papule had a well-defined rim of skin at the base and would bleed spontaneously if accidentally brushed against.

Strong growth predicted for body contouring market

THE BODY CONTOURING MARKET is expected to achieve a compound annual growth rate of 7.9% between 2015 and 2022, according to a report from research and consulting firm GlobalData. This represents an annual increase from $671.8 million to over $1.1 billion.

The report notes that the body contouring market encompasses both noninvasive and minimally invasive fat reduction procedures like lipolysis and cryolipolysis. Drivers contributing to the strong growth of this market include: the rising popularity of nonsurgical options, leading to the very fast market growth of a relatively new technology; an increase in the number of men and an aging baby boomer population seeking treatments; and rising obesity rates that prompt a quest for easier alternatives to diet and exercise.

Can you benefit from mindfulness?

Mindfulness can be integrated in dermatology management and has been demonstrated in research to improve clearance of conditions for patients and to improve anxiety and depression that patients experience associated with their skin conditions. Susan Abbey M.D., F.R.C.P.C., describes how mindfulness can be employed adjunctively to improve dermatological conditions like psoriasis as well as your experience as a compassionate physician.

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READ MORE:
bit.ly/bodycontouringmarketgrowth

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READ THE BENEFITS:
bit.ly/mindfullnessinderm

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READ THE BENEFITS:
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How does someone become a dermatologist?

Over the years, I’ve gotten used to complete strangers approaching me in a variety of different social settings after learning that I’m a dermatologist and partially disrobing to show me some problem they are having with their skin. A slightly different variation on that theme occurred recently while I was attending a very large wedding that included a number of attendees from all over the country, many of whom I did not know. I was somewhat surprised when one of the guests, a 17-year-old high school student, approached me (again after she learned I was a dermatologist) and asked point blank: “How does someone become a dermatologist?”

It seems she had developed a strong interest in skin diseases, as she had long been under the care of a dermatologist for treatment of atopic dermatitis and she enjoyed those interactions very much. As a result, she wanted to know what she had to do to become a dermatologist and I was the lucky person she had chosen to answer her questions.

After ascertaining that she was indeed serious about this, I agreed to help.

I generally enjoy this type of interaction, just not at the exact time and venue she had selected for this discussion to take place. I was able to postpone our phone discussion for a few days later after she had returned home. This also gave me the advantage of some time to organize my thoughts and try to be a better mentor for her.

Over the next few days, I gave this subject a lot of thought, trying not to make the whole process seem too overwhelming to a high school senior. I came up with these suggestions.

After all, I remember when I was a high school senior trying to decide if I even had to do to become a dermatologist and I was the lucky person she had chosen to answer her questions.

Disclaimer: Even though I have been chair of three different dermatology departments and a member of three others, these are my thoughts about preparing for a career in dermatology and while they are valid in my experience, there are certainly other points of view that are also valid.

Attend college

Yes, certainly go to the college of your choice, apply yourself and get the best grades you can without sacrificing the enjoyment of being in college, like participating in social activities, making new friends, joining clubs that interest you and volunteering for some worthwhile cause.

If you don’t already play a musical instrument or sing or dance, take lessons! Do things that appeal to you but also help to make you a well-rounded individual.

If you have time, get a part-time job so that you get to learn how to handle money and be at least partly responsible for your educational expenses and activities. This will also give you a chance to meet more people and also learn how to work effectively as a member of a team.

Choose your major

I’m not a believer that to get into medical school you must major in one of the sciences, but I do believe you should have a good foundation in the sciences, perhaps just as a minor.

Remember, medical schools are trying to train doctors who can best care for their patients. In my opinion, that requires someone who can understand a patient’s concerns, effectively communicate information and answers to the questions being asked and do so without sounding like “Doc Martin” on PBS!

In my experience, these physician qualities are found more commonly in an individual who has a broad background and greater life experiences.

Make a sincere effort to get to know your professors and teaching assistants. If they have office hours, go see them to learn if there are things you can do to assist them that also interest you, perhaps assisting in a research project or developing a public information pamphlet, brochure or a lecture that may be of interest to seniors or elementary school students.

Your professors are the same people who will be asked to write you letters of recommendation for medical school, but they can only do that if they know you.

Apply to medical school

Where to apply to medical school is the hardest question for me to answer. It is dependent upon a number of interrelated factors, including:

- The quality of your college performance. If you did well in school, but not great, you might consider a state school over a private one.
- Your family’s financial situation. Medical school is expensive and you need to think about how you can pay for it.
- Availability of scholarships for which you qualify. Look around, there are a number of smaller clubs or organizations that offer special scholarships to top students and you might qualify for one of these.
- Where you have residence. Theoretically, if you live in a state with multiple medical schools, like Ohio, Texas and California you might have an advantage getting accepted over someone who lives in a state with only a single medical school. However, it is also true that these states have large populations so the number of undergraduate students applying may also be greater, but I still believe there is an overall advantage when you have multiple schools to which you can apply.

Be flexible in medical school

Many of the ideas I suggest are done while attending college are the same for medical school:

- Study hard
- Get to know your professors
- Work to learn, not to just get grades
- Volunteer for some worthwhile cause that is of interest to you.

Editorial Advisory Board

Insight & Opinion From Our Advisory Board Leaders

Ronald G. Wheeland, M.D.,
is a private practitioner
in Tucson, Arizona

Disclaimer:
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BIG for Widespread Inflammatory Dermatoses

Trianex® 0.05% (Triamcinolone Acetonide Ointment, USP)

Where size and cosmetic elegance meet

- 430g size, great for patients with widespread inflammatory dermatoses
- Nongreasy, cream-like formulation

INDICATION AND IMPORTANT SAFETY INFORMATION

Trianex® 0.05% (Triamcinolone Acetonide Ointment, USP) is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. The most common adverse events with Trianex Ointment include burning, itching, irritation, dryness, and folliculitis. Trianex Ointment is contraindicated in patients who are hypersensitive to any of the ingredients of this product. As with all topical corticosteroids, systemic absorption can produce reversible HPA-axis suppression.

Please See Full Prescribing Information on reverse side.

Trianex is a registered trademark of CMP Pharma, Inc. ©2015 Promius Pharma, LLC. All rights reserved.
Triamcinolone Acetonide Ointment, USP

Proprietary Hydrous Emulsified Base
Rx Only

DESCRIPTION
Topical corticosteroids, such as Triamcinolone Acetonide Ointment, USP, constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. Each gram of Triamcinolone Acetonide Ointment, USP contains 0.5 mg of Triamcinolone Acetonide USP in a water-in-oil emulsion composed of Light Mineral Oil NF, Purified Water USP, White Petrolatum USP, Heavy Mineral Oil USP, Mineral Wax, and Lanolin Alcohols NF. The white ointment is for topical use only. Triamcinolone Acetonide has the molecular formula of \( \text{C}_{24}\text{H}_{31}\text{FO}_6 \) and is designated chemically as Pregna- 1, 4-diene-3, 20-dione, 9-fluoro-11, 21-dihydroxy - 16, 17- \([\text{1-methylethylidene}]\text{bis} [\text{oxy}])\). It has a molecular weight of 434.50 and the following structural formula:

![Triamcinolone Acetonide Structure](image)

CLINICAL PHARMACOLOGY
Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics
The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses (see DOSAGE AND ADMINISTRATION). Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE
Triamcinolone Acetonide Ointment, USP is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

CONTRAINDICATIONS
Triamcinolone Acetonide Ointment, USP is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS
General
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifested by decreased adrenocorticotropic hormone (ACTH) levels and suppression of cortisol. HPA axis suppression may cause ועדת פיזיולוגיה רגילה, תאי עיסון, וגלוקוזוריה של התאים ונהיים של некоторых טיפוסים. נשים. תנאים שגדלים את מערכת הֶרֶמֶס בין כדי להתקיים תאי הֶרֶמֶס, תאי המרינה של שיניים, העיכובים בהכנת, או תאי נוזל potentiol steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS-Pediatric Use). If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient
Patients using topical corticosteroids should receive the following information and instructions:
1. This medication is to be used as directed by the physician. It is for external use only.
2. Avoid contact with the eyes.
3. Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.
4. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests
The following tests may be helpful in evaluating the HPA axis suppression:
- Urinary free cortisol test
- ACTH stimulation test

Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C
Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers
It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use
Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing’s syndrome than mature patients because of a larger skin surface area to body weight ratio. Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing’s syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:
- Burning, Itching, Irritation, Dryness, Folliculitis, Hypertrichosis, Acneiform eruptions, Hypopigmentation, Perioral dermatitis, Allergic contact dermatitis, Maceration of the skin, Secondary infection, Skin atrophy, Shrive, and Milia.

OVERDOSAGE
Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION
Triamcinolone Acetonide Ointment, USP is generally applied to the affected area as a thin film from two to four times daily depending on the severity of the condition. Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions. If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED
Triamcinolone Acetonide Ointment, USP is supplied in 430 g jars (NDC 67857-806-19).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Promius Pharma, LLC at 1-888-966-8766.

STORE AT CONTROLLED ROOM TEMPERATURE 15°– 30° C (59°– 86° F).

DISPENSE IN A WELL-CLOSED CONTAINER.

CAUTION: Federal law prohibits dispensing without prescription
For external use only. Not for ophthalmic use.

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Skin microbiome

Skin is subjected to harsh environmental conditions that favor the growth of primarily gram positive organisms. Gram positive species such as Propionibacterium, Staphylococci, Micrococcocci and Corynebacteria are resident bacteria of the skin. Malassezia yeast and a variety of bacteriophage species complete the resident flora.

Resident bacteria are capable of reproducing and are commensal with the host when skin is healthy. When skin is compromised, resident bacteria can become pathogens as is seen in acne and folliculitis. Transient bacteria are contaminants that are acquired from the environment. Escherichia coli, Pseudomonas aeruginosa and Bacillus species are transient species incapable of sustained growth under normal skin conditions. Skin microbiota controls the colonization of potentially pathogenic organisms, modulates immune response, skin barrier function and is integral for skin health.

The skin microbiome is influenced by pH, sebum content, barrier function and hydration. A slight acidic pH favors the growth of Propionibacterium, while more alkaline pH encourages the majority of resident species. Moist areas such as the armpit and behind the knees favor Staphylococci and Corynebacterium species, while Propionibacterium species are more plentiful where sebaceous glands are present. Dry areas of the skin have the greatest diversity of species while having the lowest absolute number of bacteria. Additionally, extrinsic factors such as geographic location, occupation, the use of antibiotics or cosmetics can influence skin microbiota. Studies indicate that alterations in skin microbiota play a significant role in conditions such as atopic dermatitis, psoriasis, acne and skin cancer.

Probiotics, prebiotics and bacterial cell lysates

Probiotics are live bacterial cultures that, when applied topically, influence the composition of skin microflora. Through the fermentation process, probiotic bacteria produce acidic compounds like lactic acid, reducing the pH of skin. Acidifying the skin discourages the growth of most pathogens favoring growth of resident flora. Probiotic strains produce potent antimicrobials such as bacteriocidins, organic acids and H2O2 that prevent pathogen adhesion. Although probiotic bacteria have documented skin benefits, live cultures are generally not preferred in cosmetics.

Prebiotics are non-digestible plant-based carbohydrates that discourage the growth of pathogens while preserving beneficial bacteria. Prebiotics can be readily incorporated into skincare products and are an excellent alternative to live bacteria. Bacterial cell lysates are also used in cosmetic formulations. Lysates contain cell walls, bacterial metabolites and dead bacteria. Beneficial ingredients in probiotic bacterial lysates include hyaluronic acid, sphingomyelinase, lipoteichoic acid, peptidoglycan, lactic acid, acetic acid and diacetyl. Hyaluronic acid improves moisturization and barrier function, while sphingomyelinase upregulates ceramide production. Lipoteichoic acid and peptidoglycan stimulate the production of antimicrobial peptides (AMPs), including beta defensins, and stimulate innate immunity via induction of toll-like receptors (TLR). Diacetyl is antibacterial against gram negative pathogens including Pseudomonas and E. coli. Acetic acid also has antibacterial effects. Lactic acid acts as a natural moisturizing factor and antimicrobial, and acts on epidermal and dermal remodeling. Thus, bacterial cell lysates provide broad biologic activity that can be harnessed to provide skin benefits.

Topical probiotic benefits

Topical probiotics and their lysates have been shown to be of value in treating acne. A topical product containing a 5% extract of Lactobacillus plantarum was found to reduce erythema, acne lesion size and improve skin barrier in patients with acne. A lactic acid bacterial strain, Enterococcus faecalis SL-5, isolated from human feces, was found to have antimicrobial activity against P. acnes. A clinical study using a topical lotion containing a cell-free extract of E. faecalis SL-5 showed a significant reduction in inflammatory lesions compared to placebo lotion. The authors suggest that topical probiotics may be suitable alternatives to topical antibiotics for treating acne.

A cosmetic product with specific probiotic extracts including ginseng, black currant or pine was found to significantly reduce colonization of P. acnes in patients with acne. Topical probiotics have also been evaluated for treating sensitive and dry skin. Strep-tococcus thermophilus is a bacterial strain known for its high levels of sphingomyelinase. A cream containing the lysate of S. thermophilus was found to significantly increase stratum corneum ceramide levels in healthy females after two weeks of application. Skin hydration was also improved following use of the probiotic lysate-containing cream.

At this time, it appears that more studies are really worth the hype. They demonstrated that a cream containing 10% B. longum lysate improved sensitive skin after two months compared to vehicle control. There was a reduction in stinging after lactic acid, TEWL and barrier dysfunction after tape stripping, as well as an improvement in clinical dryness. In vitro studies on B. longum lysate suggest that it may reduce skin sensitivity by reducing neuron reactivity and neuron accessibility.

The studies reviewed suggest that topical probiotics, prebiotics and bacterial cell lysates do provide demonstrable skin benefits.

Skincare products containing these are well positioned for treating conditions characterized by an altered microflora. Cosmetics containing probiotics may also be helpful for improving skin health and beauty.

At this time, it appears that more studies are warranted to determine if these products are really worth the hype.
Special dermatologic needs for men who have sex with men

RANDY DOTINGA | SENIOR STAFF CORRESPONDENT

KENNETH A. KATZ, M.D., M.Sc., M.S.C.E., a dermatologist in San Francisco, occasionally finds himself asking male patients about their sex lives: Do they have intercourse with men? What about multiple partners? Condom use?

He has both their skin health and their overall health in mind. According to him, men who have sex with men—a category that includes gay and bisexual men—face unique risks of skin conditions because they’re more likely to suffer from HIV and other sexually transmitted diseases.

“Sexual orientation doesn’t put someone at risk, but behavior linked to these conditions does,” he tells Dermatology Times in an interview prior to making a presentation at the summer meeting of the American Academy of Dermatology in Boston.

“Dermatologists should appreciate that men who have sex with men are at higher risk of HIV and other sexually transmitted diseases,” he says.

According to him, more than 80% of 20,000 syphilis cases in the United States were in gay and bisexual men, as were 75% of 45,000 new HIV cases.

These men also face higher risks of skin cancer, MRSA and meningococcal meningo-encephalitis, a rare bacterial infection.

Earlier this summer, health officials reported an outbreak of meningococcal meningo-encephalitis in Southern California among gay and bisexual men; one man died.

Other outbreaks have been reported over the past two years in the Chicago, Los Angeles and New York City areas.

Dr. Katz urges dermatologists to look for these signs that could indicate sexually transmitted diseases:

- Rashes or sores in the genital and perineal areas are a possible sign of syphilis or meningococcal meningitis.
- In addition, he says, “a full body rash can be a manifestation of acute HIV infection and is a hallmark of secondary syphilis.”
- Purpuric lesions, non-blanching spots of blood that escaped the blood vessels under the skin, can be a sign of meningococcal meningitis, among other diseases.

Spots on the soles and palms are a hallmark of secondary syphilis.

TALKING TO PATIENTS

How can a dermatologist sensitively bring up a patient’s sexual history when his or her condition suggests a possible link to an STD?

Dr. Katz says something like this: “I ask all my patients with a rash like yours some sensitive questions about their sexual history because it’s important to my care for you. Is that OK with you?”

If the patient agrees, he says, “then I’ll ask in a straightforward and nonjudgmental way: Are you sexually active? What are the genders of your sex partner or partners? What’s your HIV and sexually transmitted disease status? How frequently do you use condoms during sex? What’s your vaccination history?”

Keep in mind, Dr. Katz says, that gay and bisexual men often haven’t felt comfortable discussing their sexual history with physicians. DT

Disclosure: Dr. Katz reports no relevant disclosures.

Can stress cause skin disease?

RANDY DOTINGA | SENIOR STAFF CORRESPONDENT

IT MAY SEEM obvious that stress worsens inflammatory skin conditions like psoriasis and atopic dermatitis. But proving this assumption has been anything but simple.

For one thing, stress is difficult to measure: Nobody has no stress at all, and levels go up and down day by day. For another, randomized double-blind studies are a difficult proposition. If one group of psoriasis patients take part in stress reduction via mindfulness meditation and another group doesn’t, for example, blinding is impossible.

Now, we’re getting more insight from science. New research is finally offering confirmation of the role of stress, Richard D. Granstein, M.D., tells Dermatology Times. “It’s establishing physiologic mechanisms to explain how stress can make skin disease worse. We knew it was true, but nobody knew why it was true.”

Dr. Granstein, chairman of dermatology at Weill Cornell Medicine, spoke in an interview prior to making a presentation about stress and skin disease at the summer meeting of the American Academy of Dermatology in Boston.

“A number of pathways have been delineated that show stress can really affect inflammatory skin disease,” he says.

The nervous system appears to be especially important. Stress seems to affect the peripheral nervous system and disrupt immunity levels in the skin, he says.

His team is examining whether stress works through the sympathetic nervous system to worsen inflammatory skin disease.

How can this kind of research be helpful? The uncovering of these pathways can reveal ways to help people recover with the help of medication, he says.

What should doctors do now? Dr. Granstein tells dermatologists to remember that stress isn’t a one-way street: “Not only does it appear that stress makes these diseases worse, but having these diseases causes stress.”

As a result, dermatologists should consider stress in their patients. “Sometimes we refer people for psychotherapy, and we have support groups for people with skin disease,” he says. “They feel better knowing that other people have the same problem they have.” DT

Disclosure: Dr. Granstein is an advisor to Elly- sium Health and Velius. He has served on advisory boards for Gaderma and Castle Biosciences.
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Never mind your IQ, are you focusing on QI?

Randy Dotinga | Senior Staff Correspondent

You’ve probably been doing it your entire career: Aiming for the elusive but invaluable Quality Improvement. "When we implement a change to make our practice safer, smarter, more efficient, and better for our patients, we are really practicing quality improvement," says Margo J. Reeder, M.D., assistant professor with the department of dermatology at the University of Wisconsin School of Medicine and Public Health.

Now, Quality Improvement, or QI, has a name and a bigger role in practices of all types. "The changing landscape of healthcare payment and reimbursement has brought quality improvement to the leading edge of our practice," Dr. Reeder says. "As the country shifts to value-based healthcare, QI and outcomes will become a central part of what makes a ‘good’ dermatologist. By understanding the process for quality improvement, dermatologists can demonstrate their good work using valid quality improvement methods.”

Dr. Reeder and her co-presenter, Daniel D. Bennett, M.D., discussed QI in an interview with Dermatology Times before their presentation about the topic at the summer meeting of the American Academy of Dermatology in Boston.

QI may sound like a fuzzy buzzword or something that’s simply obvious—try to do a better job. But there’s more to it than that, says Dr. Bennett, vice chair of Clinical Affairs with the department of dermatology at the University of Wisconsin School of Medicine and Public Health. It even has a history.

The quality improvement movement largely arose in as a way to improve manufacturing processes, he says. "Patient care is obviously very different from manufacturing, but there are many elements in healthcare that are amenable to improvement through QI processes like PDSA" — Plan-Do-Study-Act.

### PLAN-DO-STUDY-ACT

Plan-Do-Study-Act, says Dr. Bennett, "is a tool to implement and study small changes which produces significant improvement in a system."

Here are the four parts of PDSA:

- **Plan** — What question are you trying to answer?
- **Do** — What happened?
- **Study** — How did what happened compare with the plan?
- **Act** — What is the next step?

“These ‘small tests’ can help you try out several different possible options on the course to developing a new process,” Dr. Reeder says. “A PDSA cycle is a limited trial, and the process of quality improvement involves many PDSA cycles.”

For example, “a PDSA cycle can be as simple as placing exam gloves in a new corner of the room or testing out a new camera to take biopsy site photos,” Dr. Reeder says.

A PDSA cycle is also limited, meaning the trial may be a success and could lead to other creative solutions. Or it could reveal unforeseen consequences which must also be taken into account.

### HOW TO EMBRACE QI

It’s important to understand that “real QI work” is not simply a way to follow regulations, Dr. Bennett says. “There may be some overlap between QI work and regulatory requirements, but QI must be motivated by a desire to improve patient care, lower costs, and create a fulfilling work environment.”

In his academic center, he says, “we are using QI processes, for example, to create uniform processes to improve clinic efficiency and patient safety. In my experience, many private practices excel in these areas, but with decreasing payments and increased regulatory burden, all practices will be challenged to improve efficiency without sacrificing patient care.”

Disclosures: Dr. Reeder and Dr. Bennett report no relevant disclosures.

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Options for treating drug-resistant lice

Randy Dotinga | Senior Staff Correspondent

**Don’t be a louse:** If you want to protect your patients against head lice, you need to understand the threat of these super-powered bugs—now often resistant to drugs—and the many ways to kill them off.

Lice are becoming more immune to over-the-counter drugs like Rid and Nix, says Raegan Hunt, M.D., Ph.D. Earlier this year, a study¹ examined head lice in 48 states (all but Alaska and West Virginia) and found 98% had developed mutations.

The good news: “There are several fairly recently FDA-approved topical lice treatments that can be used to combat the resistant ‘super lice,’” says Dr. Hunt, a pediatric dermatologist at Texas Children’s Hospital.

Dr. Hunt spoke about lice in an interview with Dermatology Times prior to her presentation at the summer meeting of the American Academy of Dermatology in Boston.

She offers these tidbits about the world of nits: head lice die in one to two days without feeding, and nits die within a week and cannot hatch if they are not near the scalp.

What can be done? Hygiene is helpful, she says. Machine wash and dry all clothing and bed linens worn in the two days before treatment. Items that can’t be washed should be placed in plastic bags for two weeks. Soak combs and brushes in hot water (at least 130°F) for five minutes. And vacuum the floor and furniture around where the infested person sits or sleeps.

Dr. Hunt also offers these pearls:

- Lice move by crawling. They cannot hop or fly.
- Pets do not play a role in transmission of human lice.
- Nits alone do not indicate contagiousness.
INDICATION AND USAGE
Enstilar® (calcipotriene and betamethasone dipropionate) Foam is indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older.
Apply Enstilar® to affected areas once daily for up to 4 weeks. Patients should discontinue use when control is achieved. Instruct patients not to use more than 60 g every 4 days.

IMPORTANT SAFETY INFORMATION
For topical use only. Enstilar® is not for oral, ophthalmic, or intravaginal use. Instruct patients to avoid use on the face, groin, or axillae, or if atrophy is present at the treatment site, and not to use with occlusive dressings, unless directed by a physician.
The propellants in Enstilar® are flammable. Instruct patients to avoid fire, flame, or smoking during and immediately after using this product.
Hypercalcemia and hypercalciuria have been observed with use of Enstilar®. If hypercalcemia or hypercalciuria develop, patients should discontinue treatment until parameters of calcium metabolism have normalized.
Topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticoid insufficiency. Risk factors include use of high-potency topical corticosteroids, use over a large surface area or on areas under occlusion, prolonged use, altered skin barrier, liver failure, and use in pediatric patients. If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent steroid. Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase total systemic corticosteroid exposure.
Adverse reactions reported in <1% of subjects treated with Enstilar® in clinical trials included application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, urticaria, and exacerbation of psoriasis.
Patients who apply Enstilar® to exposed skin should avoid excessive exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc. You may wish to limit or avoid use of phototherapy in patients who use Enstilar®.
There are no adequate and well-controlled studies of Enstilar® in pregnant women. Enstilar® should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. Because many drugs are excreted in human milk, caution should be exercised when Enstilar® is administered to a nursing woman. Do not use Enstilar® on the breast when nursing.
The safety and effectiveness of Enstilar® in pediatric patients have not been studied.

Please see Brief Summary on following page.

*Must be 18 years of age or older to be eligible. For specific eligibility requirements and program restrictions, visit Enstilar.com or call 1-855-772-7224.
Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% for topical use

Initial U.S. Approval: 2006

BRIEF SUMMARY: Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

Enstilar® (calcipotriene and betamethasone dipropionate) Foam is indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Flammability

The propellants in Enstilar® Foam are flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

Hypercalcemia and Hypercalcitria

Hypercalcemia and hypercalcitria have been observed with use of Enstilar® Foam. If hypercalcemia or hypercalcitria develop, discontinue treatment until parameters of calcium metabolism have normalized. The incidence of hypercalcemia and hypercalcitria following Enstilar® Foam treatment of more than 4 weeks has not been evaluated.

Effects on Endocrine System

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticoid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment area surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age. Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test. If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hyperglycemia, and gluocosuria.

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios.

Use of more than one corticosteroid-containing product at the same time may increase total systemic corticosteroid exposure.

Allergic Contact Dermatitis

Allergic contact dermatitis has been observed with topical calcipotriene and topical corticosteroids. Allergic contact dermatitis to a topical corticosteroid is usually diagnosed by observing a failure to heal rather than a clinical exacerbation. Corroborate such an observation with appropriate diagnostic patch testing.

Risks of Ultraviolet Light Exposures

Patients who apply Enstilar® Foam to exposed skin should avoid excessive exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc. Physicians may wish to limit or avoid use of phototherapy in patients who use Enstilar® Foam.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The rates of adverse reactions given below were derived from three randomized, multicenter, prospective vehicle and/or active-controlled clinical trials in subjects with plaque psoriasis. Subjects applied study product once daily for 4 weeks, and the median weekly dose of Enstilar® Foam was 24.8 g.

Adverse reactions reported in <1% of subjects treated with Enstilar® Foam included: application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, urticaria, and exacerbation of psoriasis.

Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Postmarketing reports, local adverse reactions to topical steroids include atrophy, striae, telangiectasia, dryness, perioral dermatitis, secondary infection, and milia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Pregnant women were excluded from the clinical studies conducted with Enstilar® Foam. Enstilar® Foam should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with Enstilar® Foam. Enstilar® Foam contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topically administered calcipotriene or corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Enstilar® Foam is administered to a nursing woman. Instruct the patient not to use Enstilar® Foam on the breast while nursing.

Pediatric Use

Safety and effectiveness of the use of Enstilar® Foam in pediatric patients have not been studied. Because of a higher ratio of skin surface area to body mass, children under the age of 12 years are at particular risk of systemic adverse effects when they are treated with topical corticosteroids. They are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency with the use of topical corticosteroids. Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients treated with topical corticosteroids.

Local adverse reactions including striae have been reported with use of topical corticosteroids in pediatric patients.

Geriatric Use

Of the total number of subjects in the controlled clinical studies of Enstilar® Foam in plaque psoriasis, 97 were 65 years or older, while 21 were 75 years or older. No overall differences in safety or effectiveness of Enstilar® Foam were observed between these subjects versus younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

PATIENT COUNSELING INFORMATION

[Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions For Use)]

Inform patients of the following:

• Instruct patients to shake before use.
• Instruct patients not to use more than 60 g every 4 days.
• Discontinue therapy when control is achieved unless directed otherwise by the physician.
• Avoid use of Enstilar® Foam on the face, underarms, groin or eyes. If this medicine gets on face or in mouth or eyes, wash area right away.
• Wash hands after application.
• Do not occlude the treatment area with a bandage or other covering unless directed by the physician. Instruct the patients not to use other products containing calcipotriene or a corticosteroid with Enstilar® Foam without first talking to the physician.
• Instruct patients who use Enstilar® Foam to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.). Physicians may wish to limit or avoid use of phototherapy in patients who use Enstilar® Foam.
• Enstilar® Foam is flammable; avoid heat, flame, or smoking when applying this medication.

The foam can be sprayed holding the can in any orientation except horizontally.

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Strategies to avoid diagnostic errors

RANDY DOTINGA | SENIOR STAFF CORRESPONDENT

By the numbers, it’s estimated that every single one of us will encounter a serious diagnostic error over our lifetime. Gordon Schiff, M.D., who studies medical errors, seems to have already surpassed his allotment.

Dr. Schiff, who was slightly out of breath when he spoke with Dermatology Times, says he suffers from an unusual form of pneumonia that was misdiagnosed by multiple doctors. It took eight weeks to get a correct diagnosis.

What goes wrong when this kind of thing happens? Plenty, says Dr. Schiff, who discussed medical errors in an interview before his presentation about misdiagnoses at the summer meeting of the American Academy of Dermatology in Boston.

“Diagnosis errors are common, often not even recognized, and there is a lot of ground for improvement on multiple fronts,” says Dr. Schiff, who’s associate director of the Center for Patient Safety Research and Practice at the Brigham and Women’s Hospital Division of General Medicine, safety director at the Harvard Center for Primary Care Academic Improvement Collaborative, and associate professor of Medicine at Harvard Medical School.

Indeed, Johns Hopkins University researchers estimated in a study last May that medical errors as a whole account for 10% of all deaths in the United States, making them the third leading cause of death.

The world of skin care is no stranger to diagnosis errors, Dr. Schiff says.

“It’s something that’s probably obvious to all the dermatologists every day,” he says. “They’re getting a lot of patients coming from primary care doctors who are misdiagnosed: I’m calling things acne; they’re saying it’s more serious. I’m saying something is cancer; they’re saying it’s not.”

Create a safety net to make sure that there are opportunities to notice and repair errors. To do this, take advantage of the power of technology to automate processes and ease burdens on staff.

Unfortunately, Dr. Schiff says, technology is often a hindrance: “Systems are clumsy to learn, they’re distracting, and there’s lot of potential for unintended consequences.”

As for Dr. Schiff himself, he didn’t let his own misdiagnosis slip quietly into the past. Instead, he tried to get information about the error back to his primary-care physician. But he didn’t seek a confrontation. “The idea is not to fight,” he says. “The idea is to improve.”

WHAT TO DO?

Dr. Schiff points to two key strategies:

Situational awareness. To accomplish this, worry about what can go wrong, develop ways to prevent errors, and be open about failures.

To that end, Dr. Schiff calls for an end to the conspiracy of silence around diagnosis mistakes. There needs to be more error reporting so physicians can learn from each other, he says, and gain more awareness of conditions that are frequently misdiagnosed. “What are the pitfalls,” he says, “the traps that people frequently fall into?”

Disclosure: Dr. Schiff reports grants/research funding from MedAware.

REFERENCE:
1. Makary MA, Daniel M. Medical error—the third leading cause of death in the US. BMJ. 2016;353:i2139.

LICE:
Treatment tips from page 14

Suspect sexual abuse if another kind of lice, pubic lice, appears in young or adolescent children.

TREATMENTS

Pyrethrins—pyrethrins like Rid and permethrin lotion 1% (Nix) — may not work due to the development of drug resistance.

Malathion lotion 0.5% (Ovide) works in a single application for most patients, but is limited to those aged 6 years and older. Resistance has been reported in the United Kingdom.

Ivermectin lotion 0.5% (Sklice) received FDA approval in 2012. It kills baby lice (nymphs) and works as a single application on dry hair without nit combing. It’s approved for children aged 6 months and older.

Spinosad 0.9% topical suspension (Natroba) was approved by the FDA in 2011. It’s approved for children aged 4 and up, and is also effective as a single application on dry hair without nit combing. Treatment is usually not needed.

Benzyl alcohol lotion 5% (Ulesfia) received FDA approval in 2009 and requires repeat treatment on the ninth day. It’s approved for those ages 6 months to 60 years.

Professional nitpicking services are available at $75-$100 an hour.

The AirAllé Lice Treatment, which uses heated air in a different way than a blow dryer, costs $170. One treatment is needed (it includes an hour of nit-picking and an hour of device usage), and it’s approved for ages 4 and up.

Keep in mind, Dr. Hunt says, that if you see large, live lice, they may be a sign of a reinestation. Also, she says, lice of different sizes can be a sign of possible resistance.

And be aware of how lice may affect patients and their families. “Patients diagnosed with an infestation or their family members may express embarrassment that the diagnosis reflects poorly on their home cleanliness or personal hygiene,” Dr. Hunt says. “Additionally, prior partial treatments or treatment failures may result in patients feeling reluctant to accept the diagnosis and treatment plan. Being aware of and sensitive to these potential patient concerns helps facilitate communication about infestations.”

REFERENCE
Protocols for drug reaction tx

Lack of awareness results in delayed diagnosis

LOUISE GAGNON | STAFF CORRESPONDENT

**QUICK READ**

There can often be delays in identifying SCARs and related conditions like TEN and SJS. Optimal management of these presentations involves multidisciplinary care.

**TREATMENT PROTOCOL**

Dr. Dodiuk-Gad and colleagues designed an assessment and treatment protocol for patients with SJS/TEN. Symptoms usually present within four days to a month after initiation of a drug therapy. Investigators note that SJS/TEN consists of “flu-like” symptoms in initial phases and progresses to cutaneous and mucous membranes with other systemic involvement. The culprit drug is withdrawn and patients are transferred to a specialist unit.

The challenge around studying conditions like DRESS, SJS, TEN, and AGEP is that the conditions are rare, explains Dr. Dodiuk-Gad. To respond to this challenge, Dr. Dodiuk-Gad and fellow researchers have established international research collaborations to investigate severe cutaneous adverse reactions (SCARs). Of note, researchers met in person at the World Congress of Dermatology in Vancouver, Canada, holding the 9th International Congress on Cutaneous Adverse Drug Reactions.

One study that has served as evidence for treatment of SJS/TEN is an open, phase 2 trial of cyclosporine, which was found to decrease mortality and the risk of epidermal detachment.

Treatment of DRESS involves ceasing treatment of the culprit drug, and subsequent treatment will depend on the severity and extent of systemic involvement, as well as the diagnosis of viral reactivation of herpes viruses, explains Dr. Dodiuk-Gad.

If there is no severe systemic involvement, options include topical corticosteroids, emollients, and H1-antihistamines. If there is severe systemic involvement, systemic corticosteroids equivalent to 1mg/kg/day of prednisone should be initiated. If there are life-threatening signs present, such as hemophagocytosis with bone marrow failure, severe hepatitis, or renal failure, systemic steroids in addition to intravenous immunoglobulin at dose of 2mg/kg over five days should be administered.

“In all cases of SCARS, counselling both the patient and family members about drug avoidance is necessary,” Dr. Dodiuk-Gad says.

Other health professionals such as ophthalmologists, gynecologists, clinical pharmacologists, pharmacists and plastic surgeons are typically involved in the care of patients with SJS/TEN, according to Dr. Dodiuk-Gad.

Researchers have developed a novel cell-based strategy for the treatment of psoriasis. According to the study’s senior author, synthetic biology–based gene circuits “can autonomously couple the detection of disease biomarkers with the production of therapeutic proteins... in the future, dermatologists could implant engineered autologous cells containing the cytokine converter and the implanted device takes full control of the therapy.”

LEARN THE DETAILS: BIT.LY/FUTUREOFPSORIASIS
Two fully solubilized active ingredients.¹
One water-based gel.¹

Let that sink in.

VELTIN® (clindamycin phosphate and tretinoin) Gel 1.2%/0.025% is an effective and tolerable topical treatment for acne.¹

Indication
VELTIN® (clindamycin phosphate and tretinoin) Gel 1.2%/0.025% is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

Important Safety Information Regarding VELTIN® (clindamycin phosphate and tretinoin) Gel 1.2%/0.025%

- VELTIN Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.
- Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea (with or without mucus), and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. VELTIN Gel should be discontinued if significant diarrhea or severe abdominal cramps occur. Severe colitis may result in death.
- Avoid exposure to sunlight and sunbathing when using VELTIN Gel. Patients with sunburn should be advised not to use VELTIN Gel until fully recovered. Use of sunscreen products and protective apparel are recommended. Weather extremes (e.g., wind and cold) also may be irritating to patients using VELTIN Gel.
- Observed local treatment-related adverse reactions (≤1%) in clinical studies with VELTIN Gel were application site reactions, including dryness, irritation, exfoliation, erythema, pruritus, and dermatitis. Sunburn was also reported. Incidence of newly assessed local skin reactions peaked at week 2 and then gradually decreased.
- VELTIN Gel should not be used in combination with erythromycin-containing products due to antagonism to the clindamycin component.
- Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. VELTIN Gel should be used with caution in patients receiving such agents.
- VELTIN Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- It is not known whether either clindamycin or tretinoin is excreted in human milk following use of VELTIN Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Due to possible serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug. Exercise caution if administering VELTIN Gel to a nursing woman.
- The efficacy and safety have not been established in pediatric patients below the age of 12 years.
- VELTIN Gel is not for oral, ophthalmic, or intravaginal use.

Please see brief summary of Prescribing Information on the next page.

REFERENCE: 1. VELTIN® (clindamycin phosphate and tretinoin) Gel 1.2%/0.025% Prescribing Information. Exton, PA: Aqua Pharmaceuticals; 2016.
VELTIN Gel
(clindamycin phosphate and tretinoin) Gel 1.2%/0.025%

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE
VELTIN® (clindamycin phosphate and tretinoin) Gel, 1.2%/0.025% is indicated for the topical treatment of acne vulgaris in patients 12 years and older.

2 CONTRAINDICATIONS
VELTIN Gel is contraindicated in patients with regional enteralis, ulcerative colitis, or history of antibiotic-associated colitis.

3 WARNINGS AND PRECAUTIONS
5.1 Colitis
Systemic absorption of clindamycin has been demonstrated following topical use. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. If significant diarrhea occurs, VELTIN Gel should be discontinued.

6 ADVERSE REACTIONS
6.1 Adverse Reactions in Clinical Trials
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

7 DRUG INTERACTIONS
7.1 Erythromycin
CLINICAL STUDIES
Vehicles

7.2 Neurouromuscular Blocking Agents
Clindamycin has shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, VELTIN Gel should be used with caution in patients receiving such agents.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C.

There are no well-controlled studies in pregnant women treated with VELTIN Gel. VELTIN Gel should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus. A limited teratology study performed in Sprague Dawley rats treated topically with VELTIN Gel or 0.025% tretinoin gel at a dose of 2 ml/kg during gestation days 8 to 15 did not result in teratogenic effects. Although no systemic levels of tretinoin were detected, craniofacial and heart abnormalities were described in drug-treated groups. These abnormalities are consistent with retinoid effects and occurred at 16 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison. For purposes of comparison of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of VELTIN Gel applied daily to a 50-kg person.

Clindamycin: Reproductive developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 180 mg/kg/day (480 and 240 times the recommended clinical dose based on body surface area comparison), respectively or subcutaneous doses of clindamycin up to 180 mg/kg/day (140 and 70 times the recommended clinical dose based on body surface area comparison, respectively) revealed no evidence of teratogenicity.

Tretinoin: Oral tretinoin has been shown to be teratogenic in mice, rats, hamsters, rabbits, and primates. It was teratogenic and fetotoxic in Wistar rats when given orally at doses greater than 1 mg/kg/day (32 times the recommended clinical dose based on body surface area comparison). However, variations in teratogenic doses among strains of rats have been reported. In the cynomolgus monkey, a species in which tretinoin metabolism is slower to humans than in other species examined, fetal malformations were reported at oral doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (32 times the recommended clinical dose based on body surface area comparison), although increased skeletal variations were observed at all doses. Dose-related teratogenic effects and increased abortion rates were reported in pigtail macaques.

With widespread use of any drug, a small number of birth defect reports associated temporally with the antenatal use of the drug would be expected to occur by chance. Thirty cases of temporally associated congenital malformations have been reported during 2 decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, hypoplasia/cleft (associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to fetus is not known.

8.3 Nursing Mothers
It is not known whether clindamycin is excreted in human milk following use of VELTIN Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VELTIN Gel is administered to a nursing woman.

8.4 Pediatric Use
Clinical trials of VELTIN Gel did not include sufficient numbers of subjects aged 16 and older to determine whether they respond differently from younger subjects.

9 NONCLINICAL TOXICOLOGY
9.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of VELTIN Gel or the effect of VELTIN Gel on fertility. VELTIN Gel was negative for mutagenic potential when evaluated in an in vitro Ames Salmonella reversion assay. VELTIN Gel was equivocal for clastogenic potential in the absence of metabolic activation when tested in an in vitro chromosomal aberration assay.

Clindamycin: One-day dermal administration of 1% clindamycin as clindamycin phosphate in the gel vehicle (32 mg/kg/day, 13 times the recommended clinical dose based on body surface area comparison) to mice for up to 2 years did not produce evidence of tumorigenicity.

Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (240 times the recommended clinical dose based on body surface area comparison) revealed no effects on fertility or mating ability.

Tretinoin: In 2 independent mouse studies where tretinoin was administered topically by 0.025% or 0.1% 3 times per week for up to 2 years no carcinogenicity was observed, with maximum effects of dermal amyloidyosis. However, in a dermal carcinogenesis study in mice, tretinoin applied at a dose of 5.1 mg/kg (4.1 times the recommended clinical dose based on body surface area comparison) 3 times per week for 20 weeks acted as a weak promoter of skin tumor formation following a single application of dimethylbenz(a)anthracene (DMBA).

In a study in female SENCAR mice, papillomas were induced by topical exposure to DMBA followed by promotion with 12-O-tetradecanoyl-phorbol-13-acetate or mezerein for up to 28 weeks. Topical application of tretinoin prior to each application of promoting agent resulted in a reduction in the number of papillomas and their size. However, papillomas resistant to topical tretinoin suppression were observed earlier for pre-malignant progression.

Tretinoin has been shown to enhance photocarcinogenicity in properly performed specific studies employing concurrent or intercurrent exposure to tretinoin and UV radiation. The photocarcinogenic potential of the clindamycin tretinoin combination is unknown. Although the significance of these studies to humans is not clear, patients should avoid exposure to sun.

The genotoxic potential of tretinoin was evaluated in an in vitro Ames Salmonella reversion test and an in vitro chromosomal aberration assay in Chinese hamster ovary cells. Both tests were negative.

In oral fertility studies in rats treated with tretinoin, the no-observed-effect-level was 2 mg/kg/day (64 times the recommended clinical dose based on body surface area comparison).

10 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Patient Information)

Instructions for Use
• At bedtime, the face should be gently washed with a mild soap and water. After patting the skin dry, apply VELTIN Gel as a thin layer over the entire affected area (excluding the eyes and lips).
• Patients should be advised not to use more than a pea-sized amount to cover the face and not to apply more often than once a day (at bedtime) as this will not make for faster results and may increase irritation.
• A sunscreen should be applied every morning and reapplied over the course of the day as needed. Patients should be advised to avoid exposure to sunlight, suntan, ultraviolet light, and other medicines that may increase sensitivity to sunlight.
• Other topical products with a strong drying effect such as abrasive soaps or cleansers may cause an increase in skin irritation with VELTIN Gel.

Skin Irritation
VELTIN Gel may cause irritation such as erythema, scaling, itching, burning, or stinging.

Colitis
During the 12 weeks of treatment, each local skin reaction peaked at Week 2 and gradually reduced thereafter.

11 CLINICAL PHARMACOLOGY
11.1 Absorption
2 mL/kg during gestation days 6 to 15 did not result in teratogenic effects. Although no systemic levels of tretinoin were detected, craniofacial and heart abnormalities were described in drug-treated groups. These abnormalities are consistent with retinoid effects and occurred at 16 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison. For purposes of comparison of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of VELTIN Gel applied daily to a 50-kg person.

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DRUG REACTIONS:
Screening tests may be indicated in at-risk populations from page 18

“The appropriate treatment of severe cutaneous drug reactions, mainly SJS/TEN is based on multi-disciplinary collaboration due to involvement of various organ systems,” she says.

Sandra Knowles B.Sc. Phm., a pharmacist at St. Michael’s Hospital in Toronto, Canada, and drug policy research specialist with the Ontario Drug Policy Research Network, spoke earlier this year about the identification, diagnosis and treatment of SCAR at the annual meeting of the Canadian Society of Hospital Pharmacists.

“In the community setting, severe adverse skin reactions may be missed,” Ms. Knowles says.

It is key that clinicians like pharmacists have a knowledge base about pharmacotherapies that cause SCARs, Ms. Knowles says.

Ms. Knowles echoes Dr. Dodiuk-Gad’s view that the rarity of the conditions has resulted in a sparse number of clinical trials being conducted, and as a result, there is an absence of high-level evidence for therapies.

Patient predictors have emerged to help detect which patients are at risk of developing SCAR. While it is a rare occurrence, patients who are being treated for gout with allopurinol, for example, can develop SJS/TEN if they carry HLA-B*5801. The drug abacavir can induce DRESS in patients who carry HLA-B*5701.

Screening tests to identify patients who carry relevant HLA alleles should be conducted in populations at risk before initiation of therapy, Dr. Dodiuk-Gad stresses. Access to the screening tests may vary across countries, she points out.

A survey conducted during the 9th International Congress on Cutaneous Drug Adverse Reactions in 2015 found that of 80 respondents, only 15 per cent reported that genetic screening is regularly conducted in their practice prior to initiation of allopurinol therapy. A total of 21 per cent reported that genetic screening is regularly conducted in their practices before initiation of carbamazepine, a drug that can induce SJS/TEN in patients who carry HLA-B*1502 and which can induce SJS/TEN and DRESS in patients who carry HLA-A*3101.

There is a direct economic cost to SCARs such as SJS/TEN, for patients can face long extended stays in hospital, according to Dr. Dodiuk-Gad. DT

References

STEM CELLS:
Hope beyond manufactured topicals from page 1

applied topically in commercial creams is minimal, and its benefit has not yet established.”

The field of dermatology, Dr. Geronomus says, will likely benefit from research underway with induced pluripotent stem cells, also known as iPSCs or iPS cells.

“These cells (taken from skin biopsies) can be grown and differentiated into almost any disease and subsequently used to evaluate the potential efficacy of new drugs and also used to predict drug toxicity,” Dr. Geronomus says.

TOPOLOGICAL USE NOT YET SUBSTANTIATED

“Stem cells don’t work in topical antiaging creams and treatments,” is the headline in a recent Miami Herald column, by Miami, Fla.-based dermatologist Leslie Baumann, M.D., CEO of Baumann Cosmetic and Research Institute. Dr. Baumann runs Skin Type Solutions Franchise Systems LLC, a dermatologist-developed resource that provides skin care education for dermatologists, their patients and their staff.

“It makes me sad when I see a dermatologist promoting stem cell products, because we need to be the expert resource on skincare that our patients can trust,” Dr. Baumann tells Dermatology Times. “I posted my newspaper column … and asked dermatologists to tell me if they agreed with it. About 60 of them said yes and none said no. That tells me that most dermatologists—or at least the ones that are my Facebook friends—understand that stem cells in topical products are worthless.”

Plant-based stem cells are simply too large to penetrate the skin and cannot live in the cream while it stays on the shelf for months or even years, Dr. Baumann says.

Dermatologist Richard Hope, M.D., of Lubbock Dermatology and Skin Cancer Center, in Lubbock, Texas, agrees.

“I believe the current use of stem cells’ in topical skincare products is of no value at this point. The stem cells’ are plant derived, dead and basically have no activity in human skin. This is marketing to a poorly informed public,” Dr. Hope says.

But there is hope, according to Dr. Hope, when one looks beyond manufactured topicals.

“Human stem cells will likely have an impact on skin rejuvenation and hair restoration. Probably similar to how PRP (platelet rich plasma) is used today,” Dr. Hope says. “These will be cosmetic procedures and not likely to be in topical skin care regimens, as the stem cells need to be harvested from the patient, and they do not directly penetrate the epidermis.”

WHERE THE SCIENCE LOOKS STRONG

Angela Bowers, M.D., of Southlake Dermatology, Southlake Texas, says that while there isn’t a physical or chemical way to make stem cells penetrate the skin that actually works, there are ways in which to stimulate these cells.

“However, there is an newest cosmetic product that uses defenses to stimulate our stem cells at the bulge of our hair follicles. The product is called Defenage [Progenitor Biologies] and has shown incredible

STEM CELLS see page 22
results for our patients,” Dr. Bowers says. “I believe this is the next biggest gamechanger in topical products for anti-aging, wound healing and a variety of other skin diseases and conditions.”

Amy Forman Taub, M.D., medical director, founder of Advanced Dermatology/skininfo.com, in Lincolnshire, Ill., and assistant clinical professor of dermatology at Northwestern University Medical School, Chicago, is among the researchers for Defenage. She says that to understand the basic cosmeceutical application of stem cells and how they regulate biological activity within the skin, dermatologists must first understand that there is no such thing as “generic” stem cell batch.

“Similar to people discussing curing cancer, as if it were all one illness, there are a myriad of different stem cell types,” Dr. Taub says. “Scientists from various groups have identified at least 10 stem cell types that reside within the hair follicle, although not all of them stimulate hair growth. Specifically one, the LG6+ stem cell, is targeted by Defenage, the new skincare product. Subsequent to application of this topical product on the skin, this LG6+ stem cell is stimulated to increase production of new keratinocytes.

LG6+ usually springs into action after we have experienced a cut or scrape, a reparative mechanism.”

This is a paradigm shift away from the application of a “soup” of multiple different growth factors to the targeting of one or multiple specific pathways of growth within the body.

“This change in thought reminds me of the shift from generalization reduction of the immune system with methylotrexate or cyclosporine for psoriasis and toward specific receptor blockade in the aberrant biochemical pathway,” Dr. Taub says. “Hair growth is a very complex biological process in which there are probably four to 10 factors that play a role at any given time. If we could target the specific molecules responsible for the pathways leading to the signal to hair follicles to change from a telogen hair to an anagen hair, then we would be closer to growing hair. PRP has been very popular but does depend on the older paradigm of flooding the tissue with intact growth factors (e.g., those in the serum) and hoping these native proteins or peptides will trigger growth. Newer technology will use biomimetic or manu-
“We use our NS-532 laser every day. It is easy to operate and very effective for vascular and pigmented lesions. We are very satisfied with the reliability and performance of this system.” David Goldberg, MD - NY / NJ
in vitiligo. Studies suggest that these cyto-toxic lymphocytes are increased in the blood and infiltrating into the epidermis in the areas of damaged melanocytes, she says: “Interferon (IFN)γ is key in mediating the destruction of melanocytes. This cytokine stimulates CXCL10, a chemokine that serves as a homing molecule that helps to attract CD8 cytotoxic lymphocytes into the skin.”

**WHITE PATCHES, BRUISED SOULS**

Far from just a skin ailment, the white patches of vitiligo can devastate patients’ self-image. For example, a beautiful 40-year-old patient recently told Dr. Grimes that the final straw of her self-esteem snapped when the mere sight of her face caused a stranger’s toddler to point at her and cry.

“In response to that incident, the patient said, ‘I don’t go out. I don’t date anymore. I have isolated myself, and I feel ugly.’ That’s a common story on the spectrum of patients’ experiences.”

When a patient presents with vitiligo, “It’s probably the longest and most detailed consultation I do. We take a very detailed history—looking at family history, time of disease onset, disease progression, associated symptoms, associated autoimmune illnesses and medications—to tease out any other causative factors that may be contributing to pigment loss.”

While getting the patient’s medical history, Dr. Grimes also subtly explores the disease’s psychological impact. Rather than asking direct, probing questions, “I go about it in a subdued, roundabout way—trying to let them talk about it first. I want them to be comfortable.” Instead of asking what impact vitiligo has had on their quality of life, she may ask about changes in patients’ daily routines, activities or hobbies. “Some will say, ‘I wear makeup all the time, even on my hands.’” Many patients limit social and recreational activities that require going out in public.

**QUICK READ**

Promising treatments under investigation for vitiligo include afamelanotide, prostaglandin analogues and JAK inhibitors. But don’t overlook established treatments such as phototherapy and steroid minipulses, an expert says.

Dr. Grimes also performs a detailed physical exam, complete with photos, and a thorough laboratory assessment. “By the time I finish that consultation, I’m able to put together a treatment regimen based on that patient’s symptoms.” She also assembles a healthcare team for each patient that, if needed, includes an immunologist or rheumatologist and a mental-health professional.

If a patient has limited disease, “I can treat them with a topical regimen involving topical corticosteroids and topical calcineurin inhibitors.”

**STABILIZATION AND REPIGMENTATION**

Patients with more than 10% to 15% involvement often will need phototherapy, which helps with both stabilization and repigmentation, according to Dr. Grimes. “I tell patients they must be in for the long haul—treatment for six to 12 months—and we will continue beyond that if patients are achieving an optimal response.”

Phototherapy is safe and easy to perform, she says. Although complications such as sunburn, “We are not seeing any skin cancers—melanoma or nonmelanoma. Vitiligo is probably protective for melanoma.” Phototherapy stimulates melanoblasts in the outer root sheaths of hair follicles to migrate to areas that need repigmentation, Dr. Grimes says. “But it’s also immunosuppressive in that it decreases the inflammatory immune response. It also has the ability to upregulate growth factors for melanocytes, such as alpha-melanocyte-stimulating hormone (α-MSH),

**“By the time I finish that consultation, I’m able to put together a treatment regimen based on that patient’s symptoms.”**

Pearl E. Grimes, M.D.

Los Angeles

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**EMERGING TREATMENTS**

For repigmentation, afamelanotide upregulates melanoblasts in the outer root sheath of the hair follicle, stimulating melanoblast differentiation and increased melanin production. Dr. Grimes says, “It probably also stimulates melanocyte proliferation.” A linear analog of basic fibroblast growth factor, endothelin 1 and others. And it decreases production of pro-inflammatory cytokines. It creates a more favorable environment for repigmentation.”

Home phototherapy is ideal for patients who can’t get to the office two or three times weekly, she says. “That’s the situation for many adults,” especially if they have children with vitiligo and otherwise busy lives. Dr. Grimes’ practice possesses 15 years’ experience with home-based narrowband UVB (NBUVB) phototherapy, which in one study proved superior to office-based excimer laser treatment.

“Home phototherapy is safe and extremely well-tolerated. We’ve had very few complications. But you must teach patients how to use the unit. The key value is that they are more consistent” with treatment than they would be if they had to go to the office. “I’m not going to say it’s better than what we can achieve in the office. But there’s enough efficacy to suggest that it’s clearly value added for someone who can’t come into the office regularly.”

Among oral options for stabilizing vitiligo, says Dr. Grimes, steroid mini-pulse therapy delivers therapeutic doses while minimizing—although not entirely avoiding—steroid side effects. “You can give dexamethasone 5 mg, or a lower dose of betamethasone on two consecutive days a week.” Multiple studies have shown that this approach can facilitate stabilization for many patients, she says.

In other recent studies, oral mini-pulses of 2.5 mg dexamethasone performed comparably to methotrexate 10 mg weekly and minocycline 100 mg daily. Along with antibacterial effects, she says, “Minocycline has antioxidant and anti-inflammatory properties; it can prevent cellular apoptosis; and it’s been shown that it can decrease production of a number of pro-inflammatory cytokines including IFNγ and tumor necrosis factor (TNFα), both of which have been implicated in vitiligo.”
REDISCOVER

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for Topical Solution, 20%

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Blue Light Photodynamic Therapy
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Please see full prescribing information on adjacent page.
Topical Solution Photodynamic Therapy for actinic keratoses. In 99% of active treatment patients, some or all lesions were erythematous shortly after treatment, while in 79% of vehicle treatment patients, some or all lesions were erythematous. In 35% of active treatment patients, some or all lesions were edematous, while no vehicle-treated patients had edematous lesions. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy. LEVULAN KERASTICK Topical Solution application to photodamaged perilesional skin resulted in photosensitization of photodamaged skin and in a photodynamic response (see Warnings and Precautions).

Other Localized Cutaneous Adverse Experiences: Table 1 depicts the incidence and severity of cutaneous adverse events in Phase 3 studies, stratified by anatomic site treated.

Application of LEVULAN KERASTICK Topical Solution to perilesional areas of photodamaged skin of the face or scalp may result in photosensitization. Upon exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, the treatment site will become photosensitive. After LEVULAN KERASTICK Topical Solution application, patients should avoid exposure of the photosensitized treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, or lights at close proximity) during the period prior to blue light treatment. Exposure may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Before exposure to sunlight, patients should, therefore, protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect against photosensitization reactions caused by visible light. If not been determined if perspiration can spread the LEVULAN KERASTICK Topical Solution outside the treatment site to eye or surrounding skin.

Irritation

The LEVULAN KERASTICK Topical Solution contains alcohol and is intended for topical use only. Do not apply to the eyes or to mucous membranes. Excessive irritation may be experienced if this product is applied under occlusion.

Coagulation Defects

The LEVULAN KERASTICK for Topical Solution has not been tested on patients with inherited or acquired coagulation defects.

ADVERSE REACTIONS

In Phase 3 studies, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK Topical Solution application followed by blue light exposure.

Photodynamic Therapy Response: The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK Topical Solution plus BLU-U treatment was observed in all clinical studies of LEVULAN KERASTICK for Topical Solution Photodynamic Therapy for actinic keratoses treatment. Stinging and/or burning subsided between 1 minute and 24 hours after the BLU-U Blue Light Photodynamic Therapy Illuminator was turned off, and appeared qualitatively similar to that perceived by patients with erythropoietic protoporphyria upon exposure to sunlight. There was no clear drug dose or light dose dependent change in the incidence or severity of stinging and/or burning.

In two Phase 3 trials, the sensation of stinging and/or burning appeared to reach a plateau at 6 minutes into the treatment. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of the patients at some time during treatment. The majority of patients reported that all lesions treated exhibited at least slight stinging and/or burning. Less than 3% of patients discontinued light treatment due to stinging and/or burning.

In the Phase 3 trials, the most common changes in lesion appearance after LEVULAN KERASTICK for Topical Solution Photodynamic Therapy were erythema and edema. In 99% of active treatment patients, some or all lesions were erythematous shortly after treatment, while in 79% of vehicle treatment patients, some or all lesions were erythematous. In 35% of active treatment patients, some or all lesions were edematous, while no vehicle-treated patients had edematous lesions. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy. LEVULAN KERASTICK Topical Solution application to photodamaged perilesional skin resulted in photosensitization of photodamaged skin and in a photodynamic response (see Warnings and Precautions).

Adverse Experiences Reported by Body System:

In the Phase 3 studies, 7 patients experienced a serious adverse event. All were deemed remote and not related to treatment. No clinically significant patterns of clinical laboratory changes were observed for standard serum chemical or hematologic parameters in any of the controlled clinical trials.

OVERDOSAGE

LEVULAN KERASTICK Topical Solution Overdose LEVULAN KERASTICK Topical Solution overdose has not been reported. In the unlikely event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 48 hours after ingestion. The consequences of exceeding the recommended topical dosage are unknown.

BLU-U Light Overdose

There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK Topical Solution application.

Information for Patients:

LEVULAN KERASTICK Photodynamic Therapy for Actinic Keratoses:

• The first step in LEVULAN KERASTICK Photodynamic Therapy (PDT) for actinic keratoses is application of the LEVULAN KERASTICK Topical Solution to actinic keratoses located on the patient’s face or scalp.

After LEVULAN KERASTICK Topical Solution is applied to the actinic keratoses in the doctor’s office, the patient will be told to return the next day. During this time the actinic keratoses will become sensitive to light (photosensitive). Care should be taken to keep the treated actinic keratoses dry and out of bright light. After LEVULAN KERASTICK Topical Solution is applied, it is important for the patient to wear light-protective clothing, such as a wide-brimmed hat, when exposed to sunlight or sources of light.

Fourteen to eighteen hours after application of LEVULAN KERASTICK Topical Solution the patient will return to the doctor’s office to receive blue light treatment, which is the second and final step in the treatment. Prior to blue light treatment, the actinic keratoses will be rinsed with tap water. The patient will be given goggles to wear as eye protection during the blue light treatment.

The blue light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, the patient will experience sensations of tingling, stinging, prickling or burning of the treated lesions. These feelings of discomfort should improve at the end of the light treatment.

Following treatment, the actinic keratoses and, to some degree, the surrounding skin, will redden, and swelling and scaling may also occur. However, these lesion changes are temporary and should completely resolve by 4 weeks after treatment.

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LAB-1442HW Rev C

DUSA PHARMACEUTICALS, INC.
**STEM CELLS:**

Hope beyond manufactured topicals *from page 22*

“Concerns include that the stem cells in some trials are generated using retroviruses, which have risks include cancer formation and other unanticipated outcomes. Many of the skin equivalents that have been created have only temporary benefit,” Dr. Kirkorian says. “As gene editing techniques are developed that are not dependent on retroviruses and can precisely repair the affected gene with durable results, this may prove a life-altering or life-saving treatment for these very unfortunate children and adults.”

**SO, WHEN?**

It could be years before dermatology sees an approved stem cell treatment for any indication.

Dr. Baumann says that might be 20 years before there’s a topical stem cell therapy that really works to rejuvenate aging skin.

“In the meantime, I believe that using topical ingredients like retinoids, glycolic acid, growth factors and defensins to influence stem cells is still the way to go,” Dr. Baumann says.

And she thinks injectable stem cell therapy for skin rejuvenation is more than a decade away from making it to market.

“It takes at least seven years to get through the FDA and, as far as I know, safe technology to inject stem cells to improve the skin’s appearance is not invented yet,” Dr. Baumann says.

Dr. Baumann concludes with a statement that most likely applies to many readers: “Hopefully they will solve this puzzle in the next 20 years because I’m getting older every day!”

**VITILIGO:**

Affect beyond the skin *from page 24*

α-MSH, afamelanotide also may possess immunomodulatory properties, she adds. “In our phase 2 study, the combination of afamelanotide and UVB was significantly superior to NBUVB monotherapy.”

A recently completed phase 2 vitiligo study in Singapore corroborates the U.S. study’s findings, says Dr. Grimes. “Hopefully, a phase 3 study will be underway in the United States within the next year.”

Additionally, she says, several studies have shown prostaglandin F2α analogues (latanoprost, bimatoprost) to be efficacious in vitiligo, either as monotherapy or in combination with NBUVB. These drugs can cause periorbital hyperpigmentation in patients with glaucoma. That was the template for our interest in using them for vitiligo. These prostaglandin F2α analogues increase melanocyte proliferation and the transfer of melanin to epidermal keratinocytes,” she says.

Because Janus kinase (JAK) inhibitors block the IFNγ-CXCL10 pathway, “There’s enormous interest in tofacitinib and ruxolitinib. Unfortunately only two cases have been published.”

Intralesional corticosteroids may also facilitate repigmentation, says Dr. Grimes. “I limit intralesional Kenalog (triamcinolone acetonide 2.5 to 3 mg/cc, Bristol-Myers Squibb) to acral areas because I don’t want patients to get any corticosteroid side effects such as atrophy in other affected areas.”

**MORE TO EXPLORE**

**Human alpha defensin 5 increases LGR stem cell migration**


**Adult hair follicles can act as multipotent stem cells in stress situations**


**Lgr6 marks stem cells in the hair follicle that generate all cell lineages of the skin**


**Epithelial stem cells and implications for wound repair**


**Disclosures:** Dr. Grimes has performed clinical research and/or served as a consultant for Allergan, Clenuvel, Galderma, Johnson & Johnson, Kythera, Procter & Gamble, Merz, Suneva and Valeant.

References


Disclosures: Drs. Geronemus, Hope, and Kirkorian report no relevant disclosures. Dr. Bowers has a financial interest in Progenitor, which owns Defenage. Dr. Taub is on the medical advisory board for MediCell Technologies, does paid research, and owns a small amount of stock. Dr. Simman is on the RenovaCare advisory board.
Postmarketing reports indicate that the effects of BOTOX®

**WARNING: DISTANT SPREAD OF TOXIN EFFECT**

Postmarketing reports indicate that the effects of BOTOX® Cosmetic and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses in children, spasticity and other approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and upper limb spasticity and at lower doses.

**CONTRAINDICATIONS**

BOTOX® Cosmetic is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

**WARNINGS AND PRECAUTIONS**

Lack of Interchangeability between Botulinum Toxin Products

The potency units of BOTOX® Cosmetic are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® Cosmetic cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect

Please refer to Boxed Warning for Distant Spread of Toxin Effect.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermalogic use of BOTOX® Cosmetic at the labeled dose of 20 Units (for glabellar lines), 24 Units (for lateral canthal lines), 44 Units (for simultaneous treatment of lateral canthal lines and glabellar lines) have been reported.

**Serious Adverse Reactions With Unapproved Use**

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX® injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX® to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX®. The safety and effectiveness of BOTOX® for unapproved uses have not been established.

**Hyersensitivity Reactions**

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea. If such reactions occur, further injection of BOTOX® Cosmetic should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent and, consequently, the causal agent cannot be reliably determined.

**Cardiovascular System**

There have been reports following administration of BOTOX® of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

**Pre-existing Neuromuscular Disorders**

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from onabotulinumtoxinA (see Warnings and Precautions).

**Dysphagia and Breathing Difficulties**

Treatment with BOTOX® and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing (see Boxed Warning).

**Pre-existing Conditions at the Injection Site**

Caution should be used when BOTOX® Cosmetic (onabotulinumtoxinA) treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

**Human Albumin and Transmission of Viral Diseases**

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

**ADVERSE REACTIONS**

The most frequently reported adverse event following injection of BOTOX® Cosmetic for glabellar lines was eyelid ptosis (3%).

The most frequently reported adverse event following injection of BOTOX® Cosmetic for lateral canthal lines was eyelid edema (4%).

**DRUG INTERACTIONS**

Co-administration of BOTOX® Cosmetic and anticholinergic drugs or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® Cosmetic may potentiate systemic anticholinergic effects.

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX® Cosmetic.

**USE IN SPECIFIC POPULATIONS**

BOTOX® Cosmetic is not recommended for use in children or pregnant women. It is not known whether BOTOX® Cosmetic is excreted in human milk. Caution should be exercised when BOTOX® Cosmetic is administered to a nursing woman.

Please see brief summary of full Prescribing Information on adjacent pages.

Please visit BotoxCosmetic.com for more information or call 1-800-BOTOXMD.

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#1 selling product of its kind in the world.*
Men are ready
It’s time to introduce them

The first and only FDA-approved treatment to temporarily improve moderate to severe lateral canthal lines* AND glabellar lines in adult patients.

*Commonly called crow’s feet.

Talk to your male patients today—they may be ready to learn more.
BOTOX® Cosmetic (onabotulinumtoxinA) for injection for intramuscular use (Brief summary of full prescribing information)

Manufactured by: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, 2525 DuPont Irvine, CA 92612

WARNING: DISTANT SPREAD OF TOXIN EFFECT
Postmarketing reports indicate the effects of BOTOX® Cosmetic and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include: muscle weakness, dryness, drooping eyelids, and difficulty swallowing. In some cases, they may have resulted from the administration of BOTOX® to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also be reported in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and upper limb spasticity and at lower doses.

INDICATIONS AND USAGE
BOTOX® Cosmetic for injection is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients.

CONTRAINDICATIONS
BOTOX® Cosmetic is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

WARNINGS AND PRECAUTIONS
Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX® Cosmetic are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® Cosmetic cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect

Postmarketing safety data from BOTOX® Cosmetic and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include: asthenia, generalized muscle weakness, dryness, drooping eyelids, dysphagia, dysphonia, dysarthria, urinary incontinence, and difficulty swallowing. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and upper limb spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of BOTOX/BOTOX® Cosmetic at the labeled dose of 20 Units (for glabellar lines), 24 Units (for lateral canthal lines), 44 Units (for simultaneous treatment of lateral canthal lines and glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX® for blepharospasm at the recommended dose (30 Units and below), strabismus, or chronic migraine at the labeled doses have been reported.

Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dryness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX® injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX® to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX®. The safety and effectiveness of BOTOX® for unapproved uses have not been established.

Hypersensitivity Reactions

Serious or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX® Cosmetic should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

Cardiovascular System

There have been reports following administration of BOTOX® of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropsychiatric diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, dryness, drooping eyelids, dysphagia, dysarthria, and respiratory compromise from onabotulinumtoxinA.

Dysphagia and Breathing Difficulties

Treatment with BOTOX® and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin (Dysphagia is a risk factor for several months, and requires use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscles may reduce the risk of dysphagia. Injections into the levator scapulae muscle may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

Pre-existing Conditions at the Injection Site

Caution should be used when BOTOX® Cosmetic treatment is used in the presence of inflammation at the proposed injection site(s), ptosis, or when excessive weakness or atrophy is present in the targeted muscle(s).

Corneal Exposure and Ulceration in Patients Treated with BOTOX® for Blepharospasm

Reduced blinking from BOTOX® Cosmetic injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with pre-existing eye disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Spatial Disorientation, Double Vision or Past-pointing in Patients Treated for Strabismus

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

ADVERSE REACTIONS

The following adverse reactions to BOTOX® Cosmetic (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects (see Warnings and Precautions)
- Hypersensitivity (see Contraindications and Warnings and Precautions)
- Dysphagia and Breathing Difficulties (see Warnings and Precautions)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates observed in clinical practice. BOTOX® and BOTOX® Cosmetic contain the same active ingredient in the same formulation but have different labeled Indications and Usage. Therefore, adverse events observed with the use of BOTOX® also have the potential to be observed with the use of BOTOX® Cosmetic. In general, adverse reactions occur within the first week following injection of BOTOX® Cosmetic and while generally transient, may have a duration of several months or longer. Extensive local pain, injection site reaction, inflammation, tenderness, swelling, erythema, and/ or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin (see Warnings and Precautions).

Glabellar Lines

Table 2 lists selected adverse reactions reported by ≥1% of BOTOX® Cosmetic treated subjects (N=456) aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of BOTOX® Cosmetic in the improvement of the appearance of glabellar lines.
Table 2: Adverse Reactions Reported by ≥1% of the BOTOX® Cosmetic treated Patients and More Frequent than in Placebo-treated Patients in Double-blind, Placebo-controlled Clinical Studies of Treatment of Glabellar Lines

<table>
<thead>
<tr>
<th>Adverse Reactions by System Organ Class</th>
<th>BOTOX® Cosmetic (N=505)</th>
<th>Placebo (N=1030)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial pain</td>
<td>6 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial paresis</td>
<td>5 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Eyelid ptosis</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Muscular Weakness</td>
<td>6 (1%)</td>
</tr>
</tbody>
</table>

Lateral Canthal Lines

Table 3 lists selected adverse reactions reported within 90 days following injection by ≥1% of BOTOX® Cosmetic treated subjects (N=526) aged 18 to 75 who were evaluated in two randomized, double-blind, placebo-controlled clinical studies to assess the use of BOTOX® Cosmetic in the improvement of the appearance of lateral canthal lines alone.

Table 3. Adverse Reaction Reported by ≥1% of BOTOX® Cosmetic treated Patients and More Frequent than in Placebo-treated Patients Within 90 Days, in Double-blind, Placebo-controlled Clinical Studies of Treatment of Lateral Canthal Lines

<table>
<thead>
<tr>
<th>Adverse Reactions by System Organ Class</th>
<th>BOTOX® Cosmetic 24 Units (N=526)</th>
<th>Placebo (N=530)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td>Eyelid edema</td>
<td>5 (1%)</td>
</tr>
</tbody>
</table>

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Treatment with botulinum toxins may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin.

In three Lateral Canthal Line trials, 916 subjects (517 subjects at 24 Units and 399 subjects at 44 Units) treated with BOTOX® Cosmetic had specimens analyzed for antibody formation. Among the 916 BOTOX® Cosmetic treated subjects, 14 subjects (1.5%) developed binding antibodies and no subjects (0%) developed the presence of neutralizing antibodies. The data reflect the subjects whose test results were considered positive or negative for neutralizing activity to BOTOX® Cosmetic in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BOTOX® Cosmetic with the incidence of antibodies to other products may be misleading.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that botulinum toxin injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

Post-marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin (see Warnings and Precautions).

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events.

The following adverse reactions by System Organ Class have been identified during post-approval use of BOTOX®/BOTOX® Cosmetic:

- **Eye disorders**
  - Diplopia, lagophthalmos; strabismus; visual disturbances; vision blurred

- **Gastrointestinal disorders**
  - Abdominal pain; diarrhea; dry mouth; nausea; vomiting

- **General disorders and administration site conditions**
  - Dehydration; malarial; pyrosis

- **Metabolism and nutrition disorders**
  - Anorexia

- **Musculoskeletal and connective tissue disorders**
  - Muscle atrophy; myalgia

- **Nervous system disorders**
  - Brachial plexopathy; dysarthria; facial palsy; hypoesthesia; localized numbness; myasthenia gravis; paresthesia; peripheral neuropathy; radiculopathy; syncope

- **Respiratory, thoracic and mediastinal disorders**
  - Apnea; respiratory depression and/or respiratory failure

- **Skin and subcutaneous tissue disorders**
  - Alopecia, including madarosis; hyperhidrosis; pruritus; skin rash (including erythema multiforme, dermatitis psoriasiform, and psoriasis vulgaris)

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with BOTOX® Cosmetic (onabotulinumtoxinA) for injection.

Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

Co-administration of BOTOX® Cosmetic and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

Anticholinergic Drugs

Use of anticholinergic drugs after administration of BOTOX® Cosmetic may potentiate systemic anticholinergic effects.

Other Botulinum Neurotoxin Products

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Muscle Relaxants

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX® Cosmetic.

USE IN SPECIFIC POPULATIONS

**Pregnancy**

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. BOTOX® Cosmetic should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

It is not known whether BOTOX® Cosmetic is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX® Cosmetic is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness in patients below the age of 18 years have not been established.

**Geriatric Use**

**Glabellar Lines**

In the two initial glabellar lines clinical studies of BOTOX® Cosmetic, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older.

**Lateral Canthal Lines**

In the two lateral canthal lines clinical studies of BOTOX® Cosmetic, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older.

**OVERDOSAGE**

Excessive doses of BOTOX® Cosmetic (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, these patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization. The person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection (see boxed Warning and Warnings and Precautions).

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raised against botulinum toxin is available from the CDC. If you do not receive a response within 30 minutes, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm.

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Based on 71823US21
APG1B16
How technology revolutionized the business of tattoo removal

RANDY DOTINGA | STAFF CORRESPONDENT

Tattoo removal has become big business with entire clinics devoted to helping people rid themselves of unwanted body art. But not too long ago, dermatologists weren’t rushing to reap rewards from regret.

“It was nothing to hear things like ‘I don’t want those people in my waiting room’ or ‘I choose to have tattoo removal clinic on a day when I don’t bring in any other patients,’” says Myrna Armstrong, Ed.D., R.N., an emeritus professor at Texas Tech University Health Sciences Center in Lubbock, TX and one of the nation’s leading tattoo researchers.

It didn’t help that physicians trended toward a shared background — white, Anglo-Saxon Protestant — that molded their prejudices about tattoos and those who had them, she says. And, of course, anti-tattoo bias in society as a whole contributed to the phenomenon of tattoo regret.

But things changed over the past decade, Ms. Armstrong says. Now, dermatologists are much more willing to work with patients who want their tattoos to go away. At the same time, laser technology is giving dermatologists more power than ever to make tattoos dim or disappear.

But tattoo removal isn’t a simple, painless or inexpensive process. “Patients are quickly discouraged by the cost and the number of treatments,” cautions Suzan Obagi, M.D., an associate professor of dermatology and plastic surgery and director of the cosmetic surgery and Skin Health Center at the University of Pittsburgh Medical Center.

Indeed, only the simplest and least colorful tattoos tend to vanish entirely after treatment. “Many patients come in with unrealistic expectations, and only about 50% of them follow through on the treatments to the bitter end,” says George J. Hruza, M.D., MBA, a dermatologist in private practice and adjunct professor of dermatology at St. Louis University. “The ones that stick with it are very motivated.”

It can cost $200-$300 per treatment for five to 10 treatments to remove a small tattoo. For larger tattoos, the treatments may cost $500-$600 for a total of as much as $5,000

QUICK READ
Changes in technology, methods, and attitudes have resulted in tattoo removal being big business. Challenges remain, including management of patient expectations, identifying optimal patients, and expense.

Three hot nonsurgical devices

✦ A radio-frequency device that helps to tighten skin, including around the vagina.

✦ A non-invasive fat removal device for sculpting.

✦ A hair grafting device that promises rapid procedures.

GET THE DETAILS: BIT.LY/3HOTNONSURGICALDEVICES

Quotable

“I felt this was extremely misleading and confusing for the general public.”

Omar A. Ibrahimi, M.D.
Stamford, Conn.

Discussing his observation of the number of specialists offering aesthetic services, which motivated him to conduct a study to identify those behind notable advances in the scientific literature.

See story page 38

DT Extra

TRENDING:

DERMS TOPS IN NONSURGICAL COSMETIC PROCEDURES
Study proves derms rank highest

COSMETIC CONUNDRUMS
Old trends returning to high fashion
TATTOOS: Advances in lasers offer hope for scarless removal from page 32

INK-BUSTING LASERS OFFER RELIEF
Up until about the mid-1980s, dermatologists didn’t have good options on the tattoo-removal front. “A tattoo could be excised or cut out, or sanded off with dermabrasion and sometimes with salt,” says Melbourne, Fla., dermatologist Terrence A. Cronin Jr., M.D. “All these methods led to scarring, and it wasn’t until lasers came along that the hope of scarless removal of tattoos began to be considered.”

Q-switched lasers changed the tattoo-removal business for good in the mid-1980s. “With the laser, you actually fragment the tattoo ink particles and kill the cells that contain them,” Dr. Hruza says. “Over several treatments, you can fade a tattoo, and the damage is confined to the area of the ink and the cells that contain it.”

This approach wasn’t ideal, however. According to Dr. Hruza, a number of treatments were needed, and they had to be separated by two months, he says. But advances in technology over the past several years have revolutionized the business of tattoo removal.

For one thing, Dr. Hruza says, physicians can perform multiple treatments on individual patients in one day instead of spreading them out over many months. Also, he says, lasers can now deliver pulses in less than a nanosecond, packing a punch of power in a short pulse that pulverizes the ink particles more efficiently.

The key, he says, is to use lower energy at first when densely packed ink can overcome the body’s ability to recover easily. “Then you increase the energy as the tattoo fades, and you have less ink,” he says.

Dr. Obagi cautions dermatologists must be careful to not burn the skin. “Otherwise, the patient will be left with a hypopigmented shadow in the shape of the tattoo,” she says. “Or worse yet, the patient can believe with hypertrophic scarring in the shape of the tattoo.”

“Many patients come in with unrealistic expectations, and only about 50% of them follow through on the treatments to the bitter end.”

George J. Hruza, M.D., MBA St. Louis, Mo.

Managing expectations is key
“A good rule of thumb for tattoo removal is to always lower patient expectations,” Dr. Cronin says. “Never promise perfection, as complete removal may not be possible, and many sessions may be required for satisfactory results.”

A variety of factors affect whether a tattoo can be fully or partially removed via laser:

✓ The best candidates still tend to be patients with light skin and dark tattoos—black and dark blue,” Dr. Obagi says. “The patient will still require multiple treatments, but fewer with picosecond laser than nanosecond lasers.”

✓ Red inks may also be removed with a smaller number of treatments, while green inks respond well to alexandrite lasers, Dr. Hruza says.

✓ Flesh-colored tattoos are the hardest to remove, Dr. Obagi says. “The flesh-tone ink contains various iron oxides that can turn from flesh color to black when hit with a laser. So a barely noticeable flesh-colored tattoo can become a black tattoo if treated. Red ink, as in lip tattoos, has the same potential risk.”

According to Dr. Hruza, skin-colored and pastel-colored tattoos can also turn permanently black with laser treatment.

✓ Black eyeliner and eyebrow tattoos can often fade easily with treatment.

Dr. Hruza says, but “the process is slower when you move farther from the head and neck.” Ankle tattoos, for example, tend to not respond as well to treatment, he says. For her part, Dr. Obagi says black tattoos on the thin skin of the wrist are the easiest to remove.

TATTOO REMOVAL ISN’T CHEAP
The cost for removal of a small tattoo can be $200-$300 per treatment for five to 10 treatments, Dr. Hruza says. For larger tattoos, he says, the treatments may cost $500-$600 for a total of as much as $5,000.

Insurance won’t cover tattoo removal except in isolated cases. “If someone is in the military, we’ve actually had their insurance cover tattoo removal,” Dr. Hruza says. And he says insurance may cover the removal of an involuntary tattoo due to dirt ground into skin in a vehicle accident.

Considering the hassle and expense, are removable tattoo inks on the horizon? Matt Lodder, Ph.D., a tattoo researcher and lecturer in contemporary art and visual culture at the University of Essex in the U.K., says researchers have been trying to design inks that are vulnerable to lasers. However, he says they have limitations and aren’t popular.

“For most tattoo collectors, the permanence is actually an important part of tattooing,” he says. “Most artists I speak to would certainly not embrace a technology which made tattooing easily removable.”

That means the big business of tattoo removal will be hard to dislodge — just like tattoos themselves. DT

MORE TO EXPLORE
The earliest firm evidence of human tattoos dates back to about 5,000 years ago. No one knows when a first human regretted a tattoo, but artists have offered “home remedies” for removal since at least the late 19th century. Read a brief history of tattoos: bit.ly/apathtotattooregret
Dermatologists claim top nonsurgical cosmetic procedures

QUICK READ
Dermatologists have had a hand in the research, development and shaping of the majority of noninvasive and minimally-invasive cosmetic medical procedures, according to a recent study. In fact, dermatology ranked higher than many other specialties. Physicians should use this data with patients to highlight their expertise.

performed by dermatologists,” says the study’s lead author Omar A. Ibrahimi, M.D., Ph.D., ASDS member, and dermatologist in practice at the Connecticut Skin Institute, Stamford, Conn.

And while the study looks at 18 commonly performed cosmetic procedures, there are other newly approved options developed in large part by dermatologists, including Kybella (Allergan) and Cellfina [Ulthera], which didn’t make it into the paper, according to Dr. Ibrahimi.

LETTER THE LITERATURE DECIDE
Dr. Ibrahimi became motivated to perform the study when he first started practicing dermatology.

“I saw that in the real world, there is an endless ‘buffer’ of providers (ranging from core specialists to other physicians to midlevel providers, nurses, medical assistants and even lay people) that were providing noninvasive and minimally-invasive cosmetic procedures and were claiming expertise,” he says. “I felt this was extremely misleading and confusing for the general public.”

Dr. Ibrahimi and colleagues looked for answers by searching the peer-reviewed scientific literature. They looked for specific procedures, came up with search terms and pulled the most cited papers on each topic.

“Studies that tend to be highly cited tend to be the most valuable from a research perspective,” he says.

The authors then identified each study’s senior author, first author and corresponding author, looked up those authors’ specialties and assigned a citation score based on the findings.

NOTABLE DIFFERENCES
That’s where the study points to some notable differences. For example, in the category of botulinum toxin for skin aging, dermatology had a citation score of 705.33, which was more than double the next closest specialty.

In laser hair removal, dermatology’s citation score of 1,425 for dermatology was markedly higher than the next highest score at 198. A citation score of 1,316.33 for dermatology in chemical peels, dwarfed the next closest specialty, plastic surgery, which had a score of 190.

Sumaira Aasi, M.D., professor and director of Mohs and dermatologic surgery at Stanford University, who is not a study author, says she thinks dermatologists probably have a sense that they are the specialists who are innovating, modifying and advancing these techniques.

“But it’s a nice visual confirmation to look at it in this scientifically quantifiable way and see that not only are we doing that, but the incredible contrast in the numbers … of citations that we have compared to other specialists,” Dr. Aasi says.

EDUCATING THE PUBLIC
Dermatologists should use the data from this study during one-on-one consultations with patients, as educational information in their waiting rooms, in marketing materials, on social media and, in general, to educate the public,

“It’s not necessarily pitting one aesthetic specialty against the other; it’s helping to bring awareness to the average Joe and average Jane that these procedures were really kind of fostered, perfected and developed by dermatologists.”

Omar A. Ibrahimi, M.D., Ph.D.
Connecticut Skin Institute, Stamford, Conn.
Kenalog®-10 Injection
(triamcinolone acetonide injectable suspension, USP)
"... patients are bombarded with so many options. They can get their Botox (Allergan) at a hair salon; they can get it at a medi spa; they can get it in an OB/gyn’s office; or at their primary care doctor’s practice,” he says. “It’s not necessarily pitting one aesthetic specialty against the other; it’s helping to bring awareness to the average Joe and average Jane that these procedures were really kind of fostered, perfected and developed by dermatologists.”

Educating the lay public takes time, persistence and effort, Dr. Ibrahimi says. The hope is that by driving patients to those most qualified clinicians to do noninvasive and minimally-invasive procedures, the specialty can help reduce complications.

"... even though these are cosmetic procedures, there is a certain amount of medicine that you have to know and master to safely do these procedures,” he says.

A dermatologist’s training centers on minimally-invasive or noninvasive treatments, while more invasive surgery is more in the realm of plastic surgeons and other cosmetic surgical specialties, Dr. Ibrahimi says.

Philadelphia dermatologist Nazanin Saedi, M.D., an assistant professor of dermatology and cutaneous biology at Thomas Jefferson University, says she isn’t surprised by the findings but thinks the general public might be.

“I think this is an important study for the specialty because it validates what we know and also gives credit to the dermatologists who have worked so hard to develop these technologies and really be innovators in the field of noninvasive procedures,” says Dr. Saedi, who is not a study author.

Dr. Aasi adds that the study might motivate and inspire current dermatologists and the specialty’s younger generation.

“[It confirms] that we really have a foothold in the health and beauty of the skin. We are the custodians of this organ, and we can continue to advance and make even further contributions,” Dr. Aasi says. DT

REFERENCE:

Tips to avoid laser device complications

LISETTE HILTON | STAFF CORRESPONDENT

There are four relatively simple things that cosmetic surgeons can do in their daily practices to avoid complications and to improve outcomes of common cosmetic procedures, according to Joel L. Cohen, M.D., director of AboutSkin Dermatology and Derm Surgery in Greenwood Village and Lone Tree, Colo., who discussed complications with lasers and other energy-based devices and combination therapy with injectables during the 36th Annual Conference of the American Society for Laser Medicine & Surgery, Boston, Mass.

① Re-evaluate each visit for recent sun-exposure and any hint of a tan

When using laser devices, physicians should re-evaluate patients for recent sun-exposure and any suggestion of a tan before every treatment, according to Dr. Cohen. “It’s important to look at the skin color for that specific day, and not just reflexively use similar settings to what we did last time or at their baseline,” he says. “The point is to always look for subtleties of a recent tan or sun exposure. [Detecting those changes] may cause you to cancel a procedure or to back off a little bit,”

② Consider looking at the literature before using antiviral prophylaxis

Physicians often prescribe antiviral prophylaxis prior to ablative resurfacing of the face, but some anti-viral oral regimens may be more effective than others. “One thing that’s clear is valacyclovir and famciclovir have better absorption and better bioavailability than acyclovir. And now that valacyclovir is generic, it’s more affordable,” Dr. Cohen says. “Valacyclovir is my go-to antiviral as I have had at least a couple of patients over the years who have actually broken through and had HSV around their mouths after resurfacing even with acyclovir prophylactic doses.”

③ Take a look at post-procedure pustules before shrugging them off as non-inflammatory from occlusive ointments

Patients often have noninflammatory pustules, with no redness or swelling, after laser and other resurfacing procedures. The skin condition is probably related to the occlusive nature of some of the ointments physicians use, such as petrolatum. It’s still a good idea, says Dr. Cohen, to have these patients come in when this does occur and to specifically evaluate them to see the distribution and to see if there is erythema or swelling, or if there’s anything else going on like staph or yeast.

④ Consider using pre-procedure botulinum toxin to improve filler, resurfacing and surgical outcomes

Dr. Cohen says studies and personal experience suggest botulinum toxin done in conjunction with fillers, resurfacing and even skin cancer surgery in some specific areas can help to improve outcomes.

“Before I do resurfacing around the mouth or around the eyes, I often use botulinum toxin a week or two before to help immobilize the area and improve results,” he says. “I also commonly do that before skin cancer surgery on an area where it may be tight and highly mobile with animation, like on the forehead. DT

Disclosure: Related to injectable aesthetic agents, Dr. Cohen consults with and does clinical trials for Allergan, Galderma, Merz. Related to the ICON and Skinfid, Dr. Cohen previously consulted and participated in clinical trials for Palomar before they were purchased a few years ago by Cynosure.

Read the complete tips: bit.ly/AvoidLaserComplications
Acne, rosacea, seborrheic dermatitis. My family has it all. Thankfully, so does AVAR.

INDICATIONS: The AVAR® (sodium sulfacetamide and sulfur) product family (AVAR® Cleanser, AVAR® LS Cleanser, AVAR® Cleansing Pads, AVAR® LS Cleansing Pads, AVAR-e® Emollient Cream, AVAR-e Green® Color Corrective Emollient Cream, AVAR-e® LS Emollient Cream, AVAR® Foam, AVAR® LS Foam) is indicated for use in the topical control of acne vulgaris, acne rosacea and seborrheic dermatitis. Sodium sulfacetamide is a sulfonamide with antibacterial activity while sulfur acts as a keratolytic agent.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: AVAR Cleanser, AVAR LS Cleanser, AVAR Cleansing Pads, AVAR LS Cleansing Pads, AVAR-e® Emollient Cream, AVAR-e Green Color Corrective Emollient Cream, AVAR-e® LS Emollient Cream, AVAR® Foam, and AVAR LS Foam are contraindicated for use by patients with known or suspected hypersensitivity to sulfonamides, sulfur or any other components of these preparations. These AVAR brand products should not be used by patients with kidney disease. Please see Brief Summary of full Prescribing Information, including use in pregnant and nursing mothers, on the following page.

*Of sodium sulfacetamide + sulfur medications, according to Source Healthcare Analytics PHAST Prescription data, accessed March 2016.
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INDICATIONS

The AVAR (sodium sulfacetamide and sulfur) product family (AVAR Cleanser, AVAR LS Cleanser, AVAR Cleansing Pads, AVAR LS Cleansing Pads, AVAR-e Emollient Cream, AVAR-e LS Emollient Cream, AVAR-e GREEN Color Corrective Emollient Cream, AVAR Foam, and AVAR LS Foam) is indicated for use in the topical control of acne vulgaris, acne rosacea and seborrheic dermatitis.

CONTRAINDICATIONS

AVAR Cleanser, AVAR LS Cleanser, AVAR Cleansing Pads, AVAR LS Cleansing Pads, AVAR-e Emollient Cream, AVAR-e LS Emollient Cream, AVAR-e GREEN Color Corrective Emollient Cream, AVAR Foam, and AVAR LS Foam are contraindicated for use by patients with known or suspected hypersensitivity to sulfonamides, sulfur or any other component of these preparations. The AVAR brand products should not be used by patients with kidney disease.

WARNINGS

Sulfonamides are known to cause Stevens-Johnson syndrome in hypersensitive individuals. Stevens-Johnson syndrome has also been reported following the use of sodium sulfacetamide topically. Cases of drug-induced systemic lupus erythematosus from topical sulfacetamide, including one case with a fatal outcome, have been reported. KEEP OUT OF THE REACH OF CHILDREN.

PRECAUTIONS: FOR EXTERNAL USE ONLY. NOT FOR OPHTHALMIC USE.

General: Nonsusceptible organisms, including fungi, may proliferate with use of these preparations.

Although rare, sensitivity to sodium sulfacetamide may occur. Therefore, caution and careful supervision should be observed when prescribing these products for patients who may be prone to hypersensitivity to topical sulfonamides. Patients who may be prone to hypersensitivity to topical sulfonamides should be carefully monitored. Systemic toxic reactions (e.g., agranulocytosis, acute hemolytic anemia, purpura hemorrhagica, drug fever, jaundice, and contact dermatitis) indicate sensitivity to sulfonamides. Particular caution should be employed if areas of denuded or abraded skin are involved. Systemic absorption of topical sulfonamides is greater following application to large, infected, abraded, denuded or severely burned areas. Under these circumstances, any of the adverse events produced by the systemic administration of these agents could potentially occur, and appropriate observations and laboratory determinations should be performed.

If the condition under treatment becomes worse, or irritation, signs of hypersensitivity, or other untoward reactions occur, the product(s) should be discontinued and appropriate therapy instituted. Patients should be carefully observed for possible local irritation or sensitization during long-term therapy. The object of this therapy is to achieve desquamation without irritation, but sodium sulfacetamide and sulfur can cause reddening and scaling of the epidermis. These side effects are not unusual in the treatment of acne vulgaris, but patients should be cautioned about the possibility.

Carcinogenicity, Mutagenesis and Impairment of Fertility

Long-term animal studies to assess carcinogenic potential of these products have not been performed. Studies on reproduction and fertility also have not been performed. Chromosomal nondisjunction has been reported in the yeast, Saccharomyces cerevisiae, following application of sodium sulfacetamide. The significance of this finding to the topical use of sodium sulfacetamide in the human is unknown.

Pregnancy

Category C: Animal reproduction studies have not been conducted with these products. It is also not known whether these products can affect reproduction capacity or cause fetal harm when administered to a pregnant woman. These products should be used by a pregnant woman only if clearly needed or when potential benefits outweigh potential hazards to the fetus.

Nursing Mothers

It is not known whether these drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when these products are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients under the age of 12 have not been established.

ADVERSE REACTIONS

Reports of local irritation and hypersensitivity to sodium sulfacetamide are uncommon. The following adverse reactions, reported after administration of sterile ophthalmic sodium sulfacetamide, are noteworthy: instances of Stevens-Johnson syndrome and instances of local hypersensitivity which progressed to a syndrome resembling systemic lupus erythematosus; in one case a fatal outcome was reported.

DRUG INTERACTIONS

These products are incompatible with silver preparations.

OVERDOSAGE

The oral LD_50_ of sulfacetamide in mice is 16.5 g/kg. In the event of overdosage, emergency treatment should be started immediately.

Manifestations: Overdosage may cause nausea and vomiting. Large oral overdosage may cause hematuria, crystalluria and renal shutdown due to the precipitation of sulfa crystals in the renal tubules and the urinary tract. Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdosage.

PATIENT COUNSELING INFORMATION

Patients should discontinue the use of any of these products if the condition becomes worse or if a rash develops in the area being treated or elsewhere. The use of these products also should be discontinued promptly and the physician notified if any arthritis, fever or sores in the mouth develop. Avoid contact with eyes, lips, and mucous membranes.

For more detailed information, please read the full Prescribing Information for each product.

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AVA-P167529-3
Old trends new again
False eyelashes, hair extensions and dry shampoo

Q: What is fueling the resurgence of false eyelashes?
A: Just when you thought the false eyelashes of the 1960s were only a thing of the past, they are back! And they are back even bigger, longer, and more innovative than before. What’s new? The false eyelashes of the 1960s were made of synthetic hair attached to a band that was glued to the base of the eyelashes. While these inexpensive lashes can still be purchased, the new fad is to glue individual lash hairs to the base of the existing lashes. The newer lashes are also made of synthetic materials, but they are lighter and able to hold a much better curl, with a tapered hair tip. The individual lashes are glued on one at a time and are shed as the natural lash to which they are glued is shed. Since the eyelashes have a much shorter anagen growth phase, the lashes need to be redone every three to four weeks. This is actually good because it can be very difficult to remove the glue from the natural eyelashes without breaking the hair.

The two most common issues associated with the newer false eyelashes are eyelash loss and infection. Eyelash loss can be avoided by using shorter lighter prosthetic eyelashes. It is also a good idea not to wear the eyelashes continually, allowing a month rest every three to six months for the hairs to regrow. This will also prevent infection. It is important to keep the false eyelashes clean, but repeated washing will loosen the prostheses.

Advise the patient to allow the shower water to run over the face and eyelashes when rinsing hair shampoo. This will provide some cleansing without damaging the prostheses.

The glue that is used with the false eyelashes does contain methacrylate, a relatively common allergen. Methacrylate allergic patients should not use false eyelashes.

Q: Can hair extensions be worn safely?
A: Hair extensions are seeing a resurgence similar to that of false eyelashes. Hair extensions are favored over wigs because they are semipermanent, less likely to be lost, and nicely simulate natural hair. Hair extensions can be used to increase length, improve fullness, and create a hairstyle. They can be fashioned from synthetic or natural human hair, but the synthetic fibers are more popular because they are cheaper, more resistant to breakage, and lighter.

There are several ways the synthetic hair can be attached to the wearer. Clumps of synthetic hair can be glued to a clump of natural hair. This is known as hair bonding and is very similar to the false eyelash technique discussed previously. The synthetic hair can also be wefted, meaning it is sewn to a woven band, and either glued to the scalp or sewn to the hair as it exits the scalp. The longer overlying hair is used to cover the sewn-in extensions. This technique is most popular, as it very quickly allows hair to be added both for fullness and length. Finally, the synthetic hair can be braided into existing braids, a technique known as hair weaving.

The only problem with all of these hair extension techniques is possible traction alopecia resulting from the weight of the hair pulling against the scalp.

Q: Why are dry shampoos again in vogue?
A: Dry shampoos were very popular and actually developed prior to the modern liquid shampoos. They were used when warm running water was not available in all homes and most women wore long hair styled into a variety of buns. The advantage of the dry shampoo was preservation of the hairstyle and odor control. Dry shampoos are used today for much the same reason.

With the new popularity of dyed hair, dry shampoos prolong the life of the hair color since permanent and semipermanent dyes fade with water contact. The use of elaborate hair extensions, discussed previously, also last longer when hair water contact is avoided.

Dry shampoos are dusted on the scalp and are a fragranced powder. The powder absorbs sebum and is then brushed out of the hair. It does not replace shampooing, but can prolong the interval between shampooing. Dry shampoos are not recommended for persons with seborrheic dermatitis or other scalp infections. Dry shampoos do appear to give the hair more body, however, as the unremoved particles increase friction between the hair shafts allowing the hair to stand further away from the scalp appearing more abundant. Many mature women who do not wish to have a wet head after shampooing prefer dry shampoos, since their sebum production is reduced and the dry shampoo can be used in between visits to the hair salon. DT
Armamentarium grows for advanced BCC

Vismodegib study confirms safety, efficacy

JOHN JESITUS | SENIOR STAFF CORRESPONDENT

The largest vismodegib trial to date reinforces the drug’s safety and efficacy in locally advanced and metastatic basal cell carcinoma (LABCC, MBCC), according to a poster presented at the American Society of Clinical Oncology Annual Meeting (June 2016, Chicago). For many patients worldwide, however, the treatment’s affordability remains in question.

STEVIE STUDY

In the “Study of Vismodegib in Patients with Locally Advanced or Metastatic Basal Cell Carcinoma” (STEVIE study; NCT01367665), vismodegib 150 mg OD provided benefit for more than 90% of patients, including 68% who responded to treatment and 26.6% who had stable disease after treatment, says study co-author Axel Hauschild, M.D. He is professor of dermatology at the University of Kiel in Kiel, Germany.

The massive number of patients treated—1,215—confirms findings of the drug’s phase 1 and 3 trials, which included 30 and 100 patients, respectively, according to Dr. Hauschild.

Dallas-based dermatologist and dermatopathologist Clay J. Cockerell, M.D., who performed a small study (unpublished) of vismodegib plus Mohs surgery in large BCCs, says, “The STEVIE paper’s findings are very similar to those we saw in our pilot study—vismodegib appears to work. It’s a major addition to our therapeutic armamentarium.”

Dr. Hauschild says, “The most important finding is the complete response rate of 33% in LABCC in a real-world setting, including multiple institutions in multiple countries.” Nearly all new drugs approved for metastatic melanoma and BCC undergo early studies in highly selected patient populations—those with no comorbidities or other underlying malignancies, he explained. As a post-approval study, the STEVIE study could include a broad variety of patients, Dr. Hauschild says. The fact that only four patients with MBCC (or 4.8% of the 84 patients with this disease) achieved complete response suggests that “we are most likely curing patients with LABCC, but not with MBCC. Here, the issue is prolonging...”

Quotable

“The results were dramatic.”

Brian Gastman, M.D.
Cleveland Clinic

Discussing the results of a study using UV-responsive microRNAs to predict melanoma.

See story page 54

DTExtra

The future of skin cancer and other disease detection could change with the development of a photonics device that listens to light. Using optoacoustics, the device delivers light waves of different wavelengths to the skin and detects ultrasound waves generated in response to the light absorption. Tomographic analysis of the ultrasound waves reveal volumetric views of the skin’s tissue and specific molecules, as well as disease manifestations.

SOURCE: BIT.LY/LIGHTLISTENINGDEVICE
European Union, he says, drug approval
tries, the drug is not affordable.” In the
lines worldwide will take a similar stance.
and MBCC, he predicts that BCC guide-
systemic treatment modality for LABCC
chemotherapy. “That’s for all patients.”
not be excised or irradiated, vismodegib
guidelines state that for any BCC that can-

Tolerable toxicities, but price may be issue from page 44

life.” Median progression-
of MBCC was 13.1 months, versus 23.2
months for LABCC.

Anthony M. Rossi,
M.D., finds it encourag-
ing to have one-year fol-
low-up data from 1,215 pa-
tients showing that vismodegib’s side ef-
fects were mostly low-grade, and expected.
He is an assistant attending physician in
dermatologic, Mohs and laser surgery at
Memorial Sloan-Kettering Cancer Cen-
ter and an assistant professor of derma-
tology at Weill Cornell Medical College.

Adverse events (AEs) that impacted
more than 50% of study patients included
muscle spasms, alopecia and dysgeusia.
Such symptoms impact quality of life, says
Dr. Hauschild. “But a large BCC, most of
which occur on the face or head, also af-
fects quality of life. If you have a benefit,
you will certainly tolerate these toxici-
"Furthermore, he says, study data reflect that AE frequency and severity de-
cline over time. "If patients can make it
through the first three months, they very
likely can make it through long-term use.”

Dr. Rossi counters that not all patients’
side effects diminish. Strategies being ex-
plored to reduce side effects include drug
holidays and pulsed treatment regimens,
Dr. Cockerell says. In the study, average
treatment interruption was 22 days.

Although serious AEs were rare, Dr.
Rossiakls, dermatologists should be aware
that seven treatment-related deaths oc-
curred in the study (though these patients
had confounding factors). Additionally,
the fact that 40% of patients lost weight,
and 25% experienced diminished appe-
tite, indicates that dermatologists should
monitor the nutritional status of patients
on vismodegib, he says.

NEW GOLD STANDARD?

Already, says Dr. Hauschild, German
guidelines state that for any BCC that
not be excised or irradiated, vismodegib
is first-line therapy; completely replacing
chemotherapy. “That’s for all patients.”
Because vismodegib is the only effective
systemic treatment modality for LABCC
and MBCC, he predicts that BCC guide-
lines worldwide will take a similar stance.

“The dilemma is that in many coun-
tries, the drug is not affordable.” In the
European Union, he says, drug approval
automatically means that government-run
healthcare systems will cover it for all pa-
tients indicated. He says that due to vismo-
degib’s cost—approximately $100,000 per
year in Germany and the United States—
private insurers elsewhere often won’t
cover vismodegib, which most patients
can’t afford out-of-pocket.

Dr. Rossi says that in the rapidly chang-
ing U.S. insurance environment, afford-
ability is “something to consider, espe-
cially if a patient is going to be on the drug
for a long time.”

Genentech offers a hotline and other
help for coding properly, battling insur-
ers and meeting copayments.4 Thanks
to the manufacturer’s advocacy efforts,
Dr. Cockerell says that in most cases he’s
seen, “We were able to get some kind of
compassionate coverage, in some cases
totaling 75% or more of the drug’s cost, for
patients in need. Unfortunately, that’s an
issue with a lot of these new drugs. They’re
very expensive, and patients have a hard
time paying for them—not only vismo-
degib, but also the biologics for psoriasis,
for example. That will probably limit use
of vismodegib.”

One fact that might help sway insur-
ers, says Dr. Hauschild, is that the
vast majority of patients only need the
treatment for three to six months. In the
study, median treatment duration was
8.6 months.

Dr. Rossi says that with vismodegib,
“Unfortunately there is no preset dura-
tion of use. It all depends on how patients
are responding” based on clinical or ra-
diologic findings. The bottom line, he
says, is that “We have to see how long pa-
tients can tolerate the drug. We know that
many patients will stop treatment because
of the adverse effects, which can be very
debilitating. So we pre-counsel patients
thoroughly before starting them on vis-
modegib.”

Henceforth, says Dr. Rossi, “We need
further studies to determine how long vis-
modegib should be given, and how pa-
tients fare with treatment breaks. We do
know that poor responders may progress”
while off therapy, so these patients need
close clinical follow-up.

Dr. Hauschild adds, “My only advice
is that patients with nonresectable, so-
called advanced BCC should be treated
with vismodegib. There’s a very high like-
lihood they will respond; two-thirds have
some response, including complete re-
ponse in one-third. It’s the treatment of
choice for nonresectable BCC.”

Dr. Cockerell says that targeting the
hedgehog pathway, as vismodegib does,
represents a major advance that several
pharmaceutical companies are using to
develop additional treatments for advanced
BCC. Researchers also have begun explor-
ing a topical hedgehog inhibitor that in se-
lected cases could replace surgery, he says.

From a scope-of-practice viewpoint,
says Dr. Cockerell, the STEVIE study
places vismodegib among a handful of
novel therapies that is helping dermatol-
ogists provide full-service skin cancer
treatments. “Most dermatologists think
of themselves as diagnosticians and per-
form relatively limited surgery,” explains
Dr. Cockerell. If they treat skin cancer,
they likely will perform basic in-office
excision or curettage, or refer the patient

STEVIE: STEVIE at a glance

Vismodegib 150 mg QD
1,215 study participants
Treatment benefited 90%+ of pa-
tients, including 68% who responded
to treatment and 26.6% who had
stable disease after treatment
Complete response rate of 33% in
LABCC in a real-world setting
including multiple institutions
in multiple countries
Median progression-free survival
in MBCC was 13.1 months, versus
23.2 months for LABCC
Side effects were mostly low-grade
and expected
Seven treatment-related deaths
occurred in the study (these pa-
tients had confounding factors)
40% of patients lost weight, 25%
expected diminished appetite
Source: See Reference 1.
Underlying chronic inflammation is a source of the primary signs and symptoms of atopic dermatitis.\textsuperscript{1-3} Th2 dominance in tissue samples from patients with atopic dermatitis is well-documented, with Th2-specific cytokines dominating the immune infiltrate.\textsuperscript{4}

\textbf{IL-4 and IL-13} represent key upstream drivers that modulate multiple downstream mediators—including IL-5, IL-31, and IgE—setting in motion the chronic underlying inflammation of atopic dermatitis.\textsuperscript{1,4-7}

Sanofi Genzyme and Regeneron are committed to provide resources to advance research in areas of unmet medical needs among patients with inflammatory and immunological diseases.
IL-4 AND IL-13 ARE KEY DRIVERS INVOLVED WITH THE UNDERLYING INFLAMMATORY PROCESS THAT DRIVES ITCH AND LESIONS\textsuperscript{1,8}

IL-4 plays a major role in driving Th2 differentiation\textsuperscript{4,9,10}

- Primarily responsible for the initial polarization of naive CD\textsuperscript{4+} Th (or Th0) cells toward the Th2 subtype\textsuperscript{4,9,10}
- Induces production of other downstream cytokines, such as IL-13 and IL-31\textsuperscript{4,11}

IL-13 is considered to be an “effector” cytokine—distinct from but overlapping roles with IL-4\textsuperscript{12}

- Plays a significant role in specific immune responses
- Involved in pathogenesis of atopic dermatitis

for Mohs surgery.

With the introduction of vismodegib and new melanoma treatments—plus the reintroduction of radiation therapy—to dermatology, Dr. Cockerell says, “Dermatologists, especially Mohs surgeons, can market themselves as cutaneous oncologists. If someone refers them a BCC, they can look at the entire palette of therapeutic options. We’re in an exciting time in medical and surgical dermatology.”

A decade ago, he says, dermatologists had nothing for advanced melanoma or large BCCs. “I’m hoping that next, we’ll see a similar breakthrough for squamous cell carcinoma,” a disease in which the lung-cancer drug nivolumab has shown success in Phase 3 research (NCT02105636).3

Disclosures: Drs. Hauschild and Rossi report no relevant financial interests. Dr. Cockerell has served as an investigator and attended medical advisory board meetings on behalf of Genentech.

Disclosures: Drs. Hauschild and Rossi report no relevant financial interests. Dr. Cockerell has served as an investigator and attended medical advisory board meetings on behalf of Genentech.

“**The most important finding is the complete response rate of 33% in locally advanced BCC in a real-world setting, including multiple institutions in multiple countries.**

Axel Hauschild, M.D.
Kiel, Germany

**REFERENCES:**


New target could predict melanoma

**LISETTE HILTON | STAFF CORRESPONDENT**

**QUICK READ**

New information could eventually help identify a high-risk population before they get cancer—even prevent skin cancer’s onset.

with Fitzpatrick skin types I or II, between the ages of 35 to 46, each with a history of having one primary melanoma.

The researchers isolated a pure population of melanocytes from a small area of skin (without melanoma) that had been intermittently exposed or unexposed to solar ultraviolet radiation.

“The results were dramatic, the mRNA’s of the cancer patients’ normal skin had many similarities, but were quite different from the aged match group of women who had not had melanoma,” according to study author Brian Gastman, M.D., plastic surgeon and director of melanoma at Cleveland Clinic. They found that miR-193b, miR-342-3p, miR186, miR-130a and miR-146a were among the miRNAs that were commonly and significantly down-regulated in the women with histories of melanoma.

“The types of mRNAs that were altered in expression allowed us to predict the type of proteins and ultimately molecular pathways that were altered in these seemingly normal appearing skin cells,” Dr. Gastman says.

By identifying mechanisms that are associated with normal appearing skin in patients with a history of melanoma, researchers may be able to identify a high-risk population that otherwise would only be identified once they have cancer, and the pathways, once fully validated, can be targeted to, hopefully, prevent the onset of skin cancer, Dr. Gastman says.

“We have already identified multiple molecular pathways and molecules that heretofore were not associated with melanoma. These will yield a multitude of potential scientific and translatable questions and studies,” he says.

The next step, according to Dr. Gastman, is to do further validation of these newly identified molecules and pathways, then test a group from the general population to assess their importance. DT

Dr. Gastman reports no relevant disclosures.
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Day7

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First do no Mohs harm

Weigh the benefits of the procedure against the big picture

LISETTE HILTON | STAFF CORRESPONDENT

THE IMPORTANCE OF DECIDING not to perform Mohs surgery is a lesson that one expert says has made him a better physician.

Carl F. Schanbacher, M.D., a clinical assistant professor of dermatology at Tufts University School of Medicine and Mohs surgeon, has treated more than 20,000 skin cancer patients. “If I’m doing Mohs on everyone, I’m really failing,” Dr. Schanbacher says. “I find that I really need to consider the circumstances of each individual patient.”

There isn’t a quota or predetermined ratio of patients that should be turned away, according to Dr. Schanbacher. Rather, it has to do with understanding each patient’s situation. “I feel for our frail patients... sometimes undergoing a Mohs procedure and then a subsequent reconstruction can really set people back. If there’s someone who has a terminal illness or some major medical problem, is it really in their best interest to have Mohs, or could they just sail into the sunset in their final year or two years of life? As long as there are no critical symptoms—the lesion isn’t ulcerated or increasingly painful—I’m inclined to let them keep it [the skin cancer] and inform them of what could take place,” he says.

Dr. Schanbacher, who made this the topic of his talk at last month’s American Academy of Dermatology Summer Scientific Session in Boston, says he didn’t always take this approach. In fact, he has operated on patients their final year or two years of life?”

CARL F. SCHANBACHER, M.D.
Boston, Mass.

“THERE ARE OPTIONS”

For patients who might suffer too much, Dr. Schanbacher says he plans a separate consultation with patients and their families. During that time, he graphically explains what patients will go through if they have Mohs, as well as what might happen if they don’t.

LOOKING BEYOND SKIN CANCER

Dr. Schanbacher examines not only each patient’s skin cancer but also whether that person’s life can accommodate what might be a difficult recovery from Mohs.

“The first thing we want to know is, does the patient live alone? What is his or her living situation like? Who is going to help with wound care?” he says. “We talk with the families and get each patient’s social situation figured out well ahead of time.”

For dermatologists, that means not looking only at the basal cell coming through the door. It’s also looking at the person who has the skin cancer and whether he or she is capable of dealing with the aftermath.

“For example, there are patients who are in their 80s and live alone. These patients are on pain medicine post-reconstruction, and they fall and break a hip. Now they’re in the hospital, all for a skin cancer on the tip of the nose that they could have kept,” he says, indicating that these are examples where the circumstances of post-operative care, and the surgery more broadly, can be more detrimental to patient’s health than the actual skin cancer.

QUICK READ

An expert advises evaluating each patient’s surrounding circumstances when determining whether Mohs surgery is indicated.

who, along with their families, were unhappy about how the recovery impacted their lives. “It was just too much,” according to the dermatologist. “I thought maybe we’re not doing it right. Maybe we need to properly inform them of the aftermath—the spectrum of activity that they’ll go through,” Dr. Schanbacher says.

For those who might suffer too much, Dr. Schanbacher says he plans a separate consultation with patients and their families. During that time, he graphically explains what patients will go through if they have Mohs, as well as what might happen if they don’t.

THERE ARE OPTIONS

For patients who might be better off not having Mohs surgery, Dr. Schanbacher says he’ll consider radiation therapy or, simply, observation.

For patients who should receive Mohs but might not be able to endure the lengthy procedure because they have Parkinson’s or dementia, for example, Dr. Schanbacher would consider a simpler reconstruction.

“We’ll really abbreviate any sort of medical encounter they have. I’ll use topical adhesive to close the wound and say, if you have a problem, call me. It’s a 20-minute procedure,” he says. “Or I’ll greatly simplify the reconstruction. The dermatologists who send me patients understand; they get it. What I don’t want is the treatment to be worse than the problem.”

Providers who have elderly skin cancer patients with several comorbidities might consider electrodesiccation and curettage, cryosurgery or topical chemotherapy as suitable alternatives to Mohs.

“I can tell you that I’ve had happier patients over the last few years,” he says. “And the families are surprised because they realize that here’s a surgeon who is giving us the option to not to undergo surgery.

“While it is an effective course of treatment for many skin cancers, Mohs is not always best for every patient. As physicians, our first obligation in every situation is to do no harm. We must ensure our treatment is never worse than the original issue, and that we thoroughly consider our patients’ values in each case.”

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New evidence supports combination therapy for metastatic melanoma

Molecular targeted therapies and immune therapies have major impact

LOUISE GAGNON | STAFF CORRESPONDENT

QUICK READ

Evidence-based data about molecular features is evolving to support the use of combination therapy as an option for treating metastatic melanoma.

“Increasingly, we are trying to develop the evidence base for the molecular features and diagnostic features that we would use to assign patients to that type of therapy [immune therapy]. We have really compelling data that suggest what the molecular features might be. We have more work to do to develop real-world tests that could be used in clinical practice to assign patients to immune therapy.”

MORE INFORMATION, BETTER CHOICES

Having information about molecular features, and not just clinical features, would better inform the choice of combination or monotherapy in terms of immune therapy, Dr. Flaherty says.

Among targeted therapies, the “overwhelming evidence” suggests that efficacy is enhanced with combination therapy compared to BRAF inhibitor monotherapy, he points out. “We have three randomized, phase 3 trials, all indicating almost identical results,” Dr. Flaherty says. “They improve response rate, progression-free survival, and overall survival across the board. That was with two different combinations of BRAF and MEK inhibitors.”

In a clinical trial that compared BRAF inhibitor monotherapy with vemurafenib (Zelboraf, Genentech) to combination therapy with the BRAF inhibitor dabrafenib (Tafinlar, Novartis) plus the MEK inhibitor trametinib (Mekinist, Novartis), the combination therapy demonstrated superiority in overall survival and progression-free survival.1

A meta-analysis of phase 2 and 3 trials with BRAF and BRAF/MEK inhibition demonstrated the greatest improvements in overall survival are with the combination of kinase inhibitors rather than use of a single kinase inhibitor.2

“Of course, we always balance the improvements with toxicity concerns,” Dr. Flaherty says. “It turns out combination therapy toxicity is not significantly different [from monotherapy toxicity], when considering the BRAF/MEK combination regimens. With toxicity not being significantly worse, we generally say that we choose combination therapy for these patients [with metastatic disease].”

The degree of impact that molecular targeted therapies offer, either as monotherapy or combination therapy, in the adjuvant setting is less clear than in the metastatic setting, Dr. Flaherty notes. That data should be available in the next one to two years, when clinical trials are completed.

THE ADJUVANT LANDSCAPE

It is critical for dermatologists to have a knowledge of what therapies are emerging in the adjuvant treatment arena for melanoma, according to Dr. Flaherty.

“When a drug comes onto the adjuvant treatment landscape, it is of high significance for oncology, but particularly for practitioners who manage patients in an earlier diagnosis setting,” Dr. Flaherty says, such as patients diagnosed with stage 2c or stage 3.

One of the concerns expressed with the use of immune therapies such as ipilimumab has been the development of auto-immune toxicity, which can be life-threatening, Dr. Flaherty says. “That is an important caveat with that therapy,” he says. DT

Disclosures: Dr. Flaherty is a consultant for Novartis, GSK, Roche, and Merck.

“...than use of a single kinase inhibitor.2

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Soaring drug costs leave derms, patients scrambling

LISETTE HILTON | STAFF CORRESPONDENT

The costs of popular drugs—even generics—in dermatology are soaring, leaving patients scrambling for coverage or financial assistance and dermatologists spending precious hours on prior authorizations, drug appeals and reviews.

Lindsey Bordone, M.D., dermatologist at Columbia Doctors and assistant professor in dermatology at Columbia University Medical Center, says she and her staff and patients are feeling the brunt of higher medication costs, rising requirements for preauthorization and increasing denials.

"Even things that used to be really cheap, like generic topical steroids, are now really expensive," Dr. Bordone says. "If someone has a high deductible or even what’s considered a low deductible (a $1,000 deductible is not considered high at all in the current market), you might still have to pay $130 for a cream."

**INCREASES OUTPACE INFLATION**

The percent increases for frequently prescribed medications in dermatology "greatly outpaced inflation, national health expenditure growth and increases in reimbursements for physician services," according to a study published February 2016 in *JAMA Dermatology.*

Of the 19 brand-name drugs researchers in the study analyzed, seven more than quadrupled in retail price from 2009 to 2015. The biggest cost offenders were topical antineoplastic drugs, for which the mean absolute increase was $10,926.58 and percentage increase was 1,240%. Anti-infective medications had the smallest mean absolute increase of $333.99, while psoriasis drugs had the smallest mean percentage increase, at 180%.

Some of the medications that dermatologists most prescribe, including acne and rosacea medications saw mean price increases of 195%, while the cost of topical corticosteroids increased a mean of 290%, according to the study.

“Drugs produced by Canadian drug firm Valeant Pharmaceuticals International saw the most significant increase in cost. While we cannot accuse Valeant of being the culprit behind rising costs, there is a strong correlation between one pharmaceutical company increasing [its] prices (or charging more for a new drug) and competing pharmaceutical companies following suit. With only a select number of drug manufacturers, a company can theoretically charge a higher price. It becomes a supply and demand game where the patient always loses,” says Travis Schneider, medical practice consultant and the co-founder of practice growth platform patientpop.com.

Spencer Malkin, D.C., C.E.O., of Prescriber’s Choice, says pharmaceutical companies essentially get to charge what they want for their drugs.

Dr. Bordone

1,240 PERCENT increase in cost of topical antineoplastic drugs from 2009 to 2015

**QUOTABLE**

"...Aesthetics represents a beachhead in this theme."

Steve Xu, M.D.
Chicago, Ill.

Patients use online ratings to decide everything from what procedure they want to how much they think it should cost. Learn how to manage their expectations.

See story page 66.

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**DRUG COSTS:**

Complex factors create difficult situations from page 60

“This represents a pretty big problem because there are few checks and balances,” Dr. Malkin says. “In the payer world, PBMs (Pharmacy Benefit Managers) are those who assist and represent the carriers in coverage determinations and paying for medications. They look at dermatological conditions as non-life-threatening and, therefore, they feel justified in either increasing the copays significantly or not covering the medications at all.”

**THE COST OF FREE SAMPLES**

Dermatologists’ use of sample medications might also be fueling the financial fire, according to Schneider.

“Dermatologists will often give samples of medications (most common with acne medications) when recommending a certain prescription. For some physicians, it gives them the chance to see if a new drug works better than an older one. Samples have also been given to uninsured or poor patients who otherwise could not afford the prescription. As a result, patients who can afford the medication end up also taking on an additional portion of the cost for samples doctors provide,” he says.

Researchers have found that dermatologists are increasingly providing samples and this correlates with their use of the branded generic drugs represented by the samples. Free drug samples have the power of altering physicians’ prescribing habits away from less expensive generic medications, according to the study.²

**One patient’s perspective: Stuck in the middle**

**MELISSA WITHEM VOSS,** from Waukegan, Ill., is 42 years old. A widower with three children, Voss was diagnosed at age 22 and has psoriasis and psoriatic arthritis. She’s on Medicaid. This is her story:

Several years ago I was trying to obtain any biologic and was told that I would have to use step therapy.

I have been given several creams and ointments, but I have moderate to severe coverage, so one tube usually doesn’t help. I have found that with some medications, the pharmacy can only disperse a small amount because there would be additional payments needed in order to cover the full medication that I need.

At my physical worst, 97% of my body [was affected]. It took having that severe of coverage for the state to agree. I was placed on Cyclosporine in the hospital. I later had to go into a drug trial offered by my amazing doctor, Stephanie Mehlis, M.D., of NorthShore University Health System, Skokie, Ill. She tried to help as many psoriasis patients as she can by pairing them to trials.

It is amazing stressful when your doctor and you agree on a medication choice but you are not able to take it. Getting help from the government is a huge hassle in triplicate! There are so many forms and authorizations for the doctors to file and sometimes for the patient. It is a long waiting game to approve something that you and your physician feel is necessary.

The horrible part is having the patience to wait. You are frustrated, in pain and itchy. The doctor wants to help you but her hands are literally tied by the government. Your physician will often prescribe other medications in the meantime. Sometimes they come with copays that you can’t afford. Then your physician gets upset because you are not following his or her suggestions. It’s not that you don’t want to—it’s that sometimes it’s a choice between groceries, school supplies or your medicine.

Another thing that is very worrisome is if you can’t take the medication due to costs [other than money]. What harm is this going to cause your body in the long run? What I mean is, are you going to become easily dehydrated or sick from the overactive immune system? What about co-morbidities?

Look for patient advice, solutions and thoughts about their experiences in future articles in this series.
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The fact that generics are suddenly increasing in price doesn’t make sense.

Generic houses do no research and development and generally have minimal research expenditure before launch.

Hilary Baldwin, M.D.
Morristown, N.J.

of 279% during the three-year period, according to a study published February 2016 in *JAMA Dermatology*.

“Patients call us all the time for generic alternatives, and we’ve already prescribed the generics,” Dr. Bordone says. “They think the cost is so high... so, they’re really upset, and we have to explain to them that’s the cheapest form available.”

Higher prices among branded drugs isn’t surprising and might even be justified.

“Much of the profits from of a branded prescription are returned to research and development into important and, perhaps, life-saving drugs. As the cost of everything has gone up, so has the price of bringing a new drug to market,” Dr. Baldwin says. “A recent study concluded that the cost is around 2.6 [billion] in 2014, up 145% since 2003. The sharp rise is attributed mostly to the increased complexities of clinical trials. After this kind of expenditure, only 8% will make it to market. The company then has a limited amount of time on their patent to recoup their losses before generics enter the market, hence the high prices which are almost excusable.”

But the fact that generics are suddenly increasing in price doesn’t make sense. Generic houses do no research and development and generally have minimal research expenditure before launch.

Hilary Baldwin, M.D., medical director of the Acne Treatment and Research Center in Morristown, N.J., says the increasing in price doesn’t make sense. Generic houses do no research and development and generally have minimal research expenditure before launch, according to Dr. Baldwin. “This is a new situation for us. Drugs that were our go-to workhorses—drugs that anyone could get anywhere, without coupons and without hassle, were suddenly more expensive than the branded products. Doxycycline hyclate 100 mg increased from 6.3 cents to $3.36 per pill between November 2012 and 2013,” Dr. Baldwin says.

The main cause for generic drug price hikes, she says, appears to be a reduction in competition, which is attributed to drug shortages, supply disruptions and consolidations within the generic drug industry.

Patents for the broad-spectrum antiparasitic drug albendazole expired longago, but no manufacturers have approached the FDA for approval for a generic version, according to a November 13, 2014 Perspective in the *New England Journal of Medicine*.

The authors write that the average wholesale price for albendazole was $5.92 per typical daily dose in the United States in late 2010. While the average wholesale price for albendazole rose to $119.58 per typical daily dose. Medicaid data shows spending on albendazole went from less than $100,000 a year in 2008 to more than $7.5 million in 2013, according to the study.

Manufactures that end up legally monopolizing drugs like albendazole are free to raise the prices of those medications, the study authors note, and the Federal Trade Commission will not intervene without evidence of a conspiracy among competitors or other anticompetitive actions that keep up the increased cost.

Albendazole’s freedom to remain at a high cost despite its generic status is not isolated. “For example, digoxin manufacturers dropped from eight to three between 2002 and 2013 and the price increased by 637%. The increase in doxycycline price was attributed to a national shortage in 2013, which was the result of fewer generic manufacturers,” Dr. Baldwin says. “So bottom line is greed. They could increase the prices and get away with it, so they did.”

**REFERENCES:**

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How patients are using online ratings

Address shortcomings of ratings to set expectations, price

LISETTE HILTON | STAFF CORRESPONDENT

The overall theme in healthcare is that patients are online more than ever, according to Steve Xu, M.D., M.Sc., resident physician, postgraduate year two (PGY2) in dermatology at Northwestern University School of Medicine, Chicago.

“We believe cosmetic surgery and aesthetics represent a beachhead in this theme,” Dr. Xu says.

Dr. Xu offered insights to colleagues around patient online reviews during the 36th Annual Conference of the American Society for Laser Medicine & Surgery (ASLMS 2016), Boston, Mass.

“Recruiting cosmetic patients often includes an adept online marketing strategy. Managing online reputations is very important,” he says.

More than 60% of patients consult reviews before selecting a provider, according to a study published in the Journal of the American Medical Association. Dr. Xu is among the authors on another study he presented at ASLMS 2016 that approaches the theme in a different way.

“Rather than investigating specific providers, our study looked at how laser and light procedures (there are many of them) are rated. In the context of aesthetics, this is important because patients are picking their doctors and have a specific procedure in mind. Understanding how real-world patients are rating procedures is useful for cosmetic [dermatologists] in setting expectations and price setting,” Dr. Xu says.

“A patient may come in and be interested in laser resurfacing with even a specific laser brand in mind, based on online reviews,” he adds. “They will have done their research on their [doctor], and have a price point in mind based on what they have read. A [doctor] should be ready to anticipate these notions, explain the imperfections in online reviews and how costs can be highly variable.”

Based on his findings, Dr. Xu says cosmetic [dermatologists] should keep these important points about patients’ online reviews in mind:

- Dermatologists should understand that reviews, before/after pictures and patient-driven discussions of specific surgeons are available online with surprising geographic specificity, he says.
- Although online review sites such as RealSelf can provide valuable information on patient mindset and geography-based pricing, patients’ interpretations of these results must be done with caution, according to Dr. Xu.
- Finally, dermatologists should have talking points ready to explain to patients why online reviews are imperfect.

“Our analysis of the information on laser/light procedures on RealSelf found that the reviews do not reach enough specificity in regards to the procedure being discussed. Reviews were posted in general terms, laser types, specific laser brands and intended outcomes,” he says.

Dermatologists know that each patient is different in regards to skin type, treatment goals, etc.; so, even if the categorization were accurate, the results couldn’t be generalized, Dr. Xu says. As a result, dermatologists should emphasize this point in counseling patients, who might have already formed their notions of procedures and laser types.

“Ultimately, experience in assessing a patient’s skin type and treatment goals, as well as real-time adjustment of laser parameters to tissue response, is the most important factor in a successful outcome,” he says.

OVERCOME ONLINE REVIEW PITFALLS

Dr. Xu says awareness is the first step to overcoming the pitfalls of online reviews. Websites, like RealSelf, will only grow in influence and popularity.

“Be ready to share your perspective on online reviews. Online reviews are useful, but they don’t tell the full story. A [dermatologist’s] experience and ability to assess tissue response, patient type and patient goals is still the most important factor in a successful outcome. At the end, this will likely be the most cost-effective solution, even if the upfront cost is higher,” Dr. Xu says.

The dermatologist concludes: “We want to delight our clients and avoid disappointment. Online reviews don’t always tell the real story. The final satisfaction scores (specific to RealSelf) may not factor in neutral or ‘not sure’ reviews. For many cosmetic procedures, it takes time before the final results are seen. Tattoo removal is a good example of a laser procedure with a lot of ‘not sure’ reviews, which explains the discrepancy between our satisfaction scores and what’s reported on RealSelf. Clinicians should recognize that online reviews of procedures and devices with a high number of total reviews and a low number of neutral reviews are less prone to bias.”

Disclosure: Dr. Xu reports no relevant disclosures.

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**Payers want more data**

**Placebo studies not enough**

JOHN JESITUS | SENIOR STAFF CORRESPONDENT

A **FIRST-OF-ITS-KIND** summit has revealed that, to optimize patient care with available resources, healthcare payers need more information than dermatology research has been providing. Such was the message from a meeting organized by International Dermatology Outcome Measures (IDEOM) and reported on at the 74th Annual Meeting of the American Academy of Dermatology (AAD) in Washington, D.C., this year.

IDEOM is a nonprofit organization that is working to establish validated, standardized outcome measures for clinical research and clinical practice that satisfy the needs of all stakeholders in the process of dermatologic care.

“From the beginning,” says IDEOM Chair Alice B. Gottlieb, M.D., Ph.D., “We’ve wanted all the stakeholders to have a say in the outcome. We’ve included patients, regulators, healthcare providers, pharmacists and scientists dealing with healthcare economics and clinical trials.” However, she says, IDEOM has found it difficult to get payers to come to the table, perhaps because they fear they’ll be “ambushed” by well-meaning clinicians. She is chair, dermatologist in chief and Harvey B. Ansell professor of dermatology at Tufts Medical Center in Boston.

To surmount this obstacle, IDEOM and the National Psoriasis Foundation convened a special meeting in Atlanta January 29, 2016, that focused on dermatologic care. IDEOM paid any such representatives who attended as consultants. Attendees included representatives from Priority Health, Aetna and Blue Cross/Blue Shield, along with pharmaceutical-industry executives and consultants.

The summit featured presentations by IDEOM and by the Psoriasis Foundation. Additionally, “We invited patients with psoriasis and psoriatic arthritis to tell their stories to the payers,” Dr. Gottlieb says.

Ultimately, “The payers were very moved by the patients’ testimonies. All the patients said biologic drugs changed their lives profoundly,” she adds. Some grew tearful as they described the devastation psoriasis had wrought upon their lives and their families, and the “roller coaster” effect of clearance followed by flares when using prior therapies, she says.

**QUICK READ**

A pioneering summit between healthcare payers and groups pursuing standardized outcome measures in dermatology has revealed that payers want outcome measures that are published, universally accepted and practical both for clinicians and payers.

“We are not providing some of the things payers said they need in clinical trials to make informed decisions.”

Alice B. Gottlieb, M.D., Ph.D.

**Boston, Mass.**

**WHAT PAYERS WANT**

To reduce practice variability and increase the predictability of payers’ costs, Dr. Gottlieb says, payers said they want outcome measures that are published, universally accepted, clinically useful and mandated by major professional societies.

“They also said outcome measures must be clinically meaningful — it’s not enough to be better than placebo. They want outcomes that can measure how the overall cost of care decreases by treatment intervention;” for example, how psoriasis treatment with biologic drugs might reduce incidence of psoriatic arthritis, or cardiovascular morbidity and mortality.

Payers need comparative trials showing more than statistical differences between drugs, or average response measures, she adds.

“They need to understand the distribution of patient responses, so that a mean isn’t overly influenced by outliers,” she explains.

Additionally, payers desire outcomes that measure treatment effects on patient productivity.

From clinical trials, she says, payers want information that indicates when to start a therapy, switch therapies, adjust dosing downward, and stop treatment that isn’t working—plus the probability that nonresponders will respond to a different treatment.

**EMR OBSTACLES**

“Payers also acknowledged that current electronic medical records are an obstacle to doing all this,” she says.

During the summit, IDEOM invited payer attendees to become active participants in its process. One such representative showed particular interest in getting more involved, she says.

“We are not providing some of the things payers said they need in clinical trials to make informed decisions. I hope that might also change. We want as many patients as possible to get access to the right doctors and treatments.”

Achieving this goal will require IDEOM to work with the AAD on updating treatment guidelines, and with regulators and the pharmaceutical industry to provide clinical trials of the type requested by payers, she says.

“We believe this is the first time that payers have been asked in a nonconfrontational way to discuss what outcome measures they need” to make decisions regarding the quality—not the cost—of care.

One of the summit’s key lessons for her, she says, was that although healthcare payers deal with large populations and limited budgets, “They also want to do the right thing by patients.”

Disclosures: Dr. Gottlieb is chair of IDEOM but reports no relevant financial interests.
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**Editorial: Advice for targeting dermatology**

As you get further along, periodically reassess your interests. Medical students often start with one goal in mind, but along the way they develop new and unexpected interests in something else.

Be open to changing your mind about what you want to do with your life. There is nothing worse than seeing a physician who has become bored with what they had selected as their career choice but finds that it is too late to start over with another residency due to family, financial or job commitments.

**Target Dermatology**

Most medical students don’t have much choice in the order of their junior year clinical rotations. However, if you have some flexibility, I believe it is beneficial to try and select a dermatology rotation as early in the third or fourth years of medical school as possible.

This will not only confirm the validity of your career choice, but also give you an opportunity to get to interact with the dermatology residents and also to know the dermatology faculty members.

Again, try to find a faculty member with whom you feel a connection, then set up an appointment with them to review your record and with their help try to find some project or other activity for which you can provide help.

I think it can also be very beneficial to take an “away” rotation at another school that may be nearby or have some special interest for you. These types of rotations are often very hard to get, so start that planning process as early as possible.

**Apply for Residencies**

It is important to understand that seeking a residency in the specialty of dermatology is extremely competitive.

There used to be an inside joke that all one needed to get a dermatology residency position was to have “AOA” (Alpha Omega Alpha—a medical school honor society) on your resume. That isn’t quite true but, in my opinion, the successful dermatology residency candidate will be able to show evidence of scholarly achievement in college and medical school, present a number of letters of recommendations from former faculty members and perform well on residency department interviews.

The one question I get asked more than any other is, to how many dermatology programs should I apply? Despite the high level of competition, I personally believe that there is no reason to apply to a huge number of residency programs. Choose the ones you are most interested in for geographic, curricular or personal reasons, but don’t overdo it.

I once had a medical student who applied to almost every dermatology program in the country. When she got invited for over forty interviews, she went to the bank and borrowed $40,000 specifically to cover the costs of going to all of these interviews! While she did obtain a residency position and is now a happy and successful practicing dermatologist, I personally think this was excessive.

I also believe the training programs are partly to blame for this situation. I don’t think it makes a training program any better when it has 200 or more applicants for every residency position. This not only wastes the time and money of the applicants, it also requires a huge commitment on the part of the training program director and faculty to review the applications and then conduct the interviews. More should be done to try to reduce these burdens on everyone by limiting both the number of applicants allowed to apply to a given program and the number of programs to which an applicant can apply. If a sufficient number of programs set these types of standards, the end result will be more equitable for all parties.

**Summary**

Assuming that one does all these things (and probably more) what can one expect from your profession as a dermatologist? In my opinion, you will be part of a fun, exciting, challenging and extraordinary profession, one in which you’ll be able to care for babies, toddlers, adolescents, young and middle-aged people and seniors.

You’ll also have the chance to do research and treat very grateful patients medically as well as surgically using conventional medications, targeted immunotherapy, chemotherapy, lasers and light therapy.

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Lastly, you’ll have the chance to get to know your patients and enjoy them while helping them conquer the many complex skin diseases that affect humans. It will be a fun and enjoyable way to spend your life.

I hope you will have some of the same wonderful experiences that I have. **DT**
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Visit: gundersenhealth.org/ MedCareers

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DERMATOLOGIST

Gundersen Health System in La Crosse, Wisconsin, is seeking a BC/BE dermatologist. Your practice will consist of:
• General medical dermatology with opportunities for dermatologic surgery (regular and cosmetic).
• Medical education and clinical research within one of the nation’s largest multi-specialty group practices in our new state-of-the-art facility.
• Services currently offered include MOHS Surgery, Photodynamic Therapy, PUVA, Broad and Narrow Band UVB, Vascular Laser Treatment and multiple IPLs.

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Dr. Plaque, although practicing in a small town, is a renowned expert in psoriasis. He has practiced for 20 years, has been involved in numerous FDA trials for biologic agents used to treat psoriasis, and offers every known treatment for psoriasis. His expertise is clearly in the use of biologics. Such patients are often difficult to treat; some have a variety of other medical issues. He often treats those psoriatic patients who are eligible for phototherapy with biologics. He routinely does a variety of blood tests and carefully follows his patients. Two years ago, one of these patients had acute onset liver failure with death in two months. It turned out the patient was using biologics to treat his psoriasis as well as taking daily acetaminophen.

The estate of this patient has now brought a multimillion-dollar lawsuit against Dr. Plaque, alleging that he should have warned his patient not to use these two drugs together. Is there any basis for such a lawsuit?

Biologic drugs have changed the face of psoriasis treatment but, with time, the warning labels have also expanded. A variety of issues are now linked to tumor necrosis factor-alpha (TNF-α) blocker use. Mention has occurred with the use of a variety of biologics. These include adalimumab (Humira, Abbvie, Inc.), etanercept (Enbrel, Amgen) and infliximab (Remicade, Janssen), known as TNF-α inhibitors. The associated risks include cases of lupus, squamous cell carcinoma (SCC), histoplasmosis and coccidioidomycosis. While the biologic ustekinumab (Stelara, Janssen), an interleukin (IL) 12/IL23 inhibitor, has not engendered litigation, it seems logical to test for possible infections before starting patients on this biologic.

**INDICATIONS AND WARNINGS**

The package insert for biologics indicate that these drugs are for patients who are candidates for other systemic agents (e.g., methotrexate) or phototherapy. Adalimumab is indicated for the treatment of adult patients with moderate-to-severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. Adalimumab’s package insert states it should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. Etanercept is indicated for the treatment of adult patients (18 years or older) with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Infliximab is indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy or phototherapy. Infliximab should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. Ustekinumab is indicated for the treatment of adult patients (18 years or older) with moderate-to-severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy.

Black box warnings are included on the labeling for adalimumab, etanercept and infliximab. Ustekinumab does not have any black box warning but, from a physician’s medical legal perspective, this drug ought to be treated similarly. Most dermatologists and rheumatologists routinely check both blood counts and liver function tests on their biologic patients. Similarly, the standard of care seems to be that patients not be placed on TNF-α inhibitors who have a family or personal history of lupus, lymphoma or multiple sclerosis.

What about the issue of liver failure? There are now over 150 reports of severe liver injury with infliximab use, including 10 cases of liver failure. Use of medications containing acetaminophen were linked to 139 cases of liver injury, but 69 cases of liver failure, making acetaminophen the most frequently cited cause of acute liver failure among medications monitored by the group.

There is no question that the use of acetaminophen in patients taking any biologic should be of concern to treating dermatologists. It would seem prudent to have such a conversation. If Dr. Plaque did not have such a discussion, an expert testifying against him might say that he deviated from the standard of care. Ultimately, if this case went to trial, a jury would need to decide if 1) not having a discussion about acetaminophen and the use of biologics represented a deviation in the standard of care and 2) if that breach actually was the cause of the death. If the jury agreed on both accounts, it is conceivable that Dr. Plaque could lose this multimillion-dollar lawsuit. **DT**
Finacea Foam Compared with Subjects Treated with Vehicle

681) subjects. Overall, 95.7% of subjects were White, 73.4% were female, and the mean age was 50.6 years.

Table 1: Adverse Reactions Occurring in ≥ 0.5% of Subjects Treated with Finacea Foam Compared with Subjects Treated with Vehicle

<table>
<thead>
<tr>
<th>System/Organ Class Preferred</th>
<th>Finacea Foam, 15% (N=681) n (%)</th>
<th>Vehicle (N=681) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and application site conditions</td>
<td>Application site pain*</td>
<td>42 (6.2%)</td>
</tr>
<tr>
<td></td>
<td>Application site pruritus</td>
<td>17 (2.5%)</td>
</tr>
<tr>
<td></td>
<td>Application site dryness</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td></td>
<td>Application site erythema</td>
<td>5 (0.7%)</td>
</tr>
</tbody>
</table>

* "Application site pain" is a term used to describe disagreeable skin sensations, including burning, stinging, paraesthesia and tenderness.

6.2 Post-Marketing Experience

Hypersensitivity, rash and worsening of asthma have been reported from the postmarketing experience of azelaic acid-containing formulations. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Local Tolerability Studies

In a 21-day cumulative irritation study under occlusive conditions, mild-to-moderate irritation was observed for azelaic acid pre-emulsion. In a human repeat insult patch test (HRPT) study, no sensitization potential was observed for azelaic acid pre-emulsion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Therefore, Finacea Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15% foam. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day [162 times the maximum recommended human dose (MRHD) based on body surface area (BSA)], rabbits given 150 or 500 mg/kg/day [19 or 65 times the MRHD based on BSA] and cynomolgus monkeys given 500 mg/kg/day (65 times the MRHD based on BSA) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose of 2500 mg/kg/day (162 times the MRHD based on BSA) that generated some maternal toxicity. In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the MRHD based on BSA). No effects on sexual maturation of the fetuses were noted in this study.

8.3 Nursing Mothers

It is not known if azelaic acid is secreted into human milk in vivo. No well-controlled studies of topically administered azelaic acid in nursing women are available. Nevertheless, the decision to discontinue nursing or to discontinue the drug should take into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Finacea Foam in children below the age of 18 years have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Finacea Foam, 18.8 percent were 65 and over, while 7.2 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

17 PATIENT COUNSELING INFORMATION

Inform patients using Finacea Foam of the following information and instructions:

- For external use only.
- Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel.
- Shake well before use.
- Avoid use of alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.
- Avoid contact with the eyes, mouth and other mucous membranes. If Finacea Foam does come in contact with the eyes, wash the eyes with large amounts of water and consult your physician if eye irritation persists.
- If allergic reactions occur, discontinue use and consult your physician.
- Wash hands immediately following application of Finacea Foam.
- Cosmetics may be applied after the application of Finacea Foam has dried.
- Avoid the use of occlusive dressings and wrappings.
- To help manage rosacea, avoid any triggers that may provoke erythema, flushing, and blushing. These triggers can include spicy and thermally hot food and drinks such as hot coffee, tea, or alcoholic beverages.
- The propellant in Finacea Foam is flammable. Avoid fire, flame, or smoking during and immediately following application.
- Discard product 8 weeks after opening.

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Manufactured for:

Bayer HealthCare
Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981
Manufactured in Switzerland
67981008S
Finacea® (azelaic acid) Foam, 15% is indicated for topical treatment of the inflammatory papules and pustules of mild to moderate rosacea.

The first and only prescription foam approved by the FDA for the treatment of rosacea.

In the art of rosacea therapy...

Proven efficacy has another profile with Finacea® Foam

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Skin Reactions: There have been isolated reports of hypopigmentation after use of azelaic acid. Because azelaic acid has not been well studied in patients with dark complexion, monitor these patients for early signs of hypopigmentation.

Eye and Mucous Membranes Irritation: Azelaic acid has been reported to cause irritation of the eyes. Avoid contact with the eyes, mouth and other mucous membranes. If Finacea® Foam does come in contact with the eyes, wash the eyes with large amounts of water and consult a healthcare professional if eye irritation persists.

Flammability: The propellant in Finacea® Foam is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).

Most Common Adverse Reactions

In clinical studies, the most frequently observed adverse reactions in ≥ 0.5% of subjects treated with Finacea® Foam included local site pain (6.2%), pruritus (2.5%), dryness (0.7%), and erythema (0.7%).

For Topical Use Only

Finacea® Foam is not for oral, ophthalmic or intravaginal use. Avoid the use of occlusive dressings or wrappings at the application site. Avoid use of alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.

Patients should be reassessed if no improvement is observed upon completing 12 weeks of therapy.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

For important risk and use information, see the full Prescribing Information at www.finaceafoam.com.

For important risk and use information, see the Brief Summary on the following page.

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