Skincare targets

IN THE PIPELINE

This Pipeline Report presents insights into drugs currently in phase 2, phase 3 or recently approved for the treatment of basal cell carcinoma and melanoma. The data were complied from the Pharmaceutical Research and Manufacturers of America 2018 Medicines in Development for Cancer Report; NIH www.clinicaltrials.gov; corporate websites, and Pubmed.

Stephan Huber | Staff Correspondent

Basal cell carcinoma (BCC) is the most common type of human skin cancer, accounting for 80% of non-melanoma skin cancers. Although most BCCs are curable by surgery, locally advanced and metastatic BCC represents a clinical challenge. BCC is driven by the aberrant activation of Hedgehog (Hh) signaling and characterized by mutations in patched or smoothened genes. Recent advances in the understanding of the Hh signaling pathway in the pathogenesis of BCC has fueled the discovery of Hh pathway inhibitors in locally advanced and metastatic BCC patients.

Patidegib Topical Gel 2% by Pellepharm

Patidegib, an investigational topical treatment designed to mitigate the tumor burden in patients with Gorlin Syndrome and Basal Cell Carcinomas (BCCs).

-Patidegib is an inhibitor of the Hedgehog (Hh) pathway that binds to and inhibits the cell membrane-spanning G-protein coupled receptor Smo, which results in the suppression of Hh pathway signaling and a decrease in tumor cell proliferation and survival. 1,2,4

-A phase 2, double-blind, placebo-controlled, randomized, clinical trial evaluated a patidegib topical therapy. Seventeen patients participated in the trial and were self-treated with topical patidegib for six months.

There was a statistically significant difference in complete response between treatment and vehicle groups in the per protocol analysis, with complete response demonstrated in 12.

Stay versed in billing codes

E/M billing, documentation changes likely within two years

Stephanie Stephens | Staff Correspondent

With coding a major determinant of what dermatologists bill and what they get paid, it's critical to keep up with changes to be both compliant and accurate, suggest Mollie MacCormack, M.D., and Murad Alam, M.D.

Demystifying current coding conundrums is even more important as insurers scrutinize the details of your business, they say.

Look for changes in evaluation and management services (E/M) documentation and payment methods within the next two years, says Dr. MacCormack, director of Mohs Surgery/Procedural Dermatology at Solution Health in Southern New Hampshire, and the American Association of Dermatology (AAD) RUC.

More in this issue

- Clinical
  PATIENTS WITH AUTISM
  Insights to effectively treat pediatric patients with ASD.

- Cosmetic
  NEW NEUROTOXIN ON HORIZON
  Clinical trials suggest 24-week duration and similar side effect profile as other neurotoxins.

- Oncology
  ADVANCED MELANOMA
  Dermatology expertise required with managing cutaneous side effects.

- Business
  PRACTICE INFLUENCES
  Population trends, looming regulatory changes, data gathering challenges.

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Provide practical analysis of recent studies, regulatory updates, techniques, devices and business solutions; and facilitate discussion to optimize practice and improve patient care.

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Dermatology has more over-the-counter (OTC) drug formulations than many areas of medicine, most of which are covered under drug monographs. The drug monographs are very important to dermatology, as the development of safe, effective nonprescription products is fast and relatively inexpensive. These formulations use Category I ingredients that are Generally Recognized As Safe and Effective (GRASE) for the claimed therapeutic indication. GRASE products are becoming more important as the price of prescription topical agents exponentially increases. I believe the monograph system is currently a relatively under-utilized but highly effective pathway to bring minimal-risk products to market.

There are a number of monographs pertaining specifically to skin disease that are worth investigating, as this is an area unfamiliar to most practicing dermatologists. The monographs contain a list of approved ingredients, the concentration in which they can be used, and if they can be combined with other monographed ingredients. These monographs are briefly discussed below:

1. **ACNE:** This monograph contains 40 ingredients that can be used for acne treatment, but the rule was finalized in 1990 with a benzoyl peroxide action in 2010.

2. **ANTI-FUNGAL:** This monograph has ingredients that can be used in the diaper area and on feet and was originally passed in 1993.

3. **ANTIPERSPIRANTS:** This monograph has 26 active ingredients and was issued in 2003.

4. **ASTRINGENTS:** These ingredients are classified as skin protectants and the monograph was issued in 2003.

5. **DANDRUFF:** These are the ingredients that can be used in dandruff shampoos and the final monograph was issued in 1991 and revised in 1992.

6. **HAIR GROWTH/HAIR LOSS:** The original monograph was issued in 1989 containing only ineffective ingredients. The monograph was updated in 1994 with topical minoxidil.

7. **PSORIASIS:** These are the ingredients designed to treat psoriasis with the tentative monograph issued in 1986 and it has yet to be finalized. The only ingredients on the monograph are coal tar and salicylic acid.

8. **SKIN BLEACHING:** There are only two ingredients on this monograph that was issued in 1982, but has yet to be finalized.

9. **SUNSCREEN:** Lists ingredients, concentrations, and combinations that can be used in sunscreens and the final monograph was issued in 2011.

10. **WART REMOVER:** Lists products used to remove warts with the final monograph issued in 1990 and updated in 1994 has 13 ingredients.

After examining this list, there are several important observations that can be made. First, the monographs deal with a significant number of the most frequent diseases dermatologists treat. This means dermatologists should familiarize themselves with the monographed ingredients and learn how to use OTC drugs effectively for patients who cannot afford higher priced prescription medications. The OTC drugs may not work as quickly or as well as prescription products, but may be a temporary treatment solution or effective for maintenance or early relapse.

Second, the monographs are sorely out of date. The FDA needs to regularly review the monographs and allow pharmaceutical companies to present additions. This would expand the number of OTC offerings and increase efficacy.

Third, consumers have many more readily available educational resources that can guide better use of OTC medications.

Fourth, sometimes the use of OTC drugs can prevent more severe disease, such as the use of sunscreens.

I believe it is time to update and expand the drug monograph system in the United States. This method of regulating OTC drugs has proven to be highly effective and could assist in decreasing the cost of healthcare in the United States. Further, dermatologists should understand the OTC options and utilize these medications when necessary.

**MONOGRAPHED INGREDIENTS:** See a list of active ingredients allowable in specified concentrations and combinations for acne and skin protectants in this month’s table. Page 74
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Do I have to give her job back?

by DAVID J. GOLDBERG, M.D., J.D.

Dr. Goldberg is director of Skin Laser and Surgery Specialists of New York and New Jersey, past director of Mohs and Laser Research, Icahn School of Medicine at Mt. Sinai; and, adjunct professor of law, Fordham Law School in New York City.

Dr. Derm has a very successful practice with multiple offices. He recognizes that one of the reasons for this success is his ability to have loyal, long-term employees. Among the most loyal is his 38-year-old office administrator. She has worked with him for more than 10 years and oversees his 63 employees. Her role is very important to him, and she is paid well.

Two years ago, this administrator notified Dr. Derm that she was pregnant and would be leaving the office to have her baby. She assured Dr. Derm that she will return to her position one month after delivery.

Dr. Derm knows that he cannot run the office without this employee. He quickly finds a replacement and makes it clear that he will rehire his loyal administrator upon her return from maternity leave. Much to Dr. Derm’s surprise the temporary employee turns out to be outstanding in her role. Because she is a new hire, she is also being paid 25% less than his long-time staff person.

On the 31st day post-delivery, Dr. Derm’s long-time employee has not returned to work. He calls her repeatedly over the next several weeks and is unable to reach her. Six weeks after she has left, Dr. Derm assumes she will not return, and he offers the new employee a permanent job.

On day 64, his former staff person returns to work expecting her old job and salary. Dr. Derm offers her a lesser job and lesser salary, saying it is unreasonable to be gone almost three months and expect to come back to the same job and salary. He tells her she will be terminated if she doesn’t take this new position. She demands her old position and salary and says she will sue Dr. Derm.

WHO IS LEGALLY IN THE RIGHT?

The U.S. Department of Labor’s Wage and Hour Division administers and enforces the Family and Medical Leave Act (FMLA) for all private, state and local government employees, as well as some federal employees. The FMLA entitles eligible employees to take up to 12 workweeks of unpaid, job-protected leave in a 12-month period for specified family and medical reasons.

Of note is the fact that under certain circumstances, employees may take FMLA leave intermittently — taking leave in separate blocks of time for a single qualifying reason — or on a reduced leave schedule, which reduces the employee’s usual weekly or daily work schedule. However, if FMLA leave is for birth and care, or placement for adoption or foster care, use of intermittent leave is subject to the employer’s approval.

It would appear that at day 64 post-delivery, under the FMLA act, Dr. Derm is required to give his office administrator back both her previous job and previous salary. If he does not, she can file a complaint with the U.S. Department of Labor. If he is in violation, and the violation is not resolved, the Department of Labor may bring action in court to compel compliance.

Lastly, his employee may also be able to bring a private civil action against Dr. Derm. He would be wise to bring his employee back to her position and salary.

The FMLA applies to all… who employ 50 or more employees in 20 or more workweeks.
A patent confers the right to exclude others from making, using, offering for sale...

Intellectual property: Patents 101

by RAYMOND A. MILLER, J.D., AND STEVE XU, M.D., F.A.A.D.

Mr. Miller is a partner, registered patent attorney and Vice Chair of the Health Sciences Department of Pepper Hamilton LLP. Mr. Miller is a former member of the firm’s Executive Committee and was former Chair of the firm’s Intellectual Property Department.

Dr. Xu is medical director of the Center for Bio-Integrated Electronics at the Simpson Querrey Institute for Bionanotechnology, Northwestern University; and, co-founder of the Advancing Innovation in Dermatology Accelerator Fund.

In this follow up to last month’s topic on intellectual property and technology transfer (see: bit.ly/technologytransfer), we will extend our discussion on ownership to patents. I know that discussions around intellectual property (IP) often include a host of new terms that can be overwhelming (e.g. patents, provisional or non-provisional, trademarks, composition of matter or method patents, PCT, etc.). However, the effective transformation of ideas into products or therapies requires a basic understanding of IP. Each type of IP may be important or applicable in protecting a creative product or new therapy, and should be considered by the dermatologist entrepreneur. The focus of this article is how to utilize patents to maximize value for your venture.

A patent confers the right to exclude others from making, using, offering for sale or selling an invention, as recited in the claims of a patent, within the jurisdiction or from importing the invention into the jurisdiction in which the patent is obtained.

The most common type of patent is a utility patent (also known as a non-provisional), which covers the functional components of a product and/or process and protects an invention for 20 years from the filing of the earliest non-provisional application (this non-provisional application is typically filed one year after a provisional application). The other types of patents include design patents (covering the physical designs) and plant patents.

The scope of a utility or non-provisional patent is defined by the numbered sentences at the end of a patent called claims. Claims follow the words “I (we) claim” in a patent. To be infringing, an article, composition or method must fall within the metes and bounds of the claims that issue.

Ownership is key, and although the United States respects the rights of the inventors, often employers (or even the government) have ownership rights in inventions and patents. See the first part of the series for more information. A citizen of the United States should file inside of the country and obtain a foreign filing license (automatic) before filing outside of the United States.

To identify what may be patentable, a patent search of the prior art should be performed by the inventor. There are now several patent engines that make patent searching easy. For example, Google patents is a good first stop. You can start with a simple natural language search that describes your idea with a few key terms. Then, you can start reviewing patents and patent applications related to your key terms to see if another individual or group has already patented your idea.

I have also found that for a patent in question, the cited patents and citing patents are extremely helpful to review, as well. Identifying relevant patents will be important as you prepare your own filing with the help of your counselor. If you do find an issued patent or a patent application that reflects your idea very closely, I would not lose heart and give up. Speak to your patent agent or IP lawyer first to discuss options.

Since patent law is exclusively a matter of federal jurisdiction, the lawyer or agent — a person with the technical background that makes him eligible to represent others before the United States Patent and Trademark Office [USPTO] — does not need to reside in your state to practice. There are a number of great patent lawyers across the country, and you should select one that matches the technical requirements needed to understand your invention.

If you want your counselor to consider broader legal issues, hire a lawyer. If your primary concern is articulating the technical components of your invention, a patent agent may be the right choice. Today you can even check statistics to find out how an individual or a firm performs at the USPTO through software programs, such as Patent Advisor by LexisNexis IP.

Do not be afraid to get a second opinion on selection of counsel; and do not select based solely on price. Many IP firms have special programs for emerging entrepreneurs that can help defray upfront costs.

A common first step in obtaining a patent is to file a provisional patent, which is a less formal application that is not reviewed by the USPTO, but acts as a declaration of your invention. This provisional application can be a cost effective way to protect your invention in a “first-to-file” environment like the United States. A provisional application, like a non-provisional application, provides you with a “patent pending” status. Within 12 months of filing a provisional application, a non-provisional patent application is usually the next step of the process. This application will be reviewed by the USPTO and must contain all of the information you plan to include in your patent, as you are not allowed to add any new material after filing.

As an entrepreneur, it is typical to file a provisional application first. Even for semi-developed ideas or concepts, a provisional patent is a very
There are many alternatives to traditional sunscreens.

Sunscreen savvy

by ZOE DIANA DRAELOS, M.D.

Dr. Draelos is a consulting professor of dermatology,
Duke University School of Medicine, Durham, NC.

Q. What is available for skin sun protection in patients who cannot wear traditional sunscreens?

There are many alternatives to traditional sunscreens, but they cannot be labeled as sunscreens because they do not contain any of the ingredients on the sunscreen monograph and are not considered OTC drugs.

Cosmetics are excellent sunscreens and can be used effectively for sun protection. The opaque camouflage and post-surgical facial foundations offer complete sun protection based on the presence of talc, kaolin, and iron oxide. While these camouflage foundations are meant to cover dyspigmentation, they can also superbly protect the skin from sun exposure in conditions such as lupus, porphyria, polymorphous light eruption, and other photosensitive dermatoses. Since the camouflage foundations are waterproof and designed for extended wear, they can be used for swimmers who experience facial sunburns with traditional sunscreens.

Opaque lipsticks are also excellent photoprotection for lips, providing long-lasting and superior protection over clear lip balm formulations. Lipsticks are an excellent way of preventing the progression of actinic cheilitis to skin cancer in mature women.

Q. Are there ways of achieving safe sun protection for eyes rather than sunscreens that may burn when they enter the eye?

Traditional liquid facial sunscreens burn when they enter the eyes, which is a common occurrence when sweating heavily. An excellent alternative, especially in children, is the use of a sunscreen-containing lip balm around the eyes. Lip balms are designed to be non-irritating on the tender lips and to stay in place. The soft lip balm will glide over the skin and the waxy base will keep the sunscreen in place. The soft stick can be used on the upper and lower eyelids. These are the same attributes required of a peri-orbital sunscreen. However, many companies are now making stick sunscreens for use in the eye area, but lip balm can be used in a pinch.

Q. Can eye cosmetics prevent cataracts and skin cancer?

Eye cosmetics were originally developed in Egypt for sun protection and the prevention of infection. Many of the popular Egyptian eye cosmetics contained kohl, a dark black pigment. This pigment absorbed light energy around the eyes, decreasing the amount entering the eye and acting similarly to modern day sunglasses. Kohl also possesses antibacterial properties.

Modern eye cosmetics can also provide protection. The opaque cream eye shadows are excellent sun protection for the eyelids. Dark colors around the eyes, such as eyeliner and mascara, can also decrease the amount of light and UV that enters the eye, possibly decreasing the chance of cataracts. The sides of the nasal root are the light concentrating sites for the eyes. Applying facial foundation, powder, or eye shadow to the sides of the nasal root can decrease the amount of light reflected into the eyes, also helping decrease cataract formation.
Leaky gut, leaky skin, or both?

by PETER A. LIO, M.D.

Dr. Lio is assistant professor of clinical dermatology and pediatrics, Northwestern University Feinberg School of Medicine and partner, Medical Dermatology Associates of Chicago, Chicago.

The central importance of the skin barrier has become clear for a number of diseases including acne, psoriasis, ichthyosis, and atopic dermatitis (AD).¹ Excitingly, the filaggrin story in AD has codified the idea that loss-of-function mutations in the FLG gene (which codes for the protein filaggrin that aggregates keratin filaments and plays an integral role in skin barrier function) is central to the pathophysiology of AD, helping paint a mechanistic picture.² Provocatively, such deficient skin barrier function has been shown in murine models to lead to higher penetration of allergens through the skin and to enhanced sensitization to allergens, suggesting that a similar process could occur for humans with AD.³,⁴ It is postulated that such epicutaneous sensitization to both food and environmental allergens may in part explain the correlation between AD, food allergy, allergic rhinitis, and asthma that defines the so-called “atopic march.”⁵ Perhaps even more convincing, recent research suggests that AD could even be prevented simply by fortifying the skin barrier with moisturizers in high-risk individuals, further emphasizing its primacy in the pathogenesis of AD.⁶³⁷

Our epithelium, however, is not limited to the skin. The intestinal epithelium plays a role similar to that of the cutaneous one, maintaining a barrier from the outside world and selectively separating luminal contents from the interstitium. Impairment of this function leads to increased intestinal permeability, often referred to as “leaky gut.”⁸ It is not much of a stretch to imagine that there could be similar consequences to those of impaired skin barrier function, and indeed, leaky gut is often touted as the primary underlying problem for a number of chronic illnesses by holistic practitioners.⁹ That does not mean it is without controversy, however. In this brief review, we will explore some of the evidence for leaky gut and its relevance in dermatology, with an eye towards finding parallels with impaired skin barrier function, which I have dubbed “leaky skin.”

While similar to the skin in many ways, the gut must also absorb nutrients and is specialized for this task. There are three major components of the human intestine: luminal microbiota with an outer mucus layer, an inner mucus layer, and an epithelial layer. The luminal microbiome within the gut consists of an enormous community of bacteria that plays a critical role in digestion, the production of hormones and vitamins, inhibiting growth of pathogens, and in assisting with drug and toxin metabolism.¹⁰⁻¹² Enterocytes prevent contents in the lumen from crossing into the blood with tight intercellular junctions, allowing for only specific nutrients to pass while blocking others.¹³ The deep part of the gut barrier is populated by a network of immune cells, organized in a specialized structure called “gut associated lymphoid tissue” or GALT. The GALT is a major lymphoid organ, containing up to 70% of the body’s immune cells and plays an important role in immune tolerance.¹⁴

As with the skin barrier, impairment of the gut barrier may occur resulting in increased intestinal permeability. Inflammation, stressors, and dysbiosis are all associated with disruption of the gut barrier, and such dysfunction has been associated with a number of diseases including inflammatory bowel disease, celiac disease, small intestinal bacterial overgrowth, cirrhosis of the liver, fibromyalgia, Parkinson’s disease, and particularly relevant for this discussion, atopic dermatitis.¹⁵⁻¹⁷ Although not fully elucidated, the thinking is that abnormal gut barrier function allows the passage of antigens from the intestine, stimulating the immune system to produce an inflammatory response in predisposed individuals.¹⁸⁻¹⁹ While skin barrier function can be quantified with measurements such as transepidermal water loss (TEWL), the intestinal barrier is often measured by administering a mixture of sugars orally — usually lactulose along with either mannitol or rhamnose — and then examining the urinary excretion of the sugars. The larger molecules (lactulose) are able to permeate the barrier only when there is significant gut barrier dysfunction, while the smaller molecules (mannitol or rhamnose) are absorbed transcellularly, independent of the barrier function, allowing one to calculate a large sugar/small sugar ratio, which is elevated in proportion to gut barrier dysfunction.²⁰

We have thus far built up a compelling narrative, but what is the actual evidence, especially as it pertains to dermatologic conditions? Remarkably, Pike et al. were able to demonstrate a significantly increased lactulose to rhamnose excretion ratio in children with AD when compared to controls,²¹ while Rosenfeldt et al. took it a step further and were able to show statistically significant positive association between the lactulose to mannitol ratio and the severity of the eczema. Moreover, the same paper explores treating the dysfunction with a probiotic and reports a statistically significant improvement in the ratio in the treatment group compared to placebo (0.073 vs 0.110, P=.001).²²

**What if there were a moisturizer for the gut?**
Similarly, the closely related allergic condition eosinophilic esophagitis (EoE) seems to follow AD, with a recent paper reporting that patients with active EoE had significantly higher lactulose-mannitol ratios when compared to controls (0.045 vs 0.033, p<0.001), but no significant difference between the group with EoE in remission compared to healthy controls, fitting nicely with what would be anticipated. And, if we extend our net, there are several lines of evidence which converge on the idea that the increased intestinal permeability appears to be correlated with acne as well.

Which leads us to the more difficult part of this discussion: what to do? Unlike the preeminent availability of the skin, the gut is a little harder to access directly. It stands to reason then, that our most readily available intervention could be diet: a somewhat contentious area in dermatology.

Many patients are quick to implicate foods as triggers for AD, but the evidence is less definitive. One small study evaluated 15 children with AD placed on a strict elimination diet. Notably, in two weeks, nine of 15 had a significant reduction in intestinal permeability. Remarkably, this improvement on the external epithelium may well lead to improvements on the internal epithelium.

There is one other fascinating possibility that I have come across: In order to fortify the skin barrier we apply moisturizer, but what if there were a “moisturizer” for the gut? As improbable as that sounds, gelatin tannate is one such candidate for this role. It is thought to form bonds with mucin within the mucus layers to strengthen the gut barrier. Despite these encouraging results, the consensus currently states that probiotics are probably not effective for the treatment of established AD. However, there is the suggestion that as with exclusionary diets, there may be different phenotypes of the disease which respond more favorably than others. Further, there remain many unanswered questions around probiotics: the appropriate strain, dose, and duration of probiotics to name a few; but there is certainly promise in the concept of probiotic therapy.

To summarize, the first step to obtaining patent protection for your invention is to get your idea down on paper: describe your invention in both pictures and words. Second, is to identify patent counsel. Third, filing your patent. Words of caution—just because your invention is not represented in the patent literature as follows:

1. Studies excluding foods in unselected people with AD did not show benefit.
2. This lack of benefit for unselected patients is notable as it also seems to exclude the existence of non-allergic mechanisms (such as non-specific inflammation) by which food could worsen AD.

Clearly, further work needs to be done in this area, with emphasis on measuring intestinal permeability as well as AD severity; perhaps there is a small subgroup for which this is an important connection and that faint signal is washed away in larger, mixed groups.

We have also discussed the gut microbiome as playing an important role in the barrier function. It follows that alterations in gut microbiota diversity may alter the immune system, and indeed, evidence exists that such perturbations can inhibit the maturation of T-regulatory cells, leading to increased inflammation.

References:
Available with article online at bit.ly/leakyskin
The Centers for Disease Control & Prevention estimates that 1 in 59 children in the United States is diagnosed with an autism spectrum disorder (ASD), meaning dermatologists who treat children are likely to see patients with autism on a regular basis.

Due to the prevalence of the condition, caregivers of patients with autism often expect dermatologists to have an understanding of the disorder, but that may not always be the case.

“Within ASD, there is great variability. There are children at high-functioning levels who are very intelligent, and then 20% with ASD are non-verbal,” said Vikash S. Oza, M.D., assistant professor of dermatology and pediatrics at New York University School of Medicine.

Most medical literature offers little insight for the dermatologic care of this patient population, but there are a few recently published reports, including a review published in the July/August 2015 issue of Pediatric Dermatology. Authored by Dr. Oza, the review highlights best practices for dermatologists to know when treating patients with autism.

Dr. Oza shared tips from the review in an interview with Dermatology Times:

**PREPARE FOR THE PATIENT VISIT**

“One of the defining features of kids who have autism is that they have a lot of difficulty with transitions,” Dr. Oza says.

New settings — like a doctor’s office — can cause intense stress.

“Many times it’s a fear of being in a new place,” he says.

You may wish to schedule appointments at the beginning or end of the day when things are less hectic. Consider giving patients a “tour” of the office and letting them wait in examination rooms, which are less stimulants than waiting rooms. Dim, quiet, uncluttered examination rooms may also be helpful.

During the office visit, Dr. Oza says, you may need to make special adjustments, for example, if a child is having a tantrum. If that is the case, maybe say you’ll call the parent on the phone and get the rest of the history then.

The good news: “With a relationship over time, they may feel more comfortable in the clinical environment,” he adds.

**BE CONSCIOUS OF TREATMENT SENSITIVITY**

Keep in mind that a strong component of autism is sensory disintegration. Children with autism may be much more sensitive than other kids to treatments such as topical agents, Dr. Oza warns. Greasy ointments, for example, may cause irritation or create a sensation of having something thick on the skin.

“It’s like dogma that we mainly use ointments as topical steroids,” he notes. “You may have to be more flexible.”

Using a lotion or foam may be a better alternative, he says. Another good idea is to apply a topical treatment to a small area first instead of suddenly covering up a larger area all at once. And if you are using Aquaphor, patients with autism may be more tolerant of a spray, he adds.

**SKIN CONDITIONS CONNECTED TO BEHAVIOR**

Children with autism may engage in behaviors like hand flapping, hand wringing, hair pulling and skin picking that could cause skin conditions. Repetitive rubbing of the skin,
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- ONEXTON Gel is contraindicated in patients with a known hypersensitivity to clindamycin, benzoyl peroxide, any component of the formulation, or lincomycin.
- ONEXTON Gel should be used with caution in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.
- Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. ONEXTON Gel should be discontinued if significant diarrhea occurs.
- Oral and parenteral clindamycin has been associated with severe colitis, which may result in death.
- Anaphylaxis, as well as other allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin/benzoyl peroxide. If a patient develops symptoms of an allergic reaction such as swelling and shortness of breath, they should be instructed to discontinue use and contact a physician immediately.
- The most common local adverse reactions experienced by patients in clinical trials were mild and moderate erythema, scaling, itching, burning, and stinging.

ONEXTON Gel should not be used in combination with erythromycin-containing products because of its clindamycin component.
- ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A decision should be made whether to use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.
- Patients should be advised to avoid contact with the eyes or mucous membranes.
- Patients should minimize exposure to natural and avoid artificial sunlight (tanning beds or UVAB treatment) while using ONEXTON Gel. To minimize exposure to sunlight, protective clothing should be worn and a sunscreen with SPF 15 rating or higher should be used.

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This Brief Summary does not include all the information needed to use ONEXTON Gel safely and effectively. See full prescribing information for ONEXTON Gel, 1.2%/3.75% for topical use.

ONEXTON® (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%, for topical use
Initial U.S. Approval: 2000

CONTRAINDICATIONS

Hypersensitivity
ONEXTON Gel is contraindicated in those individuals who have shown hypersensitivity to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin. Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use with ONEXTON Gel (see Adverse Reactions).

Colitis/Enteritis
ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis (see Warnings and Precautions).

WARNINGS AND PRECAUTIONS

Colitis
Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. If diarrhea occurs, ONEXTON Gel should be discontinued. Severe colitis has occurred following oral and parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate toxin(s) produced by Clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for Clostridium difficile and stool assay for C. difficile toxin may be helpful diagnostically.

Ultraviolet Light and Environmental Exposure
Minimize sun exposure (including use of tanning beds or sun lamps) following drug application (see Nonclinical Toxicology).

ADVERSE REACTIONS

The following adverse reaction is described in more detail in the Warnings and Precautions section of the label: Colitis (see Warnings and Precautions).

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

These adverse reactions occurred in less than 0.5% of subjects treated with ONEXTON Gel: burning sensation (0.4%); contact dermatitis (0.4%); pruritus (0.4%); and rash (0.4%). During the clinical trial, subjects were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning and stinging. Most local skin reactions either were the same as baseline or increased and peaked around week 4 and were near or improved from baseline levels by week 12. The percentage of subjects that had symptoms present before treatment (at baseline), during treatment, and the percent with symptoms present at week 12 are shown in Table 1.

Table 1: Local Skin Reactions - Percent of Subjects with Symptoms Present. Results from the Phase 3 Trial of ONEXTON Gel 1.2%/3.75% (N = 243)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Before Treatment (Baseline)</th>
<th>Maximum During Treatment</th>
<th>End of Treatment (Week 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>Mild</td>
<td>20</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Mod.*</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Scaling</td>
<td>Mild</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mod.*</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Itching</td>
<td>Mild</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mod.*</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Burning</td>
<td>Mild</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mod.*</td>
<td>1</td>
<td>0.5</td>
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<td></td>
<td>Severe</td>
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<td></td>
<td></td>
<td>0</td>
<td>0</td>
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<tr>
<td>Stinging</td>
<td>Mild</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mod.*</td>
<td>1</td>
<td>0.5</td>
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<td>Severe</td>
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<td></td>
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<td>0</td>
</tr>
</tbody>
</table>

*Mild = Moderate

Postmarketing Experience
Because postmarketing 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.

Anaphylaxis, as well as allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin phosphate/benzoyl peroxide.

DRUG INTERACTIONS

Erythromycin
Avoid using ONEXTON Gel in combination with topical or oral erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this in vitro antagonism is not known.

Concomitant Topical Medications
Concomitant topical acne therapy should be used with caution since a possible cumulative irritant effect may occur, especially with the use of peeling, desquamating, or abrasive agents. If irritancy or dermatitis occurs, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

Neuromuscular Blocking Agents
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. ONEXTON Gel should be used with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women treated with ONEXTON Gel. ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive/developmental toxicity studies have not been conducted with ONEXTON Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

Nursing Mothers
It is not known whether clindamycin is excreted in human milk after topical application of ONEXTON 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 use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of ONEXTON Gel in pediatric patients under the age of 12 have not been evaluated.

Geriatric Use
Clinical trials of ONEXTON Gel did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Clindamycin, mutagenicity and impairment of fertility testing of ONEXTON Gel have not been performed.

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered topically twice per week for 20 weeks induced skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

Clindamycin studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8, 5.4, and 30 times amount of clindamycin and 2.4, 7.2, 40 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m², respectively) did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthomas at the treated skin site of male rats in a 2-year dermal carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900 and 3000 mg/kg/day (1 2.3, 6, and 12 times amount of clindamycin and 1.6, 4.3, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m², respectively) for up to 97 weeks did not cause any increase in tumors. In a 52-week dermal photocarcinogenicity study in hairless mice, (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical administration of the higher concentration benzoyl peroxide formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation. Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in S. typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Fertility studies have not been performed with ONEXTON Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g ONEXTON Gel, based on mg/m²) revealed no effects on fertility or mating ability.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Manufactured for:
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U.S. Patent 8,288,434

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Standardized terminology for pigmented disorders

WHITNEY J. PALMER | Staff Correspondent

D
iff erent clinical and morphological types of patchy hyperpigmentation affect thousands of patients globally. However, to date, analyzing and comparing the conditions has been difficult.

Until recently, no consensus existed on the terminology used to describe the various morphologies of acquired macular pigmentation of uncertain etiology (MPUE), including ashy dermatosis (AD), lichen planus pigmentosus (LPP), erythema dyschromicum perstans (EDP), idiopathic eruptive macular pigmentation, and Riehl's melanosis.

To provide a standardized way of discussing these conditions, a panel of 39 pigmentary disorder experts from 18 countries met during three international conferences — International Pigment Cell, World Congress of Dermatology, and the American Academy of Dermatology — to draft a consensus agreement. It was published recently in the *Journal of Dermatology*.

“A global consensus statement was needed as there was much confusion about terminology,” said Prasad Kumarasinghe, a consultant dermatologist with Fiona Stanley Hospital and University of Western Australia. “Previously, because different authors used different terms, even a systematic search could not give comparable meaningful data.”

The article provides clarity, he said, by not only highlighting the need for agreed-upon terminology, but by also noting the primary feature common to these macular pigmentation conditions is melanophages in the dermis. This factor creates hyperpigmentation.

Prior to consensus discussions, participating experts circulated several questionnaires worldwide to gather views from clinicians, study authors, and researchers. They deliberated via panel discussions, face-to-face conversations, small group meetings, and telephone calls.

Ultimately, the panel reached 29 conclusions around AD, EDP, and LPP. Importantly, the panel determined typical AD, EDP, and LPP morphologies fall on the spectrum of acquired MPUE. Here is a consensus summary:

**AD:** Large (>5cm) hyperpigmented macules are common in AD, particularly on the trunk. However, a pruritus history or papules and plaques associated with pigmented lesions can rule out AD.

**LPP:** Few LPP cases have past or current evidence of typical lichen planus. LPP lesions can affect sun- and non-sun exposed areas and appears largely on the head and neck region, including the temple, forehead, and ears. LPP can also affect flexures.

**Riehl’s Melanosis:** This term should only describe numerous fine (millimeter-sized) acquired MPUEs on the face, neck, and upper chest. If a cause is known, it should be called pigmented contact dermatitis.

**AD/EDP/LPP/IEMP:** There is no uniform effective therapy for these conditions, and they can be diagnosed without the presence of interface dermatitis. They occur in communities in different regions with different eating habits, so it’s unlikely they’re due to any particular oil applied to the skin or eaten. It’s unclear why the melanophages in the dermis causing ashy pigmentation in these conditions don’t clear as rapidly as in postinflammatory hyperpigmentation. But, if you know the cause of simple postinflammatory hyperpigmentation, don’t label it AD, EDP, or LPP. Nor should you use AD, EDP, or LPP to label diffuse acquired hyperpigmentation.

**IEMP** can be used to identify small macules (0.5-2cm) of acquired pigmentation, without or without raised velvety, pigmented lesions that occur mainly in adolescents and don’t follow a known disease episode.

Be aware, though, some medicines, food additives, and food colorings can produce pigmentation identical to AD and EDP.

These consensus conclusions are important, Kumarasinghe said, because managing acquired macular pigmentation is a new frontier in dermatology. The impact could be multi-faceted. It could bring greater attention to these types of acquired macular pigmentation, stimulate additional research in this area, and bring researchers, dermatologists, and industry personnel together to collaborate on finding effective treatment methods.

“For the dark-skinned populations are very concerned about disparities of their constitutive skin color, the clinicians and researchers need to focus on this area,” he said. “The psycho-social impact of the affected persons can be enormous.”

Reference

Atopic dermatitis Tx moves past one-size-fits-all

John Jesitus | Staff Correspondent

Knowledge gleaned over the past decade about the pathogenesis of atopic dermatitis (AD) is steering drug development toward increasingly specific targets.

Over the past 10 years, a plethora of studies expanding dermatologists’ knowledge of AD pathogenesis has driven development of new treatments that will benefit all patients with AD, said Emma Guttman-Yassky, M.D., Ph.D., at the American Academy of Dermatology annual meeting in March.1

However, emerging studies also show differences between AD phenotypes in different AD populations — such as African Americans, Asians, European Americans, children and the elderly.

“So in the future, atopic dermatitis may need to be targeted with different drugs that will be tailored for these populations, particularly if initial treatment targeting all phenotypes fails,” said Dr. Guttman, Sol and Clara Kest Professor and vice chair, Department of Dermatology, Icahn School of Medicine at Mount Sinai, and president of the International Eczema Council.

All AD phenotypes share activation of the TH2 pathway, which is targeted by drugs including dupilumab and interleukin (IL)-13 blockers, she said.

“But some of these pathways also have TH22, and maybe TH17, activation. So we may have to think a little outside the box.”

In a 60-patient study of the IL-22 monoclonal antibody ILV-094 (fezakinumab, Pfizer), actively treated patients experienced an average 12.4% reduction in body surface area involvement at week 12, versus 6.2% for placebo (p=0.009). SCORAD declines met statistical significance among patients with severe AD at baseline (21.6 vs 9.6, p=0.029).

In the future, she said, dermatologists may need to employ multiple cytokine antagonists to address the multiple pathways active in some AD phenotypes.

“It’s not like psoriasis,” Dr. Guttman added. Its pathogenesis focuses heavily on TH17 and IL-23, she explained. Because she began her research into AD pathogenesis while working in a psoriasis lab, Dr. Guttman and colleagues initially compared the two diseases through molecular and cellular methods. “We saw that atopic dermatitis has increases in epidermal hyperplasia, very similar to psoriasis. And T cells are increased in both diseases. But they show different polarization, so the cytokines produced by these T cells are different.”

Still, she said, it became clear that both psoriasis and AD are immune-driven.

Increasingly, she added, studies show that patients with AD also have increased inflammatory markers in their blood.

“There are also some population-based studies that showed increases in hypertension and other cardiovascular associations in patients with atopic dermatitis. The idea is that atopic dermatitis emerges as a systemic disease.”

With newer IL-17 blockers, many patients achieve Psoriasis Area and Severity Index (PASI) 90 or even PASI 100. “In atopic dermatitis, we’re not there yet. Partly it’s because the disease is much more heterogeneous. And it’s not clear now if we can target the disease in full using just one cytokine or receptor antagonist.” To achieve 100% responses for virtually all patients, she said, physicians may need to adopt personalized medicine approaches to treat the various AD phenotypes.

Debating whether AD begins with barrier abnormalities or immune abnormalities is futile, said Dr. Guttman. Whichever is the case, she explained, immune abnormalities ultimately amplify the disease toward chronicity. Cytokines that warrant targeting are those that have effects on the epidermis, such as IL-4 and IL-13, which inhibit barrier proteins and antimicrobial activities, she said, and IL-22, which creates hyperplasia, among others. Such an approach is proving effective, Dr. Guttman said, as new biologic and small-molecule drugs target specific cytokines involved in AD.

The success of dupilumab against AD represents final proof of the immune hypothesis, Dr. Guttman added. “We target the disease specifically with a drug that targets only the IL-4 receptor. So by targeting specifically the TH2 pathway, not only do we improve the clinical disease, but we also improve the immune abnormalities and the barrier.” These findings establish the TH2 axis and the IL-4 and IL-13 cytokines as pathogenic in AD, cementing the disease as a reversible, immune-driven disease like psoriasis, she said.

In a 60-patient study of the IL-22 monoclonal antibody ILV-094 (fezakinumab, Pfizer), actively treated patients exp-

Quick Takes

AD phenotypes share activation of the TH2 pathway, but some pathways also have TH22 and/or TH17 activation.

AD is more heterogeneous than PsO, may require physicians to adopt personalized approach to treat different phenotypes.

Studies show the TH2 axis and the IL-4 and IL-13 cytokines share activation of the TH2 pathway, which is targeted by drugs including dupilumab and interleukin (IL)-13 blockers, she said.

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“...in the future, atopic dermatitis may need to be targeted with different drugs that will be tailored for these populations, particularly if initial treatment targeting all phenotypes fails.”

Emma Guttman-Yassky, M.D., Ph.D., Icahn School of Medicine, Mount Sinai, New York

Dr. Guttman and colleagues subsequently advanced the proposition that IL-22 and Th22, which produces it, may have a pathogenic effect in AD. “We showed that in half of the patients treated in the study — the patients who had increased IL-22 compared to the other patients — the drug reduced the disease quite well.” At week 12, patients in the high IL-22 cohort experienced mean transcriptome improvement of 139.4%, vs 49.9% for placebo. Conversely, patients with low baseline levels of IL-22 expression did not respond.

“This is what I consider to be the first example of personalized medicine in atopic dermatitis, and maybe in dermatology generally. It’s the first example I’m aware of in inflammatory skin diseases,” Dr. Guttman says. ≪

Disclosures
Dr. Guttman-Yassky is a consultant, investigator and/or advisory board member for AbbVie, Almirall, Amgen, Asana BioSciences, Celgene, Concert, DHI, Dermacor, Dermira, DS Biopharma, Eli-Lilly, BMS, Enzon, Escalier Biosciences, FRiB, Gol- derma, GSK, Janssen, Kyowa Kirin, LEO, Mitsubishi Tanabe, Novartis, Pfizer, Sanofi-Regeneron and Union Therapeutics. She has also received grants from Innovaderm, Janssen, Novartis and Rezalax.

References

Pediatric patients with autism require special care considerations

For example, can cause lichen simplex chronicus, while skin picking can result in prurigo nodularis, Dr. Oza says. “We may need to work hand in hand with a psychologist or a psychiatrist to try to reduce these behaviors.”

Also be aware that kids with autism may develop very restrictive diets, he says. “There are many reports of kids with autism presenting with scurvy.”

UNDERSTAND THAT PATIENT AND PARENTS MAY DIVERGE

In some cases, children with autism may not be bothered by conditions like acne or vitiligo, Dr. Oza says. “They may have something that’s outwardly disfiguring but not feel the same impacts as other children like self-consciousness or embarrassment.”

Even so, parents may still push for treatment. “This may be because they see this as an area in which they can intervene,” he says. “It can be a complex conversation when these things come up.”

CONSIDER GENETIC CONDITIONS WHEN APPROPRIATE

“While uncommon, there are certain genetic diagnoses that are associated with high rates of autism, and some have specific skin features,” says Dr. Oza. Two notable conditions to consider, he says, are tuberous sclerosis (a rare condition that causes non-cancerous tumors in the skin and other organs) and PTEN hamartoma tumor syndrome (which causes tumor-like growths known as hamartomas).

WATCH OUT FOR SIGNS OF BEHAVIOR CHANGE

According to Dr. Oza, some children with autism “are not able to effectively communicate what may be bothering them.” As a result, they may suffer silently from any one of a number of medical conditions such as constipation (which he said is extremely common in this population), other intestinal problems, dental problems like cavities and abscesses, and headaches.

Dermatologists should be aware that these children may reflect their internal stress through behavior changes such as intensified skin picking. Be prepared to ask the child’s pediatrician to follow up, he says.

In the big picture of treatment of children with autism, Dr. Oza wants dermatologists to remember that “every kid’s sensitivity and behavioral aspects are totally unique.”

At the same time, he adds, it’s unlikely that dermatologists will need to actually adjust the necessary treatment for one of these patients. “You just have to be more flexible,” he says. ≪

Disclosures
Dr. Oza reports no relevant disclosures.
Early acne intervention may prevent later scarring

INGRID TORJESEN | Staff Correspondent

A significant reduction of elastic fibers and collagen fibers combined with inflammation is observed in acne scarring, and these processes appear to be modulated by TGF-β1 signaling, a study published in the March issue of British Journal of Dermatology found.

This raises the possibility that an early treatment regimen strongly inhibiting inflammation and TGF-β1 signaling to help recovery of the extracellular matrix components may have the potential to prevent atrophic scarring, the authors suggest.

Acne scars are a major cosmetic worry for acne patients, but they do not affect all patients. The pathogenesis of acne scarring is unclear and believed to differ to that of ordinary scarring, so researchers in Korea set out to investigate in more detail how early inflammation and histological changes are involved in acne scarring, as well as the specific molecules controlling the process, by comparing the molecular profiles of skin and acne lesions in patients who are prone to scarring as against those from patients who are not.

Their study included 30 patients with Fitzpatrick skin types III to IV, who had acne on their faces. Fifteen patients were prone to atrophic scars — meaning they had 30 or more atrophic acne scars on their faces and that their acne usually developed into acne scars — and 15 patients had almost no evidence of atrophic acne scars and said that they rarely experienced them.

Skin biopsies were taken from acne lesions five times per patient: normal tissue, a papule at day 1 following the occurrence, at day three, at day seven, and mature tissue (acne occurred more than three months ago). Immunohistochemistry, and quantitative real-time polymerase chain reaction were performed on the samples.

“We observed significant deficiency of total elastic fibers in mature atrophic scars. Moreover, we discovered that the lack of elastic fibers persists from the beginning of acne inflammation,” says Dae Hun Suh, M.D., Ph.D., department of dermatology, Seoul National University Hospital, Republic of Korea.

Collagen fibers are essential in scar pathophysiology, and it has been suggested that a skewed ratio of collagen 1 to 3 but increased ratio of collagen 1 to 3 in patients prone to acne scars compared to that in non-scar prone patients, implying that degradation occurs more sensitively to collagen 3 in patients prone to acne scars,” Suh says. Increased TGF-β1, which promotes compensatory recovery of collagen 1 more than collagen 3, might be involved in this process, he suggested. The study also demonstrated significantly higher levels of proinflammatory cytokines associated with acne pathogenesis in patients prone to acne scarring. Cutibacterium acnes, or C. acnes, (formerly Propionibacterium acnes, or P. acnes) stimulates the expression of proinflammatory genes such as TNF-α, IL-6, IL-12, and CXCL8 via toll-like receptor 2 signaling, and this inflammatory landscape can encourage the synthesis of matrix metalloproteinases in fibroblasts and endothelial cells, thereby leading to proteolysis of extracellular matrix.

C. acnes drives inflammatory reactions by initiating the infiltration of Th17/Th1 cells with increased IL-17 production in the perifollicular areas. The differentiation into Th17 cells is TGF-β1 and IL-6 dependent, and Th17 cells may aggravate acne inflammation via IL-17 related proinflammatory responses. Failure of delicate control of Th17/Th1 cells may trigger a vicious cycle worsening inflammation, the researchers suggested.

The study also demonstrated that TGF-β1 plays an important role as a modulator of inflammation and scar formation at the beginning of acne lesions. TGF-β1 participates in scar formation directly regulating fibrosis or manipulating keratinocyte proliferation. It has been recognized that TGF-β1 drives extracellular matrix synthesis and fibroblast proliferation as well as myofibroblast differentiation responsible for tissue contraction during scarring. TGF-β1 can also restrict proliferation of keratinocyte through disturbing transcription of c-Myc or inducing transcription of p21.

“It is presumed that devastation of elaborate regulation of TGF-β1 signaling may have an effect on atrophic acne scarring by not only fortifying inflammation but also affecting fibrosis itself and epidermal proliferation,” Suh says. “It is postulated that faultily tuned TGF-β1 in patients who are prone to acne scars fails to restore extracellular matrix destruction normally, which is contributed by amplified inflammation and impaired epidermal proliferation.”

Approaches for improving acne scars including soft tissue fillers, microneedling and most recently use of stem cells. “Their effectiveness is often unsatisfactory because they only focus on neocollagenesis in atrophic scars which are already finalized,” Suh says. “A fundamental solution for atrophic acne scars should be based on preventing scarring through intervention during early stages of acne. Therefore, it is expected that our findings can provide molecular evidence of establishing novel strategies such as anti-inflammatory or anti-TGF-β1 agents to avoid atrophic scarring.”

Quick Takes

Study found severe destruction of collagen 1, 3 but increased ratio of collagen 1 to 3 in patients prone to acne scars.

Significantly higher levels of proinflammatory cytokines associated with acne pathogenesis in patients prone to acne scars.

TGF-β1 plays important role as a modulator of inflammation, scar formation at beginning of acne lesions.

READ MORE

RESEARCHERS HAVE GAINED NEW PERSPECTIVE ON THE ROLE OF INFLAMMATION IN ACNE, WHICH HAS RESULTED IN NEW TREATMENT APPROACHES.
Acne’s hidden scars

LISETTE HILTON | Staff Correspondent

Quick Takes
The social/emotional burden of acne can be significant.

Ask questions to assess the impact of disease that the patient is experiencing.

Let clinical exam and psychosocial burden inform your treatment plan.

When Jonette E. Keri, M.D., Ph.D., tries to convey acne’s psychosocial impact, she refers to a line in a paper published December 2004, in which researchers addressed the impacts of acne vulgaris on quality of life and self-image.

“The impact of acne may be equivalent to that of asthma or epilepsy,” notes the article by Thomas DR in The Journal of Cutaneous Medicine and Surgery.

That description put the potential psychosocial suffering of teenage and other acne patients in perspective for Dr. Keri, associate professor of dermatology and cutaneous surgery at the University of Miami School of Medicine, Miami, Fla.

“When I read that article years ago, I thought how I remembered the one young man in my whole high school who had epilepsy. Everybody knew him. And everybody knew how hard his life was. So, I think of him, and then I think acne can be as hard as that,” says Dr. Keri, who presented on acne’s psychosocial impact during the Acne Treatment Controversies panel in March 2019 at the American Academy of Dermatology (AAD) Annual Meeting in Washington, D.C. “There’s not just physical scarring. There can be emotional scarring, which is why I like to treat acne aggressively.”

TO SCREEN OR NOT TO SCREEN
There are mental health screenings that dermatologists can incorporate in practice for acne and other patients, according to Dr. Keri. While some are shorter and easier to implement, other screenings are long and better reserved for use in research, she says.

In a letter to the editor by Rea S et al published July 20, 2017 in the Australasian Journal of Dermatology, the authors suggest that dermatologists learn the Diagnostic and Statistical Manual (DSM) criteria for depression and consider implementing that as a screening tool for their acne patients.

Dr. Keri says that may be unrealistic. While there are tools for having the discussion, including questions to ask, she recommends that dermatologists practice responsibly by taking the time to talk to patients about how they feel, psychosocially.

“Ask them if they’re feeling badly about their skin. If they’re eating. If they feel self-conscious,” she says. “If the dermatologist feels comfortable with the patient, he or she might refer to the patient’s primary care, psychologist or psychiatrist, depending on the severity of the psychiatric symptoms that the dermatologist is seeing. I think we have a responsibility as dermatologists to be aware that there can be these feelings in these patients.”

Dermatologists in academic settings often have a built-in referral network, which Dr. Keri says can get patients the help they need quickly and with less effort.

“I have, for example, one young girl who had a fair amount of depression and anxiety. She would pick her skin in addition to having acne, so she had acne excoriee,” Dr. Keri says.

“I developed a rapport with her. She told me she was at a new school and the kids were tough. We got her an appointment with the pediatric psychology division. She had weekly sessions and is doing much better. Her acne is better, she’s not picking and she feels better.”

MENTAL HEALTH IMPACTS TREATMENT
It’s important to hear and factor in the child’s point of view, she says. If the impact is relatively severe for a child’s quality of life or self-esteem, Dr. Keri might suggest more aggressive therapies.

“If they’re borderline for getting isotretinoin and they really want to get better, I might use it, for example,” she says.

Those treatment recommendations should be based on the individual acne patients. Some severe acne patients don’t appear bothered by their skin, according to Dr. Keri.

“Sometimes, I’m more worried about the acne than they are. I worry about their long-term skin health, and I’m trying to prevent more scarring. So, I have to educate them about my concerns before recommending treatment,” she says.

Dr. Keri says she does not generally prescribe antidepressants for acne patients.

“I have done it a few times in my career. Within the last month, I’ve done it once prescribing paroxetine, but then I ultimately got that patient to see a psychologist and psychiatrist,” she says. “I don’t think many dermatologists feel comfortable with prescribing these medications.”

But Dr. Keri says it’s important to act on behalf of the patient. Sometimes that means contacting the patient’s primary care doctor when patients are upset about their acne or making a referral to a mental health specialist. Dermatologists should consider aligning with mental health professionals who are they feel comfortable referring to and are experienced in taking care of patients with skin conditions.

The key is to help the patient most directly get the care they need, without too many steps, to address psychosocial issues from acne, she says.

References

Disclosures
Dr. Keri is an advisor with Ortho Dermatologics, Pierre Fabre Dermatologie, Almirall, Dermira and Menlo Therapeutics.

2017 in the AAD Annual Meeting in Washington, D.C. “There’s not just physical scarring. There can be emotional scarring, which is why I like to treat acne aggressively.”
Options to limit antibiotics

LISETTE HILTON | Staff Correspondent

Dermatologists' overall antibiotic prescribing has fallen in recent years, so they and their acne patients are finally relying less on antibiotics and more on alternative treatments, according to Diane M. Thiboutot, M.D., professor of dermatology at Penn State College of Medicine.

NO SMALL ISSUE
Antibiotic resistance is among today's biggest threats to global health, food security and development. And antibiotic misuse is accelerating the problem and rendering antibiotics less effective against a growing number of infections, including pneumonia, according to a fact sheet released February 2018 by the World Health Organization (WHO).1

Dermatology, a relatively small specialty, remains a mighty force among antibiotic prescribers, with dermatologists prescribing more oral antibiotics per clinician than any other medical specialist, according to a recent review published online in JAMA Dermatology.2

The good news from that study: Dermatologists' antibiotic prescribing fell 36.6% between 2008 and 2016, largely because of decreases of use in extended courses of antibiotics prescribed for acne and rosacea, according to the authors.

“Because of concerns about the development of bacterial resistance, we have been recommending to limit the use of antibiotics for the treatment of acne. The guidelines for the treatment of acne— the more recent guidelines from the AAD in 2016—incorporate some of this information with regard to the use of antibiotics,” Dr. Thiboutot says.

Nevertheless, some dermatologists still treat patients with antibiotics for several months or years at a time. The updated guidelines recommend that oral antibiotics should be used for the treatment of acne for no more than a three-month period,” she adds.

According to the guidelines, dermatologists should consider starting acne patients on topical treatments along with antibiotics, so that patients continue topical therapies after stopping oral antibiotics.

But while the messages are clear, changes in antibiotic prescribing practice patterns have been slow in coming in dermatology, according to Dr. Thiboutot.

“We made recommendations about reducing antibiotics around 2003,” she says. “I think part of the issue is that antibiotics have been a mainstay of acne treatment.”

ANTIBIOTIC ALTERNATIVES
Among the acne treatment alternatives gaining wider acceptance: the hormonal agent spironolactone. It’s not FDA-approved for acne but is widely used to treat acne in women, according to Dr. Thiboutot.

Another way to limit antibiotic use in acne patients is to use isotretinoin sooner in those who continue to have acne despite long-term antibiotic treatment, especially when patients have acne-associated scarring, according to Dr. Thiboutot.

“Another alternative would be to maximize the use of topical therapies like benzoyl peroxide, topical retinoids, other topical agents,” she says.

Still another option—one that involves an antibiotic at lower doses—is treating acne with sub-antimicrobial doses of doxycycline.

“There have been publications on this,” Dr. Thiboutot says. “Low-dose doxycycline is not FDA approved for the treatment of acne, but it has been studied in rosacea and is FDA approved for the treatment of rosacea. It would be interesting to have some long-term studies looking at whether use of sub-antimicrobial doses of doxycycline for acne is associated with the development of bacterial resistance. Those longer-term studies have been reported in the dental literature, but no long-term studies have looked at bacterial resistance in acne patients.”

Dr. Thiboutot says that she was among the dermatologists who often would go to antibiotics for acne treatment several years ago.

“When the new information came out about bacterial resistance, it was a bit concerning to treat someone and then stop the antibiotics after about three months. I wasn’t sure how that was going to go,” she says. “I was really pleasantly surprised in a lot of cases. What I do after that three-month period is I make sure that they have other therapies onboard, usually a benzoyl peroxide or topical retinoid. In some cases, I do use low doses of doxycycline but would welcome additional data.”

Disclosures
Dr. Thiboutot consults with Botanix, Cassiopea SpA, Novartis and Sebacia. She has been advisor for Derminis, Goldmera Laboratories, Novaro and Sebacia.

References

“...”What I do after that three-month period is I make sure that they have other therapies onboard, usually a benzoyl peroxide or topical retinoid.” Diane M. Thiboutot, M.D., professor of dermatology at Penn State College of Medicine.
Cognitive behavioral therapy (CBT) can successfully treat the physical symptoms of psoriasis, a new systematic review and meta-analysis finds — and systemic treatment doesn’t seem to provide an extra boost to its effectiveness. However, the authors of the report aren’t ready to suggest that CBT become a mainstay of psoriasis treatment.

“Although the results show that CBT is effective, we cannot draw the simplistic conclusion that CBT is a universal effective therapy to all psoriasis patients because CBT is tailored for individual patients, and there is heterogeneity in the delivery of this method,” write the authors, whose findings appeared online Feb. 9 in Psychology Research and Behavior Management.

The report, led by dermatologist Yi Xiao, M.D., M.P.H., of Central South University in Changsha, China, notes that mental conditions such as anxiety and depression appear to be more common in psoriasis.

According to a 2016 review, previous research has suggested psoriasis and psychiatric disorders are highly correlated compared to other dermatologic diseases, and “patients may have specific psychopathologic features that are not commensurate with the extent of skin lesions.” In addition, the review reported that “studies have shown that these patients suffer from the same deterioration in health-related quality of life as patients with cancer and cardiovascular diseases.”

The researchers of the current review examined eight randomized controlled trials of psychological interventions for psoriasis. The trials, published in English and Chinese, were small — with intervention and control groups ranging from 20 to 83 people — and included a total of 765 subjects.

Five of the trials tested various types of CBT (including one that applied it with biofeedback). The other three trials examined “telephone-based emotional disclosure,” “group multiprofessional education” and “telephone-based motivational interviewing.

Most of the trials lasted six or 12 weeks; two lasted six months.

The researchers found a statistically significant improvement for CBT only: The pooled estimate was −1.80 (combined Psoriasis Area and Severity Index [PASI] and Self-administered Psoriasis Area and Severity Index [SAPASI]), 95% CI: −2.57 to −1.03; P<0.001). The studies measured PASI, SAPASI or both.

“The subgroup analysis shows that CBT, rather than other specific psychological interventions, is effective in PASI reduction with a moderate effect size,” the researchers write.

Some of the studies complemented CBT with systemic treatments, such as etanercept (Enbrel, Amgen), methotrexate and cyclosporine. These treatments didn’t appear to boost the effectiveness of CBT. The researchers also found that in-person CBT in groups or individual sessions appeared to be more effective than remote CBT delivered by phone or the Internet.

“CBT can reduce the stigma and confusion surrounding affective and anxiety responses to the disease, and it may improve psoriasis severity by inhibiting the inflammation associated with depression and anxiety,” the authors write. “In addition, CBT provides a tailored approach to correct misconceptions and expand knowledge about the nature of psoriasis; for example, believing it to be contagious. Moreover, CBT may be helpful in tackling feelings of despondency and hopelessness in patients, making them more participative in their treatments.”

The study was funded by the Ministry of Science and Technology of the People’s Republic of China and the Department of Science and Technology of Hunan Province.

Disclosures
The study authors report no relevant disclosures.

References
Patient-centered treatment

WHITNEY J. PALMER | Staff Correspondent

When it comes to treating psoriasis, many therapies exist that offer roughly the same level of care. But that doesn’t mean any patient will respond well to any therapy. It turns out there are many factors, including other illness or comorbidities, that should be considered when trying to find the right treatment option for a patient. Mark Lebwohl, M.D., a dermatologist with Mt. Sinai Health System, discussed factors clinicians should consider when treating patients with cardiovascular conditions during the American Academy of Dermatology Spring Meeting in Washington, D.C.

“People always ask which psoriasis drug is my favorite or which is best,” he said. “The truth is, it’s a different drug for different patients because there are a whole range of conditions that we should look for and ask the patient about.”

Certain drug classes could be risky for patients with hypertension, diabetes, a previous history or family history of heart attack or a history of smoking. In particular, Dr. Lebwohl discussed how congestive heart failure and latent tuberculosis (TB) could affect psoriasis drug choice.

For example, he said, dermatologists should consider avoiding TNF blockers for congestive heart failure patients. One infliximab study revealed higher doses of the TNF agent led to more hospitalizations and deaths. Alternately, he said, ustekinumab, methotrexate, apremilast, cyclosporine and acitretin could be good options. However, he cautioned, cyclosporine has been associated with hypertension.

Treating latent TB can also be problematic, he said. Typically, with latent TB, dermatologists can treat patients with prophylactic anti-TB drugs to limit the likelihood the TB would erupt. However, if a TB patient is also on biologic therapy, using a TNF blocker could actually initiate a TB recurrence, as could methotrexate. Instead, consider the interleukin (IL)-17 and IL-23 blockers to avoid a TB relapse, as well as apremilast, cyclosporine and acitretin.

Dr. Lebwohl also discussed psoriasis drugs for cancer patients. Individuals with squamous carcinoma or malignant melanoma or lymphoma should not receive TNF blockers as the treatment can increase certain malignancies. Instead, he said, ustekinumab and IL-17 and IL-23 blockers are preferable.

Having this information is critical to providing the best patient care possible, Dr. Lebwohl emphasizes.

“I hope dermatologists will talk with patients about their symptoms and their comorbidities and apply a greater understanding of which drugs might work best in which circumstances,” he said. “If they don’t, they’ll be relegated to trial-and-error in trying to find the right treatment, and they won’t necessarily be giving the best drug to the patient.”

Reference:

IMMUNOSUPPRESSION

If a patient is receiving immunosuppressive therapy, she should take extra precautions to avoid pregnancy.

For example, patients receiving mycophenolate mofetil should use at least two forms of contraception, including a barrier method, for at least 4 weeks prior to receiving treatment and for 6 weeks post-treatment. Additionally, women receiving azathioprine should not rely on an IUD alone for contraception.

STEROIDS

Whenver possible, steroid use should be strictly limited during pregnancy. Both betamethasone and dexamethasone can cross the placental barrier easily, putting the unborn infant at risk, she says. Topical prednisone is the preferred alternative because it doesn’t cross the placental barrier as efficiently.

Even still, you are guaranteed side effects with prednisone,” she said, recommending prednisone be limited during pregnancy when possible. “You’ll gain weight, have gestational diabetes, you’ll have high blood pressure, fat redistribution, and bone loss. It’s not a situation where you can monitor to see if you get the side effects. You will get them.”

Murase also discussed cyclosporine and its safety as an oral systemic therapy. Research data indicates it presents no malformation risk, neurodevelopmental, immunologic, or nephrogenic defect risks. Overall, Murase said, she hopes dermatologists remember these three overall take-away messages:

- **Topical steroids and anti-histamines are largely safe in pregnancy**
- **Biologics have mounting safety data around the safety of anti-TNF class drugs in pregnancy and breastfeeding**
- **IgG, immunoglobulin G, is an excellent antibody choice for treating moderate-to-severe pemphigus cases.**

**Quick Takes**
When it comes to effective management of psoriasis, different drugs work for different patients.

Assessing patient comorbidities and understanding contraindications for each drug is critical to providing the best patient care.

When treating patients of child-bearing age, it’s important to initiate discussions about potential side effects of any treatment, as half of all pregnancies happen unplanned.

**WOMEN’S HEALTH GUIDELINES**

WHITNEY J. PALMER

Treating chronic inflammatory skin conditions during pregnancy carries a different set of guidelines. Dermatologists are treating the mother, but whatever therapies they prescribe can also have an effect on the unborn infant.

Consequently, the onus is on the dermatologist to discuss any therapies and potential side effects with any woman of child-bearing age despite whether she’s sexually active. As a rule, patients don’t initiate these conversations.

Jenny Murase, M.D., a dermatologist with the Palo Alto Foundation Medical Group, discussed some risk factors and guidance for dermatologists during the American Academy of Dermatology Spring Meeting in Washington, D.C.

“A key thing for dermatologists to understand is that 50 percent of pregnancies in the United States aren’t planned with a healthcare provider, meaning an ob/gyn, family practitioner, dermatologist, etc.” she said. “So, that means the number of pregnancies planned with a dermatologist are a fraction of that 50 percent.”

Here are some guidelines she suggested:

**ANTIHISTAMINES**

Although antihistamines are largely considered safe during pregnancy for patients with chronic inflammatory skin conditions, she said, they should be avoided during the last month. During that time period, they can cause adverse effects:

- **An oxycitin-like effect** that prompts uterine contractions
- **A increased rate of retrolental fibro-blasts in premature infants exposed to antihistamines within 2 weeks of delivery**
- **Withdrawal symptoms**, including tremors, irritability, poor feeding, and diarrhea

**IMMUNOSUPPRESSION**

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**STEROIDS**

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- **IgG, immunoglobulin G, is an excellent antibody choice for treating moderate-to-severe pemphigus cases.**
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Photos provided by Dr. Michael H. Gold, M.D., FAAD
By all accounts, Revance is preparing for the FDA’s approval and market launch of its lead compound daxibotulinumtoxinA for injection (DAXI). DAXI clinical trials looking at glabellar line treatment suggest the neuromodulator with its proprietary peptide technology is at least as good as Botox (onabotulinumtoxinA, Allergan) but lasts substantially longer.

The release of a new and different neuromodulator is big news given botulinum toxin type A procedures consistently rank first among the most popular minimally invasive treatments in the United States. Since 2000, demand for botulinum type A procedures has soared 845%, according the 2018 National Plastic Surgery Statistics by the American Society of Plastic Surgeons (ASPS).

Shannon Humphrey, M.D., clinical assistant professor in dermatology and skin science, University of British Columbia, was principal investigator for a number of Revance DAXI studies and has had years of experience using the product in glabellar lines.

“This is a product that’s truly different,” Dr. Humphrey says. “In medicine we’re bombarded with me-too products that are differentiated based on price or a new label, but this really is a different product in a number of ways. One of the most important differentiators is that it creates a new category of injectable neuromodulator for glabellar lines that is longer in duration.”

**DAXI DURATION, EFFICACY & SIDE EFFECTS**

DAXI’s median duration for treatment of moderate-to-severe frown lines was 24 weeks. That’s a good eight weeks longer than top competitors on the market, according to Dr. Humphrey.

“And if you actually look at the duration to the time to return to baseline to the original frown line, you’re looking at more like 27, 28 weeks,” she says.

Other trial results that are vital to the product’s market success include that it effectively treats frown lines and appears to be at least as safe as potential rival Botox.

“There’s a very high degree of efficacy — actually the highest response rate seen across studies of competitors. Over 95% at the four-week mark. So it’s not just in one study — across a very robust, large dataset, there’s a 95% response rate,” Dr. Humphrey says.

DAXI’s side effect profile is similar to other neuromodulators on the market, according to Dr. Humphrey.

“The side effects were mild, localized to the injection treatment area and transient,” she says. “From a confidence-in-science perspective, it works and it’s safe.”

The other interesting piece is around duration. “We see 24 weeks’ duration, for moderate-to-severe frown lines effectively treated and 28 weeks before patients go back to how their frown lines looked before.”

Researchers conducted one head-to-head study, the phase 2 BELMONT study, which had multiple treatment arms, including one with 20 units of onabotulinumtoxinA (Botox).

“That is approximately equivalent to the amount of daxibotulinumtoxinA 40 units, which is what Revance has decided to go ahead with for their filing,” Dr. Humphrey says. “Again, what we found in this study is that daxibotulinumtoxinA gets approximately eight weeks longer duration than that competitor.”

**DAXI NUANCES**

DAXI is a purified protein. The 150 kilodalton toxin is exactly the same as other neurotoxins on the market. But daxibotulinumtoxinA has a proprietary peptide.

“It’s a little amino acid chain that’s added to it, and through a number of basic science mechanisms, it leads to this longer duration,” Dr. Humphrey says. “We spend a lot of time talking about differentiation but, as a foundation, the active part of this drug is the same.”
[Jeuveau] will likely be a premium product, allowing me to deliver the best long-lasting results for my patients. But I think there will still be a role for competitors’ products.”

Dr. Humphrey says dermatologists and others will learn more about how DAXI behaves compared to other neuromodulators once it has regulatory approval. She explains that in the clinical trial setting, researchers use it with a specific paradigm for injection and in a specific dose for all patients. But there is something she says she noticed when treating patients with DAXI.

“This is a personal observation — not garnered from the data. There was a lovely reshaping of the brow, a really beautiful smooth look to the glabella that I believe is slightly different from some of the competitors. But the nuances of how to capitalize on that will be garnered when we have large numbers of patients in clinical practice,” she says.

Revance started preclinical trials in early 2019 looking at DAXI to treat forehead lines and crow’s feet, according to Dr. Humphrey.

**HOW WILL DAXI AFFECT YOUR PRACTICE?**

Dr. Humphrey says colleagues have asked her how a longer-lasting neuromodulator might impact their practices’ bottom lines. She says that market research has shown the physicians think their neuromodulator patients are coming in more often than they actually are.

“The vast majority of toxin patients are coming in twice a year. Physicians overestimate it and think their patients are coming in three or four times a year,” she says.

If the FDA approves DAXI, consumer behavior will likely not change; rather patients coming in twice a year will actually have better results and more consistent improvement over the duration of the year, she says.

“From a clinical integration perspective, I like the concept of patients’ coming in twice a year. Most of my injectable patients are on a combination treatment plan where they’re having toxins and fillers and lasers and tightening treatments. And to combine those for optimal convenience, twice a year works really well for me from a treatment planning perspective,” Dr. Humphrey says.

DAXI’s potential launch, however, doesn’t mean an end to Botox, Dysport (abobotulinumtoxinA, Galderma) or Xeomin (incobotulinumtoxinA, Merz Aesthetics), according to Dr. Humphrey.

“I believe that if I have patients who are completely satisfied and happy with their current treatment, I’d be unlikely to initiate a change. I’d be happy to provide information through a number of channels I communicate with patients — media, blogs, reading material in our office. But I don’t think I would proactively plan to change treatment for all of my happy patients,” she says.

“For new patients, I think I will have the discussion about which product is right for them and make that decision that way. It will give patients another choice. It will be a differentiated product. It will likely be a premium product, allowing me to deliver the best long-lasting results for my patients. But I think there will still be a role for competitors’ products.”

Caroline A. Chang, M.D., a dermatologist practicing in East Greenwich, R.I., says she plans to incorporate Revance’s DAXI into practice if it receives FDA approval.

“The potential for longer duration of action may be useful for certain patients. Moreover, as a core aesthetic specialty, it is important for us … to stay current on new products so that we can offer them to our patients,” Dr. Chang tells Dermatology Times.

“Given its longer duration of action, I would consider it in patients who have had neuromodulator injections previously. One of the great benefits of the current neuromodulators is actually the three-month duration, especially for toxin-naïve patients. I’ve found that some patients learn they don’t like the effect that toxin has on certain areas of their face. The shorter duration is helpful in these cases. However, for those patients who’ve had toxin in the past, particularly in the glabellar area without issue, this product would be a suitable treatment.”

Atlanta, Ga., facial plastic and reconstructive surgeon Inessa Fishman, M.D., says she is excited about new neuromodulators coming to the U.S. market.

“…. mostly because I’m a fan of competition and choices,” Dr. Fishman says. “I currently use Dysport, Xeomin and Botox in my practice, and am excited about trying Jeuveau (prabotulinumtoxinAevfs, Evolus). Brand loyalty is huge in the U.S., but I find that my patients generally trust my opinion and experience in terms of their best injectable options.”

Dr. Fishman says the downside of a new product is the need for a trial period.

“I like to try new treatments on myself, friends and family, as patients can be hesitant about a new product, especially if these patients and I do not have a long-term relationship,” according to Dr. Fishman. “Another hesitation is higher dosing — literature suggests a direct correlation between dosing and longevity, and this may be fine for glabella and crow’s feet, but an overly frozen or heavy forehead — for months — is probably not going to be welcomed by most patients.”

Revance plans to file with the FDA the first half of 2019, and FDA approval could come as early as 2020, according to Dr. Humphrey.

**Disclosures**

Dr. Humphrey is an investigator and consultant to Revance. Dr. Chang and Fishman report relevant disclosures.
3 Trends in Skincare

Expert insights on the microbiome, blue light and ‘green’ products

LISETTE HILTON | Staff Correspondent

It’s hard not to notice three terms that marketers are hyping as trends in skincare: microbiome, blue light and (organic) green.

But what do they really mean? And what should dermatologists be telling their patients? Two experts offer insights and recommendations.

MICROBIOME: HELP OR HARM?

“There is a lot of discussion about the microbiome because new studies are showing a relationship between the bacteria in the gut and on the skin and skin health,” according to Miami, Fla.,-based dermatologist Leslie Baumann, M.D., author of the textbook *Cosmeceuticals and Cosmetic Ingredients*.

The association has led to a plethora of “probiotic” skincare brands — many containing one to three types of bacteria that claim to benefit the skin, according to Dr. Baumann. Dr. Baumann doesn’t recommend topical probiotics. Here’s why: “We don’t know yet what bacteria are good and bad for the skin. We have some hints but nothing conclusive,” Dr. Baumann says. “The gut flora may play a bigger role than previously thought, so topical products would not affect gut flora. Most studies are showing that diversity of flora is more important than one ‘good’ bacterium so adding exogenous probiotics might actually do harm. And the response to these topical probiotics will depend on skin type, medications, diet, environment and genetics.

“We just do not know enough about the role all of these factors play with the microbiome,” she says.

BLUE LIGHT: GOOD FOR ACNE, BAD FOR AGING

Dr. Baumann says she loved using blue light as an acne treatment to kill *Cutibacterium acnes* (*C. acnes*, formerly *Propionibacterium acnes*), but new studies suggest it ages the skin.

Indeed, researchers have found, for example, that low-level 449 nm blue light photobiomodulation kills *C. acnes*, according to a study published March 28, 2019, in *Lasers in Surgery and Medicine*.1

But there is a dark side to using blue light. Blue light contributes to skin aging similar to UVA, according to authors of a paper published July 2017 in *Free Radical Biology and Medicine*.2

“Just pressure is growing on cosmetic companies to use more environmentally friendly ingredients and packaging, we are seeing a profound increase of organic/natural and eco claims on ‘green’ beauty products.” Leslie Baumann, M.D., Miami, Fla.
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Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, hypopigmentation and allergic contact dermatitis. Some local adverse reactions may be irreversible.

STUDY RESULTS: 38.6% of patients in trial 1 and 38.4% in trial 2 achieved treatment success at week 8 (primary endpoint) vs 18.1% and 12.0% of patients with vehicle, respectively (P=0.001 in both trials).

STUDY DESIGN: The safety and efficacy of BRYHALI Lotion were assessed in 2 prospective, multicenter, randomized, double-blind, phase 3 clinical trials in >300 adult patients with moderate-to-severe plaque psoriasis. Patients were treated with BRYHALI Lotion or vehicle lotion, applied once daily. Primary efficacy endpoint was treatment success evaluated at week 8. Secondary efficacy endpoint was treatment success evaluated at weeks 2, 4, 6, and 12 (4 weeks post treatment). Tertiary efficacy endpoint was a 2-grade improvement from baseline at each time point for the individual signs of psoriasis (erythema, plaque elevation, and scaling).

“Treatment success was defined as at least a 2-grade improvement from baseline in the investigator’s Global Assessment score, and a score of “clear” or “almost clear” (primary endpoint) at week 8.”


Indication

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Warnings and Precautions

- BRYHALI Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during treatment or upon cessation of treatment; periodic evaluation may be required.
- Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hyperglycemia, and glucocorticoid-induced flushing.
- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids.
- Local adverse reactions may include atrophy, striae, telangiectasias, hypopigmentation, and allergic contact dermatitis. Some local adverse reactions may be irreversible.
- Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist.
- Use an appropriate antimicrobial agent if a skin infection is present or occurs, and if prompt response is not seen, discontinue use until infection has been adequately treated.
- Discontinue BRYHALI Lotion if allergic contact dermatitis occurs.

Adverse Reactions

- The most common adverse reactions (≥10%) were upper respiratory tract infection, application site dermatitis, and hyperglycemia.

To report SUSPECTED ADVERSE REACTIONS, contact Customer Service at 1-800-321-4576 or FDA at 1-800-FDA-1088.

Please see Brief Summary of full Prescribing Information on following page.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
This brief summary does not include all the information needed to use BRYHALI safely and effectively. See full prescribing information for BRYHALI.

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Initial U.S. Approval: 1990

INDICATIONS AND USAGE
BRYHALI® (halobetasol propionate) Lotion, 0.01% is indicated for the topical treatment of plaque psoriasis in adults.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression
BRYHALI has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment with the topical corticosteroid. The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with BRYHALI was evaluated in a study of 18 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area (BSA); HPA axis suppression was reported for 1 (5.6%) subject at Week 4 and for 3 (16.7%) subjects at Week 8. All 3 subjects had normal HPA axis suppression test with discontinuation of treatment [see Clinical Pharmacology in full Prescribing Information].

Because of the potential for systemic absorption, use of topical corticosteroids, including BRYHALI, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids due to their larger surface-to-body mass ratios [see Use in Specific Populations].

Local Adverse Reactions
Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and milia. These may be more likely with occlusive use, prolonged use, or use of higher potency corticosteroids, including BRYHALI. Some local adverse reactions may be irreversible.

Concomitant Skin Infections
Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of BRYHALI until the infection has been adequately treated.

Allergic Contact Dermatitis
Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Consider confirmation of a clinical diagnosis of allergic contact dermatitis by appropriate patch testing. Discontinue BRYHALI if allergic contact dermatitis occurs.

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 randomized, double-blind, multicenter, vehicle-controlled clinical trials, 426 adults with plaque psoriasis were treated with BRYHALI and had post-baseline safety data. Subjects applied BRYHALI once daily for up to eight weeks. Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with BRYHALI and more frequently than in vehicle-treated patients.

Table 1: Adverse Reactions Occurring in ≥1% of the Subjects Treated with BRYHALI through Week 8

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BRYHALI (N=284)</th>
<th>Vehicle (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Application Site Dermatitis</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There are no available data on BRYHALI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, increased malformations, including cleft palate and omphalocoele, were observed after oral administration of halobetasol propionate during organogenesis to pregnant rabbits. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of BRYHALI.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data
Animal Data
Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocoele was seen in rats but not in rabbits.

Lactation
Risk Summary
There are no data on the presence of halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with BRYHALI.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BRYHALI and any potential adverse effects on the breastfed child from BRYHALI.

Clinical Considerations
Advise breastfeeding women not to apply BRYHALI directly to the nipple and areola to avoid direct infant exposure.

Pediatric Use
Safety and effectiveness of BRYHALI in pediatric patients under the age of 18 years have not been evaluated.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing’s syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children [see Warnings and Precautions].

HPA axis suppression, Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema [see Warnings and Precautions].

Geriatric Use
Of 284 subjects exposed to BRYHALI in clinical trials, 61 subjects were 65 years or older.

Clinical trials of BRYHALI did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germlinal and somatic cells of rodents; or in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster micronucleus test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day indicated no impairment of fertility or general reproductive performance.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Manufactured for:
Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

By:
Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada
U.S. Patent Numbers: 6,517,847 and 8,809,307
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Based on 9652102 November 2018 BRY.0095.USA.18
BLUE LIGHT CAN CONTRIBUTE TO SKIN AGING
FROM PAGE 40

“I have patients coming in a lot now with a blue light guard on their cell phone to prevent aging. I now avoid using blue light on patients.”

Leslie Baumann, M.D., Miami, Fla.

“The many shades of ‘green’

Green Packaging

Botanicals and sustainability may be top of mind for consumers when it comes to what’s in their skincare products, but there’s a bigger picture that extends to the materials in which the products themselves are packaged. Can they be reused, recycled, composted? These may be relevant questions for skincare professionals to ask when making decisions about developing practice product lines, identifying product marketing differentiators or making product recommendations that will appeal to ‘green’-leaning patients.

THE MEANING OF ‘GREEN’

There is no accepted definition of the term organic for skincare. Many base the definition on the food classification. And long-term studies on the effects of using topical organic products or ingredients are lacking, according to Dr. Baumann.

“As pressure grows on cosmetics companies to use more environmentally friendly ingredients and packaging, we are seeing a profound increase of organic/natural and eco claims on ‘green’ beauty products. Terms such as active naturals, botanical, natural, green and organic are used; however, these terms are meaningless without standard agreed upon definitions,” Dr. Baumann writes in Cosmetics and Cosmeceuticals. “Of these terms, only the term organic has requirements for its use. Unfortunately, there are different standards in the United States and in different countries about what organic and natural mean.”

But so-called “green” skincare is actually more than a marketing push — it’s a real need — and is in demand among consumers, according to Fred Zülli, Ph.D., managing director of Mibelle Biochemistry Switzerland, a unit of the Mibelle Group, which develops and produces active ingredients for the personal care industry.

The trend in green skincare implies a fast-growing demand for more natural, organic and sustainable products, according Dr. Zülli. The challenge, he says, is that there are so many different concepts for green skincare that it is difficult to formulate the right consumer products.

“In this context, consumers are looking for plant-derived actives, as they believe that these are safer and have less side effects. Also, they are looking for more natural components in the products and less or no preservatives, colors or mineral oils,” Dr. Zülli tells Dermatology Times.

Consumers, as a result, want greater transparency of ingredients and claims.

‘Today’s consumer also is concerned about sustainability, according to Dr. Zülli.

“As naturally grown does not always meet sustainability, biotechnology is of great interest to develop and produce natural components in a sustainable way,” he says.

For example, Dr. Zülli and colleagues have developed a process to grow moss plants in photo-bioreactors so the ingredient can be used in cosmetics.

“Moss plants have not been used in cosmetics, as the plant grows very slowly, cannot be cultivated and if collected in the wild are heavily contaminated with pollutants such as heavy metals,” he says.

So, the scientists grow the moss plant as protonema tissue in a water-based media with light. The biotechnological production leads to sustainable and pure moss tissue. From the moss biomass an extract is then produced to be used as a cosmetic ingredient.

“In vitro, the product has shown an activation of cell nuclear pore genes which are down regulated in aged fibroblasts. Cell nucleus health is a new anti-aging topic, as the transport of molecules in and out of the nucleus is extremely important for the response of cells to external stress factors. In U.S. in-vivo studies, we could show that the moss extract could vitalize the skin to reduce the negative effects of heat/cold and dry/moist stress conditions,” he writes.

References


Adding the ready-to-use suspension of silver particles before laser treatment resulted in up to a 32% reduction of light hair compared to baseline.
MINOVATION

MinoLira Tablets bring immediate- and sustained-release minocycline together for the first time ever in functionally scored tablets (105 and 135mg) for broad dosing options and safety similar to placebo.¹

It’s the active ingredient you know – redefined.

INDICATION AND USAGE
MinoLira is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

MinoLira did not demonstrate a significant effect on non-inflammatory acne lesions. Safety of MinoLira has not been established beyond 12 weeks of use. This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, MinoLira should be used only as indicated.

IMPORTANT SAFETY INFORMATION
• This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.
• Minocycline, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman.

To learn more, please visit www.minolira.com

Perhaps the most important finding from the first-ever survey of nonphysician aesthetic provider compensation is that almost no two physician extenders are paid in the same way. Top-line results showed that, on average, full-time nonphysician aesthetic providers earn $158,670 annually. However, looking at numbers alone greatly understates the complexity of non-physician compensation, says Mary Beth Hagen, CEO/founder of Titan Aesthetic Recruiting, which sponsored the survey. “It’s fascinating — you can’t say, ‘this is how an injector gets paid’ because every single respondent gave us a different answer.” With variables including salary, hourly pay, commissions, bonuses and benefits, she says, virtually every respondent’s pay scheme is unique.

Distributed through social media and e-mail, the survey targeted nurse practitioners (NPs), registered nurses (RNs) and physician assistants (PAs) in the United States whose practice consisted of at least 50% aesthetic procedures (mainly neuromodulators and dermal fillers).

Although 187 potential respondents clicked into the survey, she says, only 88 (47%) completed it. “I was surprised at the low completion rate.” Several providers told Ms. Hagen off-line they didn’t know enough about how they got paid to even answer the questions.

RNs (51% of the sample) earned an average of $129,000 annually, versus $189,000 for PAs (30%) and $196,000 for NPs (19%). Years of service at the same practice strongly impacted earnings.

“We found that if you’d only been with your employer for one to two years, average earnings are about $138,000 (n = 13). But that definitely increased when you’d been at the employer for three to five years ($195,939; n = 16).”

Years of injecting experience factored into compensation as well, with average compensation of $96,000 for an injector with only one to two years’ experience (n = 6).

By practice specialty, nonphysicians who worked for plastic or facial plastic surgeons earned the most: $170,000 annually. “What you’re seeing there is that a lot of overhead is paid for by their surgical practice,” she says.

These specialists also tended to employ much more tenured injectors, adds Ms. Hagen. “This situation evolved, she says, largely because when the injectable market began exploding, surgeons typically delegated these duties to nonphysician staff wherever allowed by law. Full-time injectors who worked for dermatologists (who made up only 8% of the sample) or other specialists made approximately $142,000 yearly.

Geographically, the Southeast set the pace, with average annual earnings of $199,000. The fact that one-third of
We saw that 52% [of nonphysician aesthetic providers] expect their compensation to increase this year, by about $33,000.

Mary Beth Hagen, CEO, founder, Titan Aesthetic Recruiting, Minneapolis, Minn.

The remaining 33%, who prioritized base salary, were primarily first-or second-year injectors. Approximately half of respondents worked in physician-owned practices.

“I was surprised, though, that 23% were self-owned,” she says.

The number owned by private equity firms—seven percent—likely will grow in future editions of the survey, Ms. Hagen adds.

When she started the project last summer, she quickly realized no solid data exist to provide a basic framework for a conversation about fair compensation for nonphysician aesthetic providers. By repeating the survey annually, she says, she hopes to start the conversation about what it will cost a business owner to hire an injector, and how the injector should approach loyalty and helping build the practice’s brand.

Having worked in aesthetic medicine for 15 years, Ms. Hagen says she undertook the survey because she grew tired of hearing:

▲ “My doctor is so selfish and greedy. They make so much money and don’t give any back to the staff.”

▲ “My staff is so lazy and entitled. They have no idea how hard I’ve worked to go to school and start this practice—what I go through every day to try to keep them employed.”

The reality, she says, lies somewhere in the middle. And neither side appreciates the total picture. Ms. Hagen frequently counsels nonphysician providers entering the aesthetic space that first-year dermatologists didn’t make the average dermatologist’s annual salary in fellowship.

“They barely made enough to survive,” she says. “So for this first year or two, you’re not going to make what you made as an experienced PA, NP or hospital RN. You’re starting a different career. And you really need to be grateful to the person who is giving you an opportunity to learn how to inject.”

If a nonphysician injector brings in $500,000 in revenue, says Ms. Hagen, about half of that covers cost of goods sold. Additional expenses often covered by the practice include the provider’s malpractice and health insurance, profit-sharing, vacations, scrubs and retirement contributions. Additional overhead borne by the practice includes training, advertising and support staff.

“I tell people, if you’re bringing in a half-million dollars and getting $100,000 to $150,000 take-home, tell your physician, ‘thank you. I’m so grateful for what we have together as a practice. Can we sit down and identify how I can bring in more patients and revenue, and we can both grow together?’”

Ms. Hagen cautions against taking survey findings out of context. As the first survey of its kind, based on an 88-person sample, its findings are not meant to indicate what providers should be earning or employers should be paying, she says.

Disclosures
Ms. Hagen is a shareholder and former employee of Allergan, a former employee of Medicis and a shareholder in Revance.

References

SNA-001 is part of Sienna’s proprietary platform


systemic exposure. We are poised to begin phase 3 enrollment for SNA-120 (pegcantratinib) later this year as a potential first-in-class, non-steroidal kinase inhibitor, for other inflammatory disorders of the skin, as well as the gastrointestinal tract, the eye and the lung. Indeed, with additional funding through a business-development transaction or other means, we would plan to move SNA-125 forward with a phase 2 trial in atopic dermatitis, as well as with a proof-of-concept study in ulcerative colitis, where the need for gut-restricted drugs with low systemic exposure is high.”

References
Dermatology’s role with advanced melanoma patients

ILYA PETROU, M.D. | Staff Correspondent

Continued research has borne an array of different therapeutic drugs for the treatment of unresectable or metastatic melanoma, each agent achieving varying degrees of efficacy. What remains constant, however, is that these new and innovative targeted and immunotherapies have side effects, many of which are cutaneous. A number of these patients will receive lifelong or long-term therapy with these agents, and the new challenge that must be met head-on in this new age of targeted and immunotherapies are the cutaneous side effects that many patients with melanoma experience. Dermatologists must be able to quickly recognize, treat and manage the melanoma drug-specific symptoms seen in this growing patient population.

“Continued research has borne an array of different therapeutic drugs for the treatment of unresectable or metastatic melanoma, each agent achieving varying degrees of efficacy. What remains constant, however, is that these new and innovative targeted and immunotherapies have side effects, many of which are cutaneous. A number of these patients will receive lifelong or long-term therapy with these agents, and the new challenge that must be met head-on in this new age of targeted and immunotherapies are the cutaneous side effects that many patients with melanoma experience. Dermatologists must be able to quickly recognize, treat and manage the melanoma drug-specific symptoms seen in this growing patient population.”

We as dermatologists have a critical role to play in trying to best manage the cutaneous side effects...so that there is no limitation...for [patients] to receive these very effective targeted and immunotherapy drugs.”

Bernice Y. Kwong, M.D., F.A.A.D., Stanford University School of Medicine, Stanford, Calif.
8 out of 10 commercially insured lives in the US have preferred access with no biologic step required for Otezla.¹

Otezla is listed as preferred, with no biologic step requirement, on:

- Aetna Prescription Drug Benefit
- Cigna Prescription Drug List
- CVS Caremark Formularies* 
- Express Scripts National Preferred Formulary¹
- OptumRx ✓
- Prime Therapeutics
- UnitedHealthcare ✓

✓ Indicates no DMARD or biologic step-edit required.

Contact your Otezla representative or visit otezlapro.com for a complete list of plans

*Basic, Standard, and Advanced Control Formularies.
¹SafeGuardRx® Program has 1 biologic step for patients on certain Otezla indications.
DMARD, disease-modifying antirheumatic drug.

Please see accompanying Brief Summary of Full Prescribing Information.

For patients with moderate to severe plaque psoriasis

RESULTS — the way — THEY WANT THEM

Otezla has a proven efficacy and safety profile, oral dosing, and no label-required lab monitoring—making it a treatment experience patients can respond to

Otezla® (apremilast) significantly increased PASI-75 response (n = 562) at week 16 (primary endpoint) vs placebo (n = 282) (33% vs 5%; P < 0.0001) in ESTEEM 1,2

ESTEEM® Study Design
- Evaluated in 2 multicenter, double-blind, placebo-controlled trials of similar design. Patients with moderate to severe plaque psoriasis (N = 1257) were randomized 2:1 to Otezla 30 mg twice daily or placebo for 16 weeks after a 5-day titration
- Selected inclusion criteria: age ≥18 years, BSA ≥10%, sPGA ≥3, PASI ≥12, candidates for phototherapy or systemic therapy

INDICATIONS
Otezla® (apremilast) is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
Otezla is indicated for the treatment of adult patients with active psoriatic arthritis.

IMPORTANT SAFETY INFORMATION
Contraindications
- Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Warnings and Precautions
- Diarrhea, Nausea and Vomiting: Cases of severe diarrhea, nausea, and vomiting have been reported with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
- Depression: Treatment with Otezla is associated with an increase in depression. During clinical trials 1.3% (12/920) of patients reported depression, compared to 0.4% (2/506) on placebo. Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on
START your patients on Otezla today

- Convenient oral dosing¹
- No required lab monitoring¹
- Samples available in office
- Bridge program offers 3 years for free†
- $0 co-pay‡

Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur.

- Weight Decrease: Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla.

- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended.

Adverse Reactions

- Adverse reactions reported in ≥5% of patients were Otezla, placebo): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4).

Use in Specific Populations

- Pregnancy and Nursing Mothers: Otezla is Pregnancy Category C; it has not been studied in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether apremilast or its metabolites are present in human milk. Caution should be exercised when Otezla is administered to a nursing woman.

- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information.

*Following a 5-day titration, the recommended maintenance dosage is 30 mg twice daily.

†Certain restrictions apply; eligibility not based on income, must be 18 years or older. This offer is not valid for persons eligible for reimbursement of this product, in whole or in part under Medicaid, Medicare, or similar state or federal programs. Offer not valid for cash-paying patients. People who are not eligible can call 1-844-4OTEZLA to discuss other financial assistance opportunities.

BSA, body surface area; ESTEEM, Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PASI, Psoriasis Area and Severity Index; SPA, static Physician Global Assessment.


Please turn the page for Brief Summary of Full Prescribing Information.
OTELZA® (apremilast) tablets, for oral use

The following is a Brief Summary; refer to Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
OTELZA® (apremilast) is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

CONTRAINDICATIONS
OTELZA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [see Adverse Reactions (6.1)].

WARNINGS AND PRECAUTIONS
Diarrhea, Nausea, and Vomiting: There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

Depression: Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur. During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of patients treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (1/11308) of patients treated with OTEZLA discontinued treatment due to depression compared to none in placebo-treated patients (0/506). Depression was reported as serious in 0.1% (1/11308) of patients exposed to OTEZLA, compared to none in placebo-treated patients (0/506). Instances of suicidal behavior have been observed in 0.1% (1/11308) of patients while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated patients. In the clinical trials, one patient treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Weight Decrease: During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96784) of patients treated with OTEZLA compared to 5% (195382) treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% (16784) of patients treated with OTEZLA 30 mg twice daily compared to 1% (30382) patients treated with placebo. Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered.

Drug Interactions: Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

ADVERSE REACTIONS
Clinical Trials Experience in Psoriasis: 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. Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of patients with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for patients treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated patients.

Table 3: Adverse Reactions Reported in ≥2% of Patients on OTEZLA and With Greater Frequency Than in Patients on Placebo; up to Day 112 (Week 16)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (N=506) n (%)</th>
<th>OTEZLA 30 mg BID (N=920) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>32 (6)</td>
<td>160 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>35 (7)</td>
<td>155 (17)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>31 (6)</td>
<td>84 (9)</td>
</tr>
<tr>
<td>Tension headache</td>
<td>21 (4)</td>
<td>75 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (4)</td>
<td>55 (6)</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>11 (2)</td>
<td>39 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (2)</td>
<td>35 (4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (2)</td>
<td>29 (3)</td>
</tr>
<tr>
<td>Decrease appetite</td>
<td>5 (1)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (1)</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (1)</td>
<td>20 (2)</td>
</tr>
<tr>
<td>Migraine</td>
<td>5 (1)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>1 (0)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Depression</td>
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<td>Sinus headache</td>
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*Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.

Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) patients following discontinuation of treatment with OTEZLA (apremilast).

DRUG INTERACTIONS
Strong CYP 450 Inducers: Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

USE IN SPECIFIC POPULATIONS
Pregnancy: Pregnancy Category C: OTEZLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972. Nursing Mothers: It is not known whether OTEZLA or its metabolites are present in human milk. Because many drugs are present in human milk, caution should be exercised when OTEZLA is administered to a nursing woman.

OVERDOSAGE
In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

Manufactured for: Celgene Corporation, Summit, NJ 07901

OTELZA® is a registered trademark of Celgene Corporation.

Pat. http://www.celgene.com/therapies

Superficial radiation therapy (SRT) has again piqued the interest of dermatologists seeking the ideal treatment option for patients with challenging nonmelanoma skin cancer (NMSC). It is among one of the oldest modalities of treatment, but has been eclipsed over the years by innovative surgical approaches and newer therapeutic approaches. However, technology updates and excellent clearance outcomes rivaling those of Mohs surgery have once again popularized this treatment modality.

The incidence of NMSC, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is on a steady rise with two million to three million new cases diagnosed worldwide every year. NMSC can be challenging to treat, and the optimal choice of therapy rests on several factors, including tumor type and location, as well as the patient’s age and comorbidities.

Several treatment modalities are currently being used, including surgery, cryotherapy, curettage and electrodessication, photodynamic therapy, brachytherapy, chemotherapeutic agents and radiation therapy including SRT.1

“I am a Mohs surgeon for over 30 years and I really believe in the efficacy of Mohs, but I have recognized over the years that there are those individuals who are not really ideal candidates for Mohs surgery, or any surgery,” says David J. Goldberg, M.D., J.D., director of Skin Laser & Surgery Specialists of New York and New Jersey and clinical professor of dermatology at Mount Sinai School of Medicine in New York. “Superficial radiation therapy can, many times, be the treatment of choice for this patient subset.”

Nonmelanoma skin cancer patients who require an alternative to surgery typically fall into one of the following categories:

- Elderly
- Can’t follow appropriate post-surgery wound care instructions
- Have phobia of surgery
- Contraindicated for surgery due to a list of comorbidities
- Have very large extensive lesions considered inoperable

WHAT’S NEW?
Over the course of the last five years, SRT has been made popular again through key changes and innovations resulting in very stable, smaller and more portable devices, which allow them to be used in an out-patient environment.

“The cure rate for SRT is proven to be higher than those seen with other treatment techniques used for NMSC, such as electrodessication and curettage, standard surgery and other hospital-based forms of radiation therapy,” he says. “The cure rate of SRT when used for primary, uncomplicated NMSC is only 1% less than that achieved with Mohs surgery. As such, SRT could fill the therapeutic void for those select NMSC patients who are contraindicated for surgery and more amenable for this effective and forgiving treatment approach.”

USE SCENARIO
Superficial radiation therapy can be of particular advantage in cosmetically sensitive areas, such as the eyelid or tip of the nose, as there is little to no resultant scarring following treatments, unlike the consequences of traditional surgical approaches.

However, clinicians should not use SRT in poorly defined lesions, such as morpheaform type BCC or in any recurrent NMSC cases, Dr. Goldberg says. Rather, these lesions should be addressed with Mohs surgery.

“Superficial radiation therapy is just starting to really take off as a good treatment choice for a select subset of NMSC patients and should be considered as a good treatment option for challenging cases,” he says.

Disclosures
Dr. Goldberg reports the following disclosures: Allergan, Inc. – I(Grants/Research Funding); Almirall – C(S); Aquagen Pharmaceuticals – I(Grants/Research Funding); C²ure Inc. – I(Grants/Research Funding); Foamix – I(Grants/Research Funding); Galderma Laboratories, LP – I(Grants/Research Funding); Novan – I(Grants/Research Funding); Sebcaia, Inc. – I(Grants/Research Funding); Sensus Healthcare – I(Grants/Research Funding); Syn-eron, Inc. – I(Grants/Research Funding); SP(H)

References

Quick TAKES
Nonmelanoma skin cancer can be challenging to treat.

New technology and updated guidelines have brought SRT back into the treatment armamentarium.

Patients with NMSC treated with SRT are seeing excellent outcomes.

SRT could fill the therapeutic void for those select NMSC patients who are contraindicated for surgery and more amenable for this effective and forgiving treatment approach.”

David J. Goldberg, M.D., J.D., Mount Sinai School of Medicine, New York
SLNB may improve DFS

BRYANT FURLOW | Cancer Network

Thirteen percent of patients with high-risk primary melanoma will experience disease recurrence within two years, and routine sentinel lymph node biopsy (SLNB) should be considered in these patients to improve prognostic accuracy, according to authors of a prospective study of 700 Australian patients published in JAMA Dermatology.

Primary tumor occurring in the patient’s head or neck, melanoma-positive SLNB, worse T stage and rapid tumor growth (mitotic rate greater than 3/mm²) were each associated with elevated recurrence risk, the authors found.

“In this cohort of patients with high-risk primary melanoma treated by wide local excision with or without SLNB, two-year disease-free survival [DFS] was 95% for T1b tumors and 67% for T4b tumors,” reports lead study author Lena A. von Schuckmann, M.B.B.S., M.P.H., of the QIMR Berghofer medical Research Institute in Herston, Australia, and colleagues.

“Patients who did not undergo an SLNB had a significantly lower two-year DFS compared with patients with a melanoma of the same tumor category and a negative SLNB result, suggesting that SLNB should be considered routinely for use in high-risk patients,” they write.

Ulceration was associated with decreased survival regardless of tumor thickness, they found. Both ulceration and “many mitoses” are histopathologic features prognostic of recurrence, they report. The recent removal of mitosis from American Joint Committee on Cancer melanoma staging classification criteria “may have a detrimental effect on assessing some patients’ prognosis,” they note.

“It is likely that future melanoma staging will integrate clinical, morphologic, and other correlates of tumor biologic factors to help streamline treatment and more accurately advise on likely prognosis.”

Most (70.2%) of those patients who suffered recurrence within two years had locoregional recurrence and 29.8% had distant metastasis. More than half (57.8%) of patients with locoregional recurrence remained disease free two years after surgery, but 31% experienced distant metastasis.

The authors cautioned that they did not have information on the method of recurrence detection and that the study’s two-year recurrence follow-up time was relatively short.

“As expected, more advanced tumors generally recur more frequently and earlier,” comments surgical oncologist Daniel G. Coit, M.D., of Memorial Sloan Kettering Cancer Center in New York. “The biggest challenge in interpreting the significance of this study is the heterogeneity of the patient data set, a data set that included 442 patients with clinical T1b to T4b who did not undergo sentinel lymph node biopsy; 213 patients with pathologic T1b to T4b who had a negative SLNB result; and 38 patients with at least stage IIIa after a positive SLNB result.”

Sapna Patel, M.D., associate professor at The University of Texas MD Anderson Cancer Center, Houston, notes that “we have long known there are certain sites of the body that lend themselves to higher rates of melanoma recurrence or metastasis. These include the head and neck region and melanoma that originates from mucosal surfaces.”

“Some reasons that may explain this higher risk of recurrence specific to the head and neck region include a more complicated lymph node drainage in this area, making sentinel node identification difficult, and inconsistent surgical management of head and neck melanomas between surgical specialties and among different practice types,” Dr. Patel says. ▶

Advanced melanoma management requires dermatology expertise FROM PAGE 48

Dr. Kwong says.

Recognizing the growing need for a standardized optimal care framework for the side effects of melanoma immunotherapy treatment, as with the guidelines put forth on how to optimally treat melanoma, Dr. Kwong says that the National Comprehensive Cancer Network (NCCN) has now also put forth helpful guidelines on how clinicians can best manage immunotherapy toxicities, including skin toxicities.

Dr. Kwong also notes that when patients develop advanced or metastatic melanoma and chemotherapy comes in to play, there is still a very important role for dermatologists to have in the care of these patients. Dermatologists are equipped through their training and diagnostic expertise with the knowhow and formidable treatment modalities to help successfully address and manage the skin issues immunotherapy melanoma patients encounter.

“The cutaneous eruptions that we are seeing often rely so much on us as dermatologists to use our expertise in skin morphology and skin disease to understand what is happening there on a clinical, morphologic and histological level. This expertise allows us to bring great management strategies to our patients. If we better understand what is happening in the skin and what is happening histologically, we can oftentimes find better, more optimal, specific and effective treatment and management strategies for our patients,” Dr. Kwong concludes. ▶

Disclosures
Dr. Kwong reports the following disclosures: Genentech, Inc. – C(Fees).
PODCAST SERIES

Shining New Light on the Treatment of Rosacea with the New Vbeam Prima Laser

Sunscreen, UV-blocking car windows, less coffee, lower stress — commonsense precautions can reduce the risk of regular breakouts, but rosacea still brings patients into the exam room. How do you best address the spider veins and redness?

In this podcast, featured physician Eric Bernstein, MD, MSE, details his success with the new Vbeam Prima. Learn about the Prima’s larger spot size, 50% increased energy, ergonomic improvements that include once-daily auto-calibration, and versatility in treating a broad range of dermatologic conditions.

Listen Now:
dermatologytimes.com/vbeam

Featured physician:
Eric Bernstein, MD, MSE
### BASAL CELL CARCINOMA

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SUBA (super bioavailability) technology is designed to improve the bioavailability of orally administered drugs that are poorly soluble, such as itraconazole. SUBA-itraconazole is a patented oral formulation developed by Mayne Pharma, which is characterized by improved absorption and reduced variability compared with generic itraconazole and a more predictable clinical response.

**SUBA-ITRACONAZOLE BY HEDGEPATH PHARMACEUTICALS AND MAYNE PHARMA**

SUBA (super bioavailability) technology is designed to improve the bioavailability of orally administered drugs that are poorly soluble, such as itraconazole. SUBA-itraconazole is a patented oral formulation developed by Mayne Pharma, which is characterized by improved absorption and reduced variability compared with generic itraconazole and a more predictable clinical response.

Itraconazole is a Hedgehog (Hh) pathway inhibitor that is distinct from its anti-fungal action. A Phase 2b, multi-center, open-label study of oral SUBA-itraconazole (SUBA-Cap) in subjects with Basal Cell Carcinoma Nevus Syndrome (BCCNS) and non-metastatic BCC was initiated. The study will include 38 patients treated with 300 mg daily until disease progression.

Interim results of 13 patients and 167 analyzed lesions demonstrated that 25% of the lesions disappeared, 25% were reduced by more than 30%, 42% were stable, and 8% increased by more than 20%. No grade 2 or higher toxicities were reported for 90% of enrolled patients. SUBA-Cap appears to be a potential alternative to the repeated surgeries and associated scarring that characterizes BCCNS.

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**MELANOMA PIPELINE REPORT**

In 2018, an estimated 94,480 patients in the United States were diagnosed with melanoma, and about 7,230 patients died from this disease. Drug development in melanoma has focused on cytokine melanoma therapeutics and later stages of disease when surgery is not an option.

Melanoma has historically been a disease that is difficult to treat with pharmacotherapy and drug development has been limited progress. In recent years, developments in molecular biology, have led to an increased understanding of the molecular heterogeneity of melanoma that has resulted in introducing new insights into the role of oncoproteins, immune checkpoints, and signaling pathways which has accelerated the discovery rate of therapeutic targets and their associated novel drugs. Breakthrough drug approvals in recent years, checkpoint inhibitors and MEK/ERK/RAF combination therapies have prolonged survival and changed the treatment landscape.

Even with the impact of these breakthrough therapies, unmet needs still remain for safer and more effective therapeutics. The greatest promise in addressing these needs may come in the form of combining novel therapeutics with currently marketed therapies, in order to provide effective treatment and improve patient survival. Innovative melanoma therapeutics are on the horizon.

**APX005M BY APEXIGEN**

APX005M is a humanized monoclonal antibody and a potent CD40 agonist designed to reverse the systemic immune suppression. CD40 is a co-stimulatory receptor that is essential for activating both innate and adaptive immune systems. APX005M is administered by intratumoral injection and has the potential to be used as a single agent and in combination with other immune-oncology agents, targeted therapies and vaccines. A phase 1/2 dose escalation and cohort expansion, safety and tolerability study of intratumoral APX005M in combination with systemic pembrolizumab in 41 patients with metastatic melanoma is scheduled to be completed in June of 2020.
DAROMUN BY PHILOGEN
Daromun is a combination of Darleukin, a human vascular targeting monoclonal antibody (L19) fused to interleukin-2 (IL-2), and Fibromun, the L19 antibody linked to tumor necrosis factor (TNF). Daromun is being developed as a neoadjuvant intralausal treatment for stage IIIB and C melanoma.

Philogen received an Orphan Drug designation from the FDA in 2017. Daromun would be the first neoadjuvant therapy aimed at blocking or delaying progression to stage IV melanoma. In a phase 2 study of intralausal treatment with Daromun in stage III/I/VA melanoma patients (EudraCT No. 2012-001991-13) efficacy was demonstrated in terms of complete and partial response of the injected metastases, as well as a systemic immune response in non-injected lesions that resulted in shrinking the lesions in or some cases disappearing. In addition, a decelerated progression to stage IV melanoma of treated patients with respect to historical controls was recorded.

ANTI-PD1 therapy, 53 patients were treated. The results demonstrated 10 confirmed responses (19% ORR) with 1 CR and 9 PRs.

The responses were durable with a median duration of 13 months. An additional nine patients had stable disease for greater than six months. ENT plus Pembrolizumab is a promising combination therapy for patients with progressing melanoma on prior PD-1 blockade and both PD-1 and CTLA-4 blockade, a group with limited treatment options.

GSK3377794 (GSK794) BY GLAXOSMITHKLINE AND ADAPTTIMMUNE
GSK794 is an engineered T-cell therapy, for which a patient’s own cells have been genetically modified to express a T-cell receptor (TCR) recognizing with high affinity the tumor-specific antigen, NY-ESO. When the modified cells are re-infused into the patient, they recognize and kill tumor cells that express the NY-ESO antigen.

NY-ESO is expressed at various levels across different tumors and appears to be expressed at high levels in defined sub-types of melanoma. GSK794 is currently being studied in seven phase I/II studies assessing its effectiveness as a treatment for non-small cell lung cancer, metastatic melanoma, ovarian cancer, multiple myeloma, synovial sarcoma, and myoid round cell liposarcoma. It has been granted PRIME designation by the European Medicines Agency and Breakthrough Therapy designation by the U.S. Food and Drug Administration, underlining the significant potential benefits it can provide.

HF10 (canerpaturev) BY TAKARA BIO
Oncolytic virus/antitumor immunity (injected into tumor) Melanoma

Phase 2

MORAB-004 (ontuxizumab) BY EISAI, MORPHOTEC
MoAb against endodisidin / TEMI Angiogenesis inhibitor Melanoma

Phase 2

TILPDLC Vaccine/Elios Therapeutics
TLR4 Agonist Intratumoral Melanoma combo with ipilimumab

Phase 3

ONTUXIZUMAB
Phase 3

TILSOTOLIMOD
Phase 2

RETROP-V (birinostat) by Array Biopharma
MEK Inhibitor Unresectable or Metastatic Melanoma FDA Approved 9/2018 in combination with Braftovi

Phase 2

Array Biopharma BRAF Inhibitor Unresectable or Metastatic Melanoma BRAF-V600 mutation positive FDA Approved 9/2018 in combination with Mektovi

Phase 2
as anti-PD-1 and CTLA-4 inhibitors. An analysis of 21 patients from the ILLUMINATE-204 study was presented at the ESMO Conference in 2018. Patients were treated with binimetinib plus ipilimumab. The overall response rate was 38% which included two complete responses and six partial responses. An additional seven patients had stable disease and six had progressive disease.

Tilositolom plus ipilimumab revives the immune response in anti-PD-1 resistant tumors. Efficacy was observed in injected and un.injected distant lesions, demonstrating an abscopal effect. The combination had durable responses. The combination was well tolerated with only six subjects experiencing immune-related toxicities. There is an ongoing randomized phase 3 study comparing tilositolom plus ipilimumab to ipilimumab alone in the anti-PD-1 refractory melanoma population.

**TLPLDC VACCINE BY ELIOS THERAPEUTICS**

Tumor lysate particle loaded dendritic cells (TLPLDC) is an autologous therapeutic cancer vaccine that is made from the patient’s own cells and is designed to stimulate the immune system to recognize tumor cells and fight the patient’s specific cancer. The vaccine is made from the patient’s own tumor tissue (1mg collected during surgery) and 120 ml of the patient’s blood. It takes only 48 hours to produce the vaccine. Patients receive the initial vaccine and then three monthly follow-up vaccine inoculations.

The TLPLDC vaccine is scalable. Based on data from a Phase 1/2 trial, the vaccine is safe, with primarily grade 0–2 toxicities, and nearly 40% clinical benefit rate in varied tumors, thus warranting further study. An interim analysis of a prospective, randomized, double-blind, placebo-controlled, phase 2b trial of TLPLDC vaccine to prevent recurrence in resected stage III or IV melanoma patients was presented at the 2018 ASCO Annual Meeting. In the study, 120 participants were randomized 2:1 to receive either TLPLDC or placebo to prevent recurrence.

The analysis showed a meaningful 32% reduction in the relative risk of recurrence with a median follow-up of 12.6 months. Overall TLPLDC was safe and well-tolerated; only 33% of participants experienced an adverse event and 98% were grade 1 and 2 events. These data provide a strong rationale for developing a phase 3 study.

**TELOMELYSIN (OBP-301) BY ONCOLYS BIOPHARMA**

Telomelysin is a gene-modified oncolytic adenovirus which selectively replicates in cancer cells by introducing a human telomerase reverse transcriptase (hTERT) promoter. Oncolytic adenovirus has much potential for cancer immunotherapy because its viral replication is highly immunogenic, and oncolysis induced by such virus releases tumor antigen and provides co-stimulatory danger signals. OBP-301 has demonstrated regression in the injected and noninjected melanoma lesions (abscopal effect). An open-label, multi-center phase 2a study to evaluate efficacy and immunological response of intratumoral/intralesional oncolytic virus (OBP-301) in un resectable/unresected metastatic melanoma is active and seeking to enroll 50 patients.

**TAVO (TAVOKINOGENE TELSEPLASMD) INTRATUMORAL P1L-12 PLUS ELECTROPORATION BY ONCOCOSE IMMUNOTHERAPIES**

Oncosec’s immunotherapy platform, Intratumoral IL-12, focuses on the delivery of DNA-based interleukin-12 (IL-12), a naturally occurring protein with immune-stimulating functions. The treatment is designed to produce a localized, controlled expression of IL-12 in the tumor microenvironment, which, in turn, enables the immune system to target and attack tumors throughout the body.

The ImmunoPulse device is used to supply a sequence of short-duration electrical pulses (electroporation) to the tumor which increases the permeability of the cell membrane and facilitates the uptake of the IL-12. A multicenter phase 2, open-label trial of intratumoral P1L-12 plus electroporation in combination with intravenous pembrolizumab in patients with stage III/IV melanoma who are progressing on either pembrolizumab or nivolumab treatment is currently open and accruing patients. The primary outcome measure is overall response rate with secondary outcomes of progression-free survival, overall survival, and duration of response.

**BRAFTOVI (ENCORENAB) + MEKTOVI (BINIMETINIB) COMBINATION BY ARRAY BIOPHARMA**

Brafitvo (encorenab) is indicated in combination with Mektopi (binimetinib) for the treatment of patients with unresectable or metastatic mela noma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. Encorenab and binimetinib target two different kinases in the RAS-RAF/MEK/ERK pathway. The co-administration of these drugs resulted in a synergistic anti-proliferative activity in vitro in BRAF mutation-positive cell lines and human xenograft studies.

In a two-part, randomized, open label, multi-center, parallel group, phase 3 study comparing the efficacy and safety of LGX818 (encorenab) plus MEK 162 (binimetinib) to vemurafenib and LGX818 monotherapy in patients with locally advanced unresectable or metastatic melanoma with BRAF V600 mutations, a total of 577 patients were randomized: 192 to the encorenab+binimetinib arm, 194 to the encorenab arm, and 191 to the vemurafenib arm. Encorenab + binimetinib demonstrated a statistically significant improvement in PFS compared to vemurafenib (median PFS 10 months vs 2 months p<0.0001). The overall response rate was 63% vs 40% and the duration of response 16.6 months vs 12.3 months.

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**PipeLine insights into drugs in development for BCC, melanoma**
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Physicians can influence pay and regulatory changes

Lisa Hilton  | Staff Correspondent

Overall, dermatology’s future looks bright thanks to an aging population, according to Cincinnati-based dermatologist Brett M. Coldiron, M.D. Some 10,000 baby boomers in the United States are turning 65 years old daily, according to the Pew Research Center. “That’s a huge demographic wave. And they all go on Medicare,” says Dr. Coldiron, president of the Ohio Dermatological Foundation and clinical associate professor at the University of Cincinnati. “If they live long enough, most will have skin cancer. Even if they don’t, a lot of the dermatologic diseases become more prevalent as one gets older.”

Along with high demand comes the good news of a growing supply of new and effective treatments for dermatology patients suffering from psoriasis, atopic dermatitis and more. “We’ve come a long way beyond topical steroids with a whole host of new medications that make treating patients very rewarding,” Dr. Coldiron says.

The dermatologist workforce isn’t forecast to increase much to meet potentially increasing demand, according to Dr. Coldiron. But big increases are expected in the numbers of physician assistants (PAs) and nurse practitioners (NPs) entering dermatology, he says.

However, there are looming changes on the horizon and all dermatologists should understand how these changes could impact their practices. Knowledge is power, and dermatologists could still influence outcomes of many of the changes by getting involved, according to dermatologists who offered predictions and perspectives during the “Future of Dermatology” panel at the 2019 American Academy of Dermatology annual meeting.

It’s important for dermatologists to have realistic expectations about what they’ll make as income in the specialty, Dr. Coldiron says. “I think the first thing to recognize is you’re never going to get paid better than you’re paid today,” he says.

The opportunities for higher pay will pan out with some of the alternative or bundled payment models, and dermatology doesn’t traditionally fit too well in those, Dr. Coldiron explains. The one disease state that is evolving into an alternative payment model is actinic keratosis, according to Dr. Coldiron.

Dermatologists have to monitor one change that could hit the specialty hard, financially, he says. It has to do with changes to the 10-day global period, in which follow-up visits for benign destructions, benign and malignant excisions and other commonly performed dermatologic procedures are included in the billing code.

The problem is Medicare might eliminate pay for the follow up, Dr. Coldiron says. “There’s a follow-up visit embedded in every actinic keratosis you freeze. The follow-up visit is worth about $40 and freezing the actinic keratosis is only worth about $39, so if you take the follow-up visit out, you’re only going to get paid $30 to treat that AK,” he says. “That’s unless, of course, you see the patient back. The problem is then the patient has to pay another copay, another deductible and you have to run them through the machine again. That’s a lot more trouble than if it was just built into that 10-day global.”

Dr. Coldiron says he thinks the change will happen in the next year or two, unless there’s a legislative fix. “It would be devastating to dermatology. You’re talking a billion dollars a year going to dermatology that we’re going to lose. That’s in Medicare alone,” he says.

One solution, he says, is to donate to and get involved in the AAD’s SkinPAC (political action committee). Dr. Coldiron, who chairs the committee, says SkinPAC has established access to politicians, has successfully lobbied for the specialty in the past and is working on this and other issues.
T he future of dermatology and medicine will be data driven, according to Marta VanBeek, M.D., M.P.H., clinical professor of dermatology at University of Iowa Hospitals and Clinics, Iowa City.

“So the American Academy of Dermatology has made the commitment to make a large investment in establishing a specialty-specific comprehensive registry called DataDerm,” Dr. VanBeek says.

For dermatologists who choose to participate in the specialty’s data gathering initiative, DataDerm can extract data from most practice electronic medical records (EMRs), according to Dr. VanBeek, who spoke on the topic at AAD.

“We want people to be able to contribute to the data that defines the specialty, without having to add extra burden or work in the process,” she says.

DataDerm is also a reporting registry. So, if a dermatologist or practice wants to report its Merit-based Incentive Payment System (MIPS) reporting measures to Medicare, they can do that through DataDerm.

“If we can demonstrate that dermatologists treat diseases more quickly and more efficiently than other providers, it certainly substantiates advocating for access to dermatologists without a referral or a higher copay,” Dr. VanBeek says.

“Also demonstrating to both public and private payers that if you treat someone efficiently, whether it’s a skin cancer or an inflammatory disease, if you get the right diagnosis and get it treated expeditiously, it actually costs the system less money than if you were to drag out the treatment regimen with ineffective treatments or even have the wrong diagnosis.”

Dr. VanBeek

Legislative changes to compounding

What dermatologists do in the office to mix ingredients is not the same as the compounding that pharmacists do, according to Plano, Texas, dermatologist Seemal R. Desai, M.D., who presented on the topic of compounding at AAD and serves on AAD’s Board of Directors.

Yet, dermatologists are being lumped regulation-wise in with pharmacists in the eyes of the United States Pharmacopeia (USP), he says.

Specialty organizations including the AAD and American Society for Dermatologic Surgery (ASDS) are working to spare dermatologists from having to abide by the same regulatory burdens of pharmacists.

“For example, we’re doing a lot of advocacy on buffered lidocaine because buffered lidocaine is what we do in the office daily to mix lidocaine with sodium bicarbonate to make injecting more tolerable for patients,” Dr. Desai says. “Some of us do this 30, 40, 50 times a day.”

Potential USP regulation changes include that dermatologists would have to prepare the syringes for patients and administer them as soon as one hour after preparation.

“In a busy clinic, where we have patients who need to have multiple procedures done in a day, you may have your staff prepare your syringes in advance to get ready for the day,” he says. “With the change, you wouldn’t able to do that because once you prepare the syringe it would need to be utilized within an hour. If you are seeing 40 or 50 patients a day and are doing 20 surgeries a day, you can just imagine the issues with that. It’s quite scary to be honest.”

Dermatologists, he says, are being caught off guard as the change impacts their daily routines.

Dermatology associations are advocating for 12 hours, which would allow dermatology practices the time to prepare needed buffered lidocaine syringes for the day without violating USP’s rule.

“That way you’re not necessarily subject to the same regulations as you would be if you went beyond that time limit, which includes having to have specific gowns and gowns, installing an International Organization for Standardization (ISO) 5 hood in your clinic,” Dr. Desai says.

The same regulation change would impact things like triamcinolone (Kenalog) injections that dermatologists administer to patients.

“It also could affect things like reconstituting and diluting botulinum toxin,” Dr. Desai says.

“This whole concept of compounding being under scrutiny is because USP and FDA are worried about the meningitis outbreak that happened in 2012 at the New England Compounding Center and hasn’t happened since.”

Interestingly, Dr. Desai says there’s no truly standardized science behind any of the numbers being negotiated—whether it’s one hour or 12 or 24.

Dermatologists should stay tuned and act on calls from AAD or ASDS associations when dermatologists are needed for advocacy efforts, such as writing to USP or FDA, according to Dr. Desai.
M aybe you remember a day when being popular was important. While the same kind of popularity ranking doesn’t apply to your dermatology practice, what your peers in medicine think of you is important and can positively or negatively impact your bottom line.

To help you assess where you are — or aren’t — with referrals, Glenn Morley, senior consultant in plastic surgery and dermatology at BSM Consulting, shares best practices.

1. HAVE A PLAN
   “Hoping today’s referrals will be tomorrow’s is not enough,” says Morley, who stresses the importance of a referral management plan that prioritizes patient and referrer retention as a key strategy. “There’s no time like the present to address this important business management component — especially if yours, like many practices, depends upon referrals for a significant portion of your revenue.”

   To help you assess where you are — or aren’t — with referrals, Glenn Morley, senior consultant in plastic surgery and dermatology at BSM Consulting, shares best practices.

2. APPRECIATE TECHNOLOGY
   “Twenty years ago, before widespread use of computers and technology, doctors rarely had formalized referral management plans,” she says. “Referrals were straightforward. You knew the doctor, you were convenient to their office and you were convenient to patients. Then a sea change occurred with the advent of technology for everyman, coupled with major changes in the healthcare environment.”

   The impact has been both good and not so good, Morley says.

   “Practice consolidations have put pressure on some long-time referring physicians to change referring habits,” she adds. “Demands on staff and higher staff turnover have sometimes created fractures in communications from referring practice to dermatology practice. It’s all caused referring physicians and physician groups to rethink their referral choices.”

   Then there’s the impact of negotiating third-party contracts, says Morley.

   “Larger dermatology practices and healthcare systems realize stronger negotiating power when contracting with payers, and these relationships also play a part in determining where patients are referred,” she says.

3. KNOW THAT PATIENTS TALK
   “Today’s patient is not yesterday’s patient,” Morley says. “Because access to immediate messaging is literally at patients’ fingertips, it doesn’t take long for word of ‘mouse’ to get around.”

   Practices have changed. Physicians and staff feel pressure to see more patients in a short amount of time. As a result, patients can sometimes get caught in the middle and have a less-than-optimal experience, she says.

   “Feelings of dissatisfaction can be amplified for patients who made an appointment with a dermatologist who was highly recommended by their own doctor,” she adds. “For those patients, long wait times or overtaxed staff with abbreviated communication styles can feel like personal affronts, and their negative feedback can trickle back to the referring physician.”

   Keep tabs on patient satisfaction and get ahead of any issues in real time. Instill confidence in the referring physician that they made the right choice in sharing your name, Morley says.

4. ESTABLISH A FEEDBACK LOOP
   “Research and self-examination are the cornerstones of improvement,” says Morley. “Feedback from patients or refer-

   “Because access to immediate messaging is literally at patients’ fingertips, it doesn’t take long for word of ‘mouse’ to get around.”

   Glenn Morley, BSM Consulting, Boston

   The importance of referrals: How are yours?

   STEPHANIE STEPHENS | Staff Correspondent

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   Peer perspective of your practice is important to your practice health.
   Patient satisfaction can affect referral relationships.
   Investing in marketing materials can help to highlight and differentiate your practice.
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5 keys to collecting patient responsibility upfront

DEBRA SHUTE | Physicians Practice

Even though high-deductible health plans (HDHPs) are now ubiquitous, many physician practices still struggle to collect patient balances. In fact, 83% of physician practices with fewer than five practitioners cited slow payment of HDHP patients as their top collection challenge, according to the Black Book 2017 Revenue Cycle Management Survey. Their second biggest challenge, according to 81% of respondents: communicating patient payment accountability.

That’s a problem, considering that patient financial responsibility now accounts for one-third of healthcare organizations’ revenue, according to various estimates. Therefore, patient collections should be an area targeted for continuous improvement.

Key areas of focus include financial policies and procedures, employee training and patient engagement and communication, says Reed Tinsley, CPA, a consultant specializing in healthcare accounting. “Nine out of 10 patients couldn’t tell you what their copay or deductible is,” he says. “It’s incumbent upon the practice to educate the patient.”

Here are five expert-recommended steps that can help practices rise to the challenge.

**Draft financial policies**

A clear and reasonable financial policy is the first step in setting expectations with patients about their payment responsibilities. At Coastal Medical of Rhode Island, for example, new patients receive a copy of the practice’s financial policy as part of a welcome packet, says Marilyn Boichat, the group’s director of practice management. “When the patient checks into the office for the first time, we have them sign that they read and understand it,” she says. Patients who indicate they need further clarification are invited to come into the office and discuss the policy with the practice manager privately, she adds.

In general, the policy explains what patients are expected to bring to every visit, such as their insurance card and identification; that it’s their responsibility to contact their health plan about specific coverage questions; and that payment is due at the time of service unless alternate arrangements, such as a payment plan, have been made.

Coastal also offers a prompt payment discount for patients who choose not to use health insurance, she says. The discounted fee cannot go below the Medicare allowable and is due at the time of service. “For patients who have a hardship [out of their control], such as losing their job and their health insurance, we will discount the visit [further], and the patient is offered a payment plan to pay when they can afford to,” Boichat says.

In addition to having patients sign off on financial policies and posting them on the practice website, practices should consider placing hard copies of the policy in their reception area, says Ken Hertz, FACMPE, a principal consultant with the Medical Group Management Association (MGMA). “Particularly at the beginning of the year, when deductibles reset, it’s a good idea to make this information available for patients to review while they’re waiting to see the doctor,” he says.

**Offer ongoing staff training**

Inevitably, practice employees will encounter patients who are unclear about various insurance terminology, such as the distinctions among deductibles, coinsurance and copayments, and how that translates to their out-of-pocket expense.

“If you want to collect the money that’s owed to you, you have to be willing to invest some time in making sure staff are trained to help, as a way of showing patients you care about them,” Hertz says.

It may not be feasible for employees to keep track of the nuances of all the various health plans patients carry, but they can and should advise patients on what questions to ask when they call insurers themselves.

“In other words, employees aren’t going to interpret patients’ policies, but they can explain terminology and provide guidance for reaching out to the payer,” he says. For example, employees could instruct patients to ask what their deductible is, how much of it they’ve paid for the current year, and to what services it applies.

At the very least, billers should be well-versed in understanding the ins and outs of insurance policies in general and common issues that can arise with payers, so that they can serve as a source of expertise for staff at the front desk, Hertz says. Ideally, front desk staff are trained to field these frequent questions or common scenarios.

For example, most health plans will cover one physical per calendar year. “If patients want to have it early, perhaps
If you want to collect the money that is owed to you, you have to be...sure staff are trained to help...[to show] patients you care about them.”

Ken Hertz, Medical Group Management Association

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due to travel or another reason, our staff know to have them call their insurance company and ask whether the visit will be covered,” Boichat says. “What we don’t want to do is book it [prematurely] and have the patient get a bill.”

For staff to attain this competency, solid training is essential, experts agree. “It drives me crazy when practices hire new people and throw them into the fire without anyone sitting with them for the first few days,” Tinsley says.

Hertz adds, “You can’t assume anything. You have to train, train, train. Remember, it’s about building good relationships with our patients. The result is that they’re going to feel much more positive toward us, and it’s going to improve our cash flow.”

**CONSIDER KEEPING CREDIT CARDS ON FILE**

As HDHPs and other forms of consumer directed healthcare have grown in prevalence, so too have programs in which practices keep patients’ credit card information on file in a secure payment gateway that is PCI-DSS certified. This allows practices to charge and be paid for patient balances as they are incurred.

In 2009, when HDHPs were ramping up and the economy was sliding into a recession, Brandon Betancourt, MBA, implemented a credit card on file (CCOF) program at the pediatric practice where he was administrator — and has recommended it strongly ever since.

“The credit card policy states that all private paying patients must leave a credit card on file if they wish to be patients of our practice,” he wrote in a commentary for *FierceHealthcare*. “The practice would continue to send out claims to patients’ insurance company and bill patients for their portion of the balance, per the insurance carrier’s explanation of benefits. However, if we are unable to collect in full for our services after several attempts to collect, we reserve the right to process [payment on] the patient’s credit card.”

As an independent consultant, Betancourt now helps practices implement CCOF policies. Whenever transitioning to any new policy, practices should be prepared with an explanation, he says. “You have to anticipate that some changes might be a bit contentious, and train staff accordingly to make sure they can handle the issue.”

Beyond that, you must ensure that your practice is equipped with adequate cybersecurity to protect patients’ financial information and that your policy complies with state laws and regulations, Hertz says. “Make sure that access to credit card information is very limited internally, and totally impossible externally. And notify the patient in advance of every draft being taken out or payment being made.”

Coastal Medical adopted a CCOF program last year after Boichat learned about it at a conference. She says that not only has it helped reduce bad debt, but also that patients have welcomed the convenience of not having to pay their bills manually.

Because insurance plans frequently change and credit cards expire, Boichat recommends making sure both are updated or verified as current at least annually as part of the check-in process.

**ADOPT HELPFUL TOOLS AND TECHNOLOGY**

A few years prior, Coastal made a number of other changes intended to improve patient satisfaction, which improved collections as well. For example, the practice added a kiosk to the waiting area so that people could check in on their own if there was a line at the front desk. “We really did it to improve the patient experience and our work flow process,” Boichat says. “What we didn’t realize was that the kiosk was collecting a lot of old balances.”

When patients checked in using the kiosk, the computer would remind them of their balances and give them the option to make a partial payment, she says. Most patients ended up paying off those old balances in full, a pleasant surprise to Boichat. Using tablets for patients to input their own demographic and insurance information can achieve a similar result, Betancourt notes.

Other useful times to remind patients of their balances are when patients call to make appointments and in appointment reminder messages, whether they be via voice, text or email, she says. But perhaps the most powerful improvements have come with giving patients the ability to pay their bills online. This saves patients time from having to write a check and drop it in the mail. Plus, they can pay their bills from anywhere. “I’ve used the service myself and loved it,” Boichat says.

**DON’T TIPTOE AROUND THE MONEY CONVERSATIONS**

Finally, the cornerstone to making all financial policies and procedures effective is clear, up-front communication with patients.

“There’s always been the soft approach, which is the sign in the doctor’s office that says that copays are due at the time of service,” Tinsley says. In the age of increasing patient responsibility, he recommends upfront verbal communication. “Patients should know their financial responsibility before they even get in the car [to go to the practice],” he says. “With reimbursement continually going downhill, practices have to treat their office like a business, which it is.”

Practices shouldn’t feel the need to apologize for collecting patient balances, Betancourt says. “No margin, no mission.”

**GOODBYE, SIMPLE COPAY COLLECTION**

Patients’ annual financial liability continues to rise. According to the 2018 Kaiser Family Foundation Health Benefits Survey, family premiums for employer-sponsored health insurance plans rose 5% from 2017 to 2018, with employees contributing an average of $5,547 toward a $19,616 premium. Meanwhile, annual premiums for individual coverage increased 3%, with workers paying an average of $1,186 toward a $6,896 premium.

According to the same survey, 85% of covered employees have a deductible in their plan, which averaged $1,573 for single plans, while 26% of all covered workers carry a deductible of $2,900 or more.
A popular cruise line's current slogan encourages all of us to “Choose fun.” That mantra is especially helpful when thinking about work, in this case, your dermatology practice. We're not talking about closing up practice and heading to Disney World. But the dermatology office shouldn't be a negative experience. When it is, your patients experience it too.

When author and keynote speaker Liz Jazwiec was vice president of nursing for an emergency department in a Chicago hospital located in a less-than-desirable neighborhood, the hospital’s new CEO told the staff, “There’s no reason why customer service here can’t be just like it is at Disney World.” Jazwiec and her colleagues rolled their eyes, but she admits, that’s when she really thought about the connection between customer satisfaction and job satisfaction. Now Jazwiec is an expert in leadership, engagement and service excellence. She’s never stopped thinking about this during her 30 years in healthcare. Practicing medicine can be a tough job, but positive workplaces can help improve patient care, practice efficiencies and help reduce employee turnover.

Conversely, negativity will drain energy and prevent staff from doing their jobs effectively, she says. This lowers overall productivity.

WHAT YOU PERMIT, YOU PROMOTE
Borrowing from her first book, “Eat That Cookie!”, Jazwiec recalls being hired to help a large maternal child organization reduce negativity.

“Every Tuesday every department on every shift received a big plate of yellow cookies with smiley faces,” she says. “Yes, it’s hokey, and it insulted some professionals who thought, ‘I can’t be bought with a cookie, and that’s not going to make all the problems go away.’

“Truth is, cookies are not a problem, but negative people who see bad in everything, like someone bringing in smiley-faced bookies, are the problem,” she says.

A person thinks we appreciate their behavior and that it’s appropriate when an employee says, ‘It’s been an awful day,’ or ‘I can’t wait to get out of here,’ or ‘This place is crazy,’ as he throws a pen down, and you respond, “That’s the truth!”

“As coworkers and leaders, we must stop supporting negative people,” she says. “We have to save our support for people who are positive.”

We should want to look a person squarely in the eye and say, nicely, ‘Just eat the cookie.’

SHIFT FOCUS
Most people spend nearly 90% of their time focused on what happened negatively during their day, she says.

“Let’s start looking at what went right or went really well and that caused us to have pride and restore our pride. That also reduces negativity.”

With so many changes occurring in healthcare, people working in the field no longer feel so heroic, Jazwiec says. Most people really do take pride in what they do, and it’s good to be proud of your job. When that happens, you’re more likely to say, ‘Hey, that was a good day!’

Notice the hero that exists in you and others, Jazwiec says. These positive occurrences may be obvious but may not always be recognized.

“Maybe it was reducing someone’s anxiety by sitting with them and comforting them. Maybe it was making someone smile and laugh. Maybe you helped a coworker or they helped you — being proud of your coworkers also drives negativity out of the workplace,” she says.

What seems like a small thing can really matter, and your acknowledgement doesn’t always have to be in full view of everyone; it can be just as important.

You and your co-workers may not be able to change the job, but you can change the way you feel about the job, Jazwiec says. And that ultimately will change — for the better — the way you do the job.
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Dermatologists are most likely to be confronted by a RAC audit.

If you’re practicing ethically and coding correctly, you have nothing to fear if you are audited.

Quick TAKES
Look for changes in evaluation and management services (E/M) documentation and payment methods within the next two years.

Dermatologists are
Coding changes to know
able, numerous specialties expressed concern with the proposal as initially outlined,” Dr. MacCormack says.

The AMA has been working diligently on an alternative option, which was presented at the April RUC meeting, she says. The AMA proposal was passed, and it now travels to CMS for consideration.

“CMS could chose to adopt it, modify it or ignore it,” she says. “It is possible that information regarding CMS’s intentions will be included within the next (2020) Medicare Physician Fee Schedule Proposed Rule to be published later this summer.”

DILIGENCE AND CLARITY
While the future of E/M billing and documentation requirements may be unclear, CMS and other payers consistently pay attention to appropriate use of modifiers such as 25 and 59 — how they’re being used, reimbursed and whether instances of overpayment exist, Dr. MacCormack says.

“That being said, the AAD has spent a lot of time on coding education, dermatologists are interested in staying up-to-date on coding issues and I think instances of miscoding are the exception, not the norm,” she says.

Practitioners already know modifier 25 is a significant, separately identifiable E/M service by the same physician on the same day of the procedure or other service, and that it can’t be attached to a procedure code. The challenge is to determine what defines that, Dr. MacCormack says.

“Both payers and CMS worry that the modifier is sometimes used to obtain payment for work that should be considered part of the procedure code,” she says. “Remember that for minor procedures, or those with 0- and 10-day global periods, the evaluation of the lesion to be treated, as well as an effort spent making the decision to perform a procedure is included within the procedure payment. This work cannot be billed for separately using modifier 25.”

ETHICS AND DOCUMENTATION
Maybe you worry about “Big Brother” looking over your shoulder. If you’re practicing ethically, and correctly documenting your work, don’t worry, she says.

“Even if you are an outlier in how frequently you use modifier 25, if you use it correctly, there is no need to change your practice,” she adds. “The same holds true for being an outlier in other ways, such as level of office visits charged. And as long as you are providing appropriate, medically-necessary care — you should bill for what you are doing.”

Approximately 60% of E/M services performed by dermatologists are submitted with modifier 25 attached, compared to about 25% for the rest of medicine.

“This attracts attention and also means that changes in modifier 25 payment policy affect dermatology more than other specialties,” she says.

Remember that payers want to reduce healthcare spending, so expect “to see continued attention focused on modifier 25 usage, along with modifier 25 payment policies that are poorly constructed, not grounded in reality, and that may lead to unintended consequences,” Dr. MacCormack says.

“Private insurers are very concerned that if the spending curve doesn’t shift, they could be made irrelevant by new, disruptive healthcare delivery systems,” she says.

STAY CURRENT
Change is inevitable and changes in biopsy coding remain a frequent topic of discussion, says Dr. Alam, professor and vice-chair of dermatology at Northwestern University and an advisor to the American Medical Association (AMA) current procedural terminology (CPT) panel.

“Most important to most dermatologists, skin biopsy coding changed this year from one primary code 11100 and one additional +11101, to three primary codes and three additional codes, with primary being shave (tangential) 11102, punch 11104 or incisional 11106, with the add-ons coded as +11105, +11109 and +11107.

“Importantly, if several biopsies of different types are obtained from the same patient at the same visit, only one primary code can be used, and the remaining biopsies of all types are designated by add-on codes,” he says. “This is a deviation from standard CPT practice and important to remember.”

Coding for photodynamic therapy (PDT), for treatment of precancerous lesions using a topical chemical sensitizer followed by exposure to light, changed last year and has become slightly more complex, says Dr. Alam. The older PDT code, 96567, still exists, andshould be used when there is no physician involvement in treatment delivery.

However, if the physician applies the photosensitizer and turns on the light, then 96573 is the appropriate code, he says. If the physician, in addition to their role in 96573, also pretreats hypertrophic lesions with curettage or dermabrasion, then 96574 should be used instead.

“The PDT codes especially needed to be changed, because when they were first approved, they were put through in a hurried fashion,” Dr. Alam says. “Physician work time was not incorporated, and as a consequence, the code valuation was much lower than it should have been in many cases. In some cases, it was not accurate to say staff was doing this because the physician was frequently involved in assessing and applying the chemical. Now the original code is still there, but there’s a new code for physician involvement that provides more fair compensation.”

Dr. Alam says that in 2018, two new sets of laser codes were introduced. These include 0479T and +0480T, which are for fractional ablative laser festination of burn and traumatic scars for functional improvement.

“Wounded warriors, burn victims and others with contracted scars that restrict motion and impair the activities of daily living can benefit from the treatments described by these codes,” he says. “The other new code set, 0491T and +0492T, is for ablative laser treatment of open wounds intended to speed and improve healing. In both cases, coding is by surface area treated, with the add-on code used when larger areas are involved. So far, both these code sets are Category III codes and, therefore, are not formally valued by the RUC and not necessarily paid by CMS and most private insurers. Since insurers can choose to pay for these codes at levels they deem appropriate, these are called ‘carrier-priced’ codes.”

“A Category III code is an emerging technology code, meaning there’s a new procedure coming out, with not much evidence in support of it, and not that many people doing that procedure yet,” he says. “When data becomes available that confirms more wide-
spread usage, the Category III might be reclassified as Category I, or the type of code that is valued by RUC and generally paid for by CMS and other insurers.

The process of converting a Category III code to a Category I code includes obtaining Level 1 data, usually a randomized controlled trial to show it works, and developing clinical guidelines to show how a procedure should be done.

“Finally, there has to be widespread use of a code, which doesn’t mean two people doing it hundreds of times each, but perhaps hundreds of people doing it twice a year,” he says.

He reminds dermatologists that Category III codes exist for five years and within that time, they have to be made a Category I code or be replaced with another Category III code, “which sometimes happens.”

EQUITABLE SYSTEMS
Although the coding process may seem confusing, on the surface it’s pretty simple, Dr. Alam says. “They may choose to hire a consultant and initiate a code with or without much input from the relevant specialty society — but they should be aware that the society is there to help them understand the process and to offer useful advice.

“There is a common misperception among our corporate colleagues that getting a new code is like winning the lottery, but if the code is not properly designed and worded, it can do more harm than good and actually restrict access by allocating insufficient resources for treatment delivery,” Dr. Alam says.

“And sometimes a new device or procedure can be accommodated successfully within the existing coding framework.”

Underneath it all, Dr. Alam and other advisors say they really want to do the right thing for everyone involved. “We work to come up with a scenario in which dermatology codes are well-described, physicians are compensated fairly and patients can have access to necessary treatments,” he says.

References

DON’T FEAR AN AUDIT

By MOLLIE MACCORMACK, M.D.

AUDITS CAN BE AN UNFORTUNATE reality of practicing medicine. The good news is that as long as you are practicing and coding correctly, you have nothing to fear should you be audited. There are four main types of audits:

1. Medicare Administrative Contractor (MAC) Audits - These are intended to target improper payments and vulnerabilities. MACs are allowed to perform medical reviews for all claims and can do so by issuing an additional documentation request (ADR).
2. Comprehensive Error Rate Testing (CERT) Contractors - Statistically analyze claims and establish rates and estimates of improper payments made by MACs. Such data review may take place with or without an ADR.
3. Recovery Audit Contractors (RAC) - Designed to assess for medical necessity as well as to correct improper payments that have already been made.
4. Zone Program Integrity Contractor (ZPIC) Audits - These are the most intimidating as they are designed to identify and stop potential fraud and abuse. Cases can be referred to the Department of Health and Human Services Office of Inspector General Office of Investigations.

Dermatologists are most likely to be confronted by a RAC audit. RACs are paid on a contingency fee basis, meaning that they collect a percentage of the improper payment they find or collect. There are currently four Recovery Audit Contractors covering different geographic regions of the United States (4th RAC deals with Hospice and Home Health Services).

Each RAC designs its own claims analysis system based on Medicare rules and regulations, coding/billing practices and clinical standards of care. If a provider is identified as possibly engaging in concerning practices, records can be requested with the number of charts allowed varying based on practice size. Reviews can be fully automated, semi-automated, or complex (performed by a human with medical records required).

If a RAC audit detects an overpayment a letter requesting repayment is sent. If payment is not made within 30 calendar days interest begins to accrue. If the first letter is ignored, a second is sent. Forty-one days after the first letter is sent recoupment, recovering payment from current or future claims can begin. If the case is still outstanding at 120 days it may be referred to the Department of Treasury.

RAC findings can be appealed through rebuttal or redetermination. Once notified, you have 30 days to provide additional documentation to the RAC before the claim is sent to the MAC for adjudication. If that effort is unsuccessful you can file a formal appeal in writing. There are five levels of appeal with the final being judicial review in a US District Court.

In October 2018, CMS introduced the Targeted Probe and Educate (TPE) program targeted towards those with high denial rates of uncommon billing practices. If selected, the regional MAC will review 20-40 claims and supporting medical records. If you are complaint, you are granted a one-year reprieve. If some claims are denied, you are invited to a one-on-one education session. Anyone not improving after three rounds of review and education (most improve after a single session) is referred to CMS.

TIPS TO MINIMIZE AUDIT STRESS
Clearly, being audited is an unpleasant experience. Here are a few tips to help you avoid the situation entirely or minimize stress should you be selected for an audit.

▲ Have a billing compliance plan and stay abreast of changes in coding/documentation requirements.
▲ Document clearly and correctly. Notes should be legible, signed and dated. Data used to determine level of service (including Review of Systems) must be pertinent to the issue being addressed. Modifiers must be used correctly, with particular attention paid to modifiers 24, 25 and 59. Data related to a procedure being performed during the same encounter cannot be used to increase the level of service (LOS) of the office visit.
▲ Ensure that all services provided and billed are medically necessary.
▲ Always use the correct code to describe the work being done.
▲ If you are billing based on time, document not only total time, but also how much time was spent in face-to-face counseling and a summation of the counseling discussion.
▲ Do not ignore the audit notice or delay responding.
▲ Answer any audit requests thoroughly and document each communication.
ring practices may lead to changes in how you communicate and present yourself, as well as in how you follow up. Establishing a healthy feedback loop should be a part of any referral management plan.”

Research also means asking questions of referring practices around you.

“Survey physicians that refer to you or make time for a brief in-person visit,” she says. “Schedule a staff lunch or visit the practice. Conduct short key physician and staff interviews to ask, ‘What can we do to enhance the experience for you, your staff and the patients you refer?’ If it’s within our sphere of control, we want to do it.’ That demonstrates commitment and caring.”

5. **DO THE MATH**

“Determine what percentage of your total revenue is referral-based,” says Morley.

- What does that look like on a per-provider or per-referring practice basis?
- Are referrals increasing or decreasing?
- What is the trajectory for that revenue?
- If that revenue disappeared, would the practice still be OK?

If the last answer is “no,” you need to develop some solid plans, she says.

6. **UNDERSTAND WHAT’S HAPPENING**

Complacency is not an option in a dynamic healthcare environment.

“Practice owners and boards have a fiduciary responsibility to identify threats to the fiscal health of their organization,” Morley says. “Like a game of chess, consider your position and options for several different moves based on any external threats. Annual strategic planning should include understanding the climate around you and ways your practice may be impacted.”

7. **APPOINT CHIEFS**

Practices can realize enormous success when leadership invests in referral management and development efforts, says Morley.

“It creates intention and accountability and also helps stimulate buy-in and involvement from other employees,” she says. “For any plan to succeed there must be ownership and accountability. Think carefully about who should own referral development, and what that might look like from performance metric standpoint. Accountability is everything.”

Internal medicine and PCPs are natural referral groups but also consider marketing to other specialties or disciplines. Think “out of the box.”

Morley adds that at a recent ADAM meeting in Washington, an attendee in a referral development course said they’d reached out to naturopaths and had begun to quickly accrue referrals.

“Still another has begun marketing to independent medical spas and massage therapy groups,” she says.

8. **SPREAD THE WORD**

“Invest in marketing materials that highlight and differentiate your practice brand and tell a story about your amazing team culture and why patients come to you,” Morley says. “If your patient satisfaction rate is high, share that metric too. Your marketing should differentiate your brand and send a clear message about what you do best and most often.”

Finally, ensure critical referral revenue streams flow in an unrestricted way, no matter what changes transpire inside or outside your practice, she says.

“Solid research, thoughtful planning, appropriate resource allocation, good communication and clear accountability provide a pathway to a referral management plan that is strong and sustainable.”
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NUTRACEUTICAL FOR WOMEN INCREASES HAIR GROWTH

Nutrafol’s physician-formulated CORE FOR WOMEN promotes hair health and growth by targeting the underlying causes of hair loss, including stress, compromised nutrition, hormonal changes and more.

The product is drug free and includes botanical ingredients, such as hydrolyzed marine collagen, Sensoril Ashwagandha, EVNoMax (Tocotrienols), BCM-95 Bio-curcumin and USP1 Saw Palmetto – all of which make up the company’s patented Synergy Complex. The formula also includes biotin, cayenne pepper extract, horsetail herb extract and other botanicals that promote hair health, says the company.

A six-month, randomized, double-blind, placebo-controlled study published in May 2018 in the Journal of Drugs in Dermatology found that the nutraceutical safely and effectively promoted hair growth in women with self-perceived hair thinning by addressing micro-inflammation, stress and oxidative damage.

FOR MORE INFORMATION: nutrafol.com

DERMASET RELEASES ANTI-AGING EYE SERUM

DermaSet Skincare launched their new DERMASET PREMIUM EYE SERUM last month after two years of development.

The product features a 3D rollerball applicator that massages the skin around the eye while applying the serum. The formula includes kinetin, pentapeptide-18, arnica extract, acetyl hexapeptide-8, acetyl octapeptide-3, hyaluronic acid and hordeum distichon (known as barley extract). The serum decreases redness, puffiness and wrinkles around the eye, according to the company.

FOR MORE INFORMATION: dermasetskincare.com

DEFENAGE LAUNCHES MEN’S SKINCARE LINE

Progenitor Biologics, LLC, announced a new addition to the DefenAge Skincare product line, MEN’S KIT. The products contain DefenAge’s proprietary Age-Repair Defensins, which reprogram the skin and promote younger looking skin by minimizing pores and wrinkles, and improving brightness, evenness, oiliness, tone, texture and hydration.

The kit includes a facial cleanser, cream and serum, as well as an exfoliating mask. It also comes with a hemp sports towel and a black leather toiletry bag. The towel is anti-microbial and meant to be used to wipe sweat during workouts.

“In clinical studies, male participants...saw dramatic improvement in their facial and neck skin that appeared younger...” says Gregory Keller, M.D., the principal investigator in the initial clinical studies of DefenAge.

FOR MORE INFORMATION: defenage.com

CBD SALVE CALMS IRRITATED SKIN

Life Elements’ CBD & HONEY SKIN REPAIR product is designed to nourish and repair dry skin. According to the company, the balm can be used on blisters, rashes, burns, cracked skin, eczema and rosacea, and also has anti-aging properties.

The chemical-free formula comes in .50 oz (25 mg full spectrum CBD) and 2 oz (100 mg full spectrum CBD) tubes. It can be used twice daily as a moisturizer or it can be applied directly to dry areas.

FOR MORE INFORMATION: lifeelements.com
Title 21 of the Code of Federal Regulations provides scope, definition and regulatory guidance around Food and Drugs. Regulations included in Chapter I provide guidance on the use of ingredients in various over-the-counter products. Of particular interest to dermatologists are the acne ingredients and the skin protectant ingredients. Below is a list of active ingredients allowable in specified concentrations and combinations.

**ACTIVE ACNE DRUG INGREDIENTS**

**THE ACTIVE INGREDIENT** of the product consists of any of the following:

- Benzoyl peroxide, 2.5% to 10%.
- Resorcinol, 2%, when combined with sulfur 3% to 8%.
- Resorcinol monoacetate, 3%, when combined with sulfur 3% to 8%.
- Salicylic acid, 0.5% to 2%.
- Sulfur, 3% to 10%.
- Sulfur, 3% to 8%, when combined with resorcinol 2% or resorcinol monoacetate 3%.

**SKIN PROTECTANT ACTIVE INGREDIENTS**

**THE ACTIVE INGREDIENTS** of the product consist of any of the following, within the concentration specified:

- Allantoin, 0.5% to 2%.
- Calamine, 1% to 25%.
- Cocoa butter, 50% to 100%.
- Dimethicone, 1% to 30%.
- Glycerin, 20% to 45%.
- Kaolin, 4% to 20%.
- Lanolin, 12.5% to 50%.
- Mineral oil, 50% to 100%; Mineral oil, 30% to 35% in combination with colloidal oatmeal, provided the labeling states "temporarily protects and helps relieve minor skin irritation and itching due to: [select one or more of the following: 'rashes' or 'eczema']."
- Petroleum, 30% to 100%.
- Sodium bicarbonate.
- Topical starch, 10% to 98%.
- White petrolatum, 30% to 100%.
- Zinc acetate, 0.1% to 2%.
- Zinc carbonate, 0.2% to 2%.
- Zinc oxide, 1% to 25%.

**SOURCES:**


A paradigm shift in the treatment of acne

Researchers have gained a new perspective on the role of inflammation in acne, which has resulted in changes in recommended approaches to acne treatment and patient management.

These changes impact how dermatologists treat acne in adolescence through adulthood and include patients with mild-to-severe acne vulgaris, according to Valerie D. Callender, M.D., professor of dermatology at Howard University College of Medicine, Washington, DC.

In the past, dermatologists thought acne’s initial pathophysiology involved abnormal desquamation of the keratinocytes that line the sebaceous follicle. That, they thought, triggered hyperkeratinization and comedogenesis, according to Dr. Callender, who presented “Acne through the Ages,” at the Generational Dermatology Palm Springs Symposium this past March.

“We all knew that increasing circulating androgens in puberty and increasing sebum production was followed by P. acnes (now called Cutibacterium acnes or C. acnes). The inflammation came later,” she says. “Now we know that’s not true. The inflammatory response occurs initially during that hyperkeratinization and at every stage in the development of acne.”

Researchers started the conversation that inflammation was part of acne lesion initiation in a paper published in the Journal of Investigative Dermatology (JID) in 2003. Kircick LH addressed this “paradigm shift” in acne in 2016 in a paper in the Journal of Drugs in Dermatology (JDD).

As a result, dermatologists’ approach to acne treatment has changed, according to Dr. Callender. Dermatologists, she says, should target inflammation and hyperkeratinization early on with topical retinoid therapy.

GUIDELINES OF CARE

The recommendation is for dermatologists to start topical retinoids as a first-line therapy when managing teens and adults with mild, moderate and severe acne, according to Guidelines of Care for the Management of Acne Vulgaris, published May 2016 in the Journal of the American Academy of Dermatology (JAAD).

“By doing that and attacking the hyperkeratinization, you’re going to have less inflammation and less sequelae, particularly in patients with skin of color who commonly get post-inflammatory hyperpigmentation,” Dr. Callender says.

As for other topicals, dermatologists should consider using benzoyl peroxide or combinations with erythromycin or clindamycin to treat acne, says Dr. Callender. The guidelines recommend these as monotherapy for mild acne, or in conjunction with a topical retinoid or systemic antibiotic therapy for moderate to severe acne.

Topical antibiotics, including erythromycin and clindamycin, are effective acne treatments but dermatologists are using topical antibiotics less, especially as monotherapy, because of the risk of bacterial resistance, she says.

“Topical dapsone 5% or 7.5% gel is recommended for inflammatory acne, particularly in adult females with acne. There is limited evidence to support recommen-
dations for sulfur, nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride and zinc in the treatment of acne,” according to Dr. Callender.

**UPDATES IN ANTIBIOTICS FOR ACNE**

Oral antibiotics, particularly in patients with moderate-to-severe acne and inflammatory acne that is resistant to topical treatments, remain important for acne treatment. But because of antibiotic resistance concerns, the guidelines recommend dermatologists have acne patients on and off oral antibiotics in three months’ time.

“In the past, dermatologists would prescribe tetracycline for several years,” Dr. Callender says. “We know that’s no longer the case.”

When treating acne with oral antibiotics, dermatologists should keep in mind that doxycycline and minocycline are similar in their effect and are more effective than tetracycline for treating acne. Dermatologists should restrict use of erythromycin due to the increased risk of bacterial resistance, according to Dr. Callender.

“Use of systemic antibiotics, other than the tetracyclines and macrolides, is discouraged because there are limited data for their use in acne,” according to Dr. Callender.

There is another antibiotic option for acne patients according to recent research. Sarecycline, a novel narrow spectrum antibiotic, is available for the treatment of moderate-to-severe acne. Researchers report in a phase 3 study published September 1, 2018, in *JDD* that once-daily oral sarecycline 1.5 mg/kg given for 12 weeks is effective, well tolerated and appears to be safe for moderate-to-severe acne vulgaris.

Dermatologists’ decreasing reliance on oral antibiotics as a long-term treatment strategy highlights the need to be aggressive with topical retinoids and benzoyl peroxide, she says.

Isotretinoin remains a go-to treatment for severe nodular acne, and dermatologists continue to use it appropriately to treat moderate acne that is treatment resistant or to manage acne that is causing scars or psychosocial distress.

What has changed with isotretinoin use are recommendations for lab testing.

“There is always the issue about routine laboratory monitoring in patients on isotretinoin therapy. There are several studies that show it’s best to do a baseline lab test, that includes liver function, serum cholesterol and triglycerides, then to repeat that in two to three months and again at the end of the therapy, which is in six months,” Dr. Callender says. “Before we would have to do these tests every single month.”

Dermatologists and their patients on isotretinoin also can skip routine complete blood count monitoring because researchers have found that isotretinoin does not affect those numbers, she says.

Recommendations for monthly pregnancy testing in women of child bearing age has not changed.

**ACNE AND ANDROGENS**

It’s important to note that hormones are not just...
associated with the adult female patient, according to Dr. Callender.

“All acne is hormonal,” she says. “Androgens play a role.”

Research has shown that estrogen-containing combined oral contraceptives are effective and recommended for treating inflammatory acne in women.

The FDA approved three oral contraceptives for treating acne:
1. Ortho Tri-Cyclen (norgestimate/ethinyl estradiol, Janssen Pharmaceuticals)
2. Estrostep (ethinyl estradiol and norethindrone, Allergan)
3. Yaz (drospirenone/ethinyl estradiol, Bayer).

While studies suggest the efficacy is similar among the approved oral contraceptives, Rachel V. Reynolds, M.D., assistant professor of dermatology at Harvard Medical School and vice chair Dermatology Beth Israel Deaconess, says she favors Yaz, which has androgen receptor blocking activity in addition to anti-androgen benefit.

Dr. Callender says she and other dermatologists use spironolactone in select female acne patients.

“It is off-label. But I think we’re using spironolactone a little more for adult female acne than before. The dosage ranges from 50 to 200 mg a day. Basically, it’s an antiandrogen and reduces sebum production in vivo. We have studies that show that. Side effects that we’re concerned about include hyperkalemia,” she says.

However, dermatologists might not have to monitor patients’ potassium levels while they’re on spironolactone if those patients are young and healthy. Dr. Callender cites a study published in 2015 in *JAMA Dermatology*, in which the authors conclude: “The rate of hyperkalemia in healthy young women taking spironolactone for acne is equivalent to the baseline rate of hyperkalemia in this population. Routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne.”

To Target Trouble Spots

Zitsticka KILLA is a transparent acne patch that is covered with 24 microdarts composed of salicylic acid, hyaluronic acid, niacinamide and oligopeptide-76. According to the company, microdarts completely dissolve in just 2 hours and result in a reduction of both size and redness of the area treated.
Patients on spironolactone might experience irregular menses, according to Dr. Reynolds, who presented on hormonal treatments for acne during the March 2019 American Academy of Dermatology Annual Meeting in Washington D.C.

“If I’m going to start an antiandrogen medication like spironolactone, when possible, I like to have the patient also on the birth control pill because it helps to regulate menses,” Dr. Reynolds says.

Dr. Reynolds also says she often prescribes hormonal therapies for acne along with topical retinoids.

Sometimes, she’ll add a topical antibiotic combined with benzoyl peroxide.

**ACNE AND SKIN OF COLOR**

Inflammatory acne lesions can result in acne scars and post-inflammatory hyperpigmentation in skin of color, Dr. Callender says.

“Usually we use our acne therapy, like a topical retinoid, which actually helps to minimize some of the pigmentation. We add topical hydroquinone when needed, but also use topical azelaic acid, which is off-label, but helps the acne and discoloration,” Dr. Callender says. DT

**Disclosures:** Dr. Callender performs clinical research, is on the advisory board, consults with and/or speaks for Almirall, Aclaris, Aerolase, Allergan, Avon, Dermira, Eli Lilly, Foamix, Galderma, L’Oreal, Menlo, Merz Aesthetics, Novan, Ortho, Pfizer, Revance and Unilever. Dr. Reynolds reports no relevant disclosures.

**REFERENCES**


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**To Mitigate Mild Adult Acne**

This Illuminating Day Serum and Intensive Overnight Repair combo from Joyome is formulated with 11 actives and a patent-pending Microbiome Balancing Complex that the company says increases the beneficial microbe *S. epidermidis* and combats the damaging microbe *S. aureus*.

**To Balance Out Blemished Skin**

NEOVA’s Balancing Control line includes two advanced skincare formulas, the Purifying Cleanser to wash, exfoliate and control oil — without over drying — and the Retinol Rapid Tx to improve clarity with stabilized retinol and DNA repair enzymes.
Acne treatment alternatives

by Lisette Hilton | Staff Correspondent

In dermatology the first line of defense against acne vulgaris has largely been the use of antibiotics. However, the need to limit antibiotic use means acne treatment protocols are starting to shift.

“We’re trying to limit the amount of antibiotics people are taking, as well as the number of people who are taking antibiotics,” says William James, M.D., professor and chair of dermatology at Penn Medicine. “There’s been a major push over the past few years to do that. So, it changes how we treat people, particularly women in many cases.”

It’s no secret that antibiotics have been successful in treating and controlling most acne cases. The efficacy has led dermatologists to be among the highest prescribers of antibiotics. However, frequent and long-term antibiotic use can also present problems, such as the development of antibiotic resistance in patients over time. Additionally, existing research indicates long-term use can also be associated with irritable bowel syndrome. Consequently, the American Academy of Dermatology’s standing recommendation is to limit antibiotic use to less than three months.

To abide by this suggestion and to comply with the non-antibiotic treatment paradigm shifts, says Dr. James who addressed acne treatment options at the American Academy of Dermatology’s (AAD) 2019 spring meeting in Washington, D.C., dermatologists must consider alternative therapies. In particular, he says, providers should examine spironolactone or isotretinoin as options to treat moderate-to-severe acne.

SPIRONOLACTONE FOR ACNE

Originally designed as a high blood pressure medication, spironolactone is frequently used off-label to treat moderate-to-severe acne in women. It’s inappropriate for men because it blocks the function of male hormones.

“This is an excellent medication for acne, and many women respond very well to it,” he says. “And, dermatologists should be more comfortable prescribing it.”

According to existing research, a 200-mg daily dose — lower than levels needed to control high blood pressure — has been shown to reduce acne levels equivalent to those seen with antibiotics. Patients treated with spironolactone also experience low relapse rates, and few report discontinuing use.

Overall, spironolactone is well tolerated with few side effects, according to Dr. James. Fatigue, increased urination, irregular periods, breast tenderness, muscle pain and irregular heart beat are possible. Additionally, dermatologists should ask patients if they have low blood pressure before writing the prescription.

Despite evidence of efficacy, however, some dermatologists remain reticent to recommend spironolactone, he says. Based on older research, the medication carries a black box label warning, cautioning providers that the medication is associated with several types of tumors. However, the warning is based on studies that included doses from 10-to 500-times the highest dose given to humans, Dr. James says. And, additional research has shown little-to-no evidence that the medication causes tumors.

Sharing this updated information, Dr. James says, “This discussion is alerting dermatologists that spironolactone is available and safe,” Dr. James says. “It’s been around for many years, so it’s not new. But,
Energy-based options

DEVICES ENHANCE OUTCOMES WHEN ORAL, TOPICAL MEDICATIONS FALL SHORT

by Lisette Hilton | Staff Correspondent

Medications to treat acne take time to work and might not clear acne completely. To enhance outcomes from acne medications, Michael H. Gold, M.D., uses energy-based devices.

“Energy-based devices for acne have been around for a long time. We have better devices now,” says Dr. Gold, medical director of Gold Skin Care Center and Tennessee Clinical Research Center, Nashville, Tenn. “In my opinion, the energy-based device world allows us to use devices to make people better than with medicines alone.”

Dr. Gold starts acne patients on medicine. If the medicines aren’t enough to clear the skin in a reasonable period of time, he says he recommends treatment with devices. The devices not only improve the acne condition, but also enhance the quality of the skin, he says.

ENERGY-BASED OPTIONS

Lasers treat acne in various ways. Dr. Gold focuses on using devices that destroy Cutibacterium acnes, or C. acnes, formerly Propionibacterium acnes, or P. acnes.

Intense pulsed light (IPL) devices work exceptionally well in that regard, according to Dr. Gold.

Among the IPL technologies that work to treat acne: The Isolaz 2 (Solta Medical), which is an IPL therapy combined with vacuum technology. The vacuum helps to bring target tissue closer to the light, he says.

“Acne patients like IPL treatment. Dermatologists can use any IPL. There are acne settings on most IPLs today. There are cutoff filters that work for the acne bacteria where the acne lesions are,” Dr. Gold says.

The AdvaTx (AdvaLight) dermatology laser is another good acne treatment option, according to Dr. Gold.

“AdvaLight works by two different lasers lights. It’s a 589 nm — almost like a pulsed dye laser, without the dye. It’s a yellow light laser. Then there’s also a 1319 nm, which works really nicely to help subtly smooth scarring,” he says.

Another option is the Aerolase Neo, which is a short-pulsed 650 micron 1064 nm laser.

“It works by targeting the C. acnes, and it’s fast and painless. It’s one of our go-to devices because of the pain part. It works by targeting the appropriate bacteria — the wavelength targets the absorption spectrum of the C. acnes,” Dr. Gold says. “There are studies that support how well this and other devices work. We’re just finishing a long, large study on Neo showing it works and the results are spectacular.”

There are other devices that Dr. Gold is not likely to use for acne patients. Those that target the sebaceous glands, for example. Dr. Gold says clinicians don’t tend to use those devices anymore because there aren’t many of those machines left on the market.

“Then there’s photodynamic therapy (PDT), which destroys the C. acnes and a little bit of the sebaceous glands. PDT for acne is really good. The problem is it’s not covered by insurance because it’s not FDA cleared. So, it’s off label, and PDT medicines are really expensive,” Dr. Gold says. “We don’t do a lot of PDT anymore for acne; although, for really bad cases, I will.”

MONEY MATTERS IN ACNE

Dermatologists should keep in mind that energy-based device treatments for acne are generally not covered by insurance; rather, patients pay cash.
Market studies have been done that show that people will pay for it if it’s within reason,” Dr. Gold says. “I tell my colleagues all the time that these are not procedures that you can charge thousands and thousands of dollars for. This is a treatment. It is not a cure. Most of these patients are kids and young adults. Therefore, money is important. So, I keep the prices really reasonable.”

Dr. Gold says most acne patients need between two and four sessions with energy-based devices to treat acne. He’ll usually perform treatments every other week. Some come back for touch-up treatments. Still, Dr. Gold keeps the price of each treatment affordable.

Unless Dr. Gold is performing a study on a device that does not allow additional treatments, he treats acne patients with a combination of medicines and an energy device.

“Devices, he says, work well as adjuncts to medical management, even when patients are on an antibiotic. “You can still use a laser because the antibiotics are not on the same wavelength areas as the laser light,” Dr. Gold says.

Dermatologists who don’t consider energy-based options in acne treatment are missing an opportunity to make acne patients happier and keep them coming back for treatments other than just acne.

“Everything in aesthetic medicine is targeting the millennial world. Once you make their acne better, guess what? They’re coming in to me for every cosmetic procedure,” Dr. Gold says. “They come to me because I took care of them when others said here’s your prescription, goodbye.”

Alternatives continued from page 6

it’s a matter of trying to make people aware of these newer studies that indicate its safety and efficacy so more people feel comfortable using it.”

ISOTRETINOIN FOR ACNE

Previously known on the market as Accutane, isotretinoin has been considered the topline in efficacy for treating acne, according to Dr. James. But, historically, it has not been the initial defense due to many concerns.

“In the past, if people weren’t responding to antibiotics, they might go to isotretinoin as a final effort to control acne,” he says. “Now, as dermatologists are trying to utilize antibiotics less and less, they’re turning to isotretinoin for more and more people.”

This move stems from recent research that shows patients treated with isotretinoin experience roughly the same level of efficacy as those who undergo an antibiotic regimen. Normally, patients receive a 120 mg/kg to 150 mg/kg dose, and they must complete the full course even if they achieve 100% acne clearing. However, lower beginning doses can be recommended to help side-step initial acne flares.

Researchers have also found the body best absorbs isotretinoin when patients take it with a high-fat meal.

Updated studies also reveal a need to potentially change conventional complete blood panel monitoring practices. Traditionally, dermatologists have performed these tests as frequently as once a week. Instead, new data indicates lipids, liver function and triglycerides can be checked roughly once a month. This change is both convenient and cost-effective for patients.

Ultimately, Dr. James says, he wants dermatologists to have new information about how to best treat acne.

“...RECENT RESEARCH THAT SHOWS PATIENTS TREATED WITH ISOTRETINOIN EXPERIENCE ROUGHLY THE SAME LEVEL OF EFFICACY AS THOSE WHO UNDERGO AN ANTIBIOTIC REGIMEN.”

“...I think it would be good to consider spironolactone when treating women for acne. You’ll be able to improve outcomes for a wider array of women while limiting the use of antibiotics. And, I think of isotretinoin similarly,” he says.

DISCLOSURES: Dr. Gold has consulted and performed research for Solta, Aerolase, AdvaLight and Lumenis.
New and pipeline acne therapies

by Erin Johanek, PharmD, RPh | Staff Correspondent

According to the American Academy of Dermatology, acne vulgaris, also known as acne, is the most common skin condition in the United States. Acne affects up to 50 million Americans annually, and approximately 85% of people between the ages of 12 and 24 have experienced at least minor acne. In 2013, the costs associated with the treatment and lost productivity among those who sought medical care for acne (approximately 5.1 million people) exceeded $1.2 billion.

The current guidelines of care for the management of acne, published by the American Academy of Dermatology in 2016, recommend different combinations of therapies based on severity — including mild, moderate and severe. Current first-line treatments include topical benzoyl peroxide, topical retinoids, oral and topical antibiotics and oral isotretinoin. Alternative treatments listed in the guidelines include topical dapsone, oral contraceptives and oral spironolactone.

According to BioPharmCatalyst, there were 12 drugs in the pipeline as of this publication.

One of these medications, currently in phase 3 clinical trials is Novan’s SB204, a first-in-class, nitric oxide-releasing topical drug for the treatment of acne. SB204 is being studied as a once-daily, topical monotherapy. Localized nitric oxide delivery is thought to provide anti-inflammatory activity by inhibiting the NLRP3 inflammasome, decreasing downstream release of cytokines and killing Propionibacterium acnes.

In March 2019, the U.S. Food and Drug Administration (FDA) accepted for review the New Drug Application (NDA) for FMX101 (Foamix Pharmaceuticals) for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris in patients nine years of age and older. FMX101 is a novel minocycline topical foam.

In August 2018, the FDA approved Altreno (tretinoin, Ortho Dermatologics) 0.05% lotion for the treatment of acne vulgaris in patients nine years of age and older. Altreno is the first and only tretinoin product available in a lotion for acne and is provided in a formulation with known moisturizers, hyaluronic acid, glycerin and collagen.

“In addition to bringing a new formulation of tretinoin to market this past fall, we are continuing to make progress on two new combination treatments for acne in our pipeline,” says Bill Humphries, U.S. President, Ortho Dermatologics. “IDP-126 and IDP-120 are in

Continues next page
Phase II and Phase III clinical trials, respectively.”

IDP-126 and IDP-120 are both topical gel products currently being studied for the treatment of acne. According to Humphries, Ortho Dermatologics is planning to file an NDA for an acne treatment during the first half of this year.

**FUTURE OF ACNE TREATMENT**

According to Future Market Insights Moderate-to-Severe Acne Therapeutics Market Report, growing prevalence of moderate-to-severe acne over the globe is expected to generate high demand for new treatments. The report explains that increasing adoption of innovative acne treatment therapies, such as photodynamic therapy and laser therapy has led to further revenue generation in the acne market. However, the safety issues associated with the anti-acne drugs such as complications in pregnancy and the adverse effects of retinoids such as skin irritation and dryness, restrain the moderate-to-severe acne therapeutics market growth.

“Acne affects Americans of all ages and backgrounds, and like so many patients, those with acne have varying treatment needs,” says Humphries. “We believe that the development of treatments for this condition will continue to increase and improve in the future, which we hope will ultimately result in better health and quality of life for all patients.”

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**LATE-STAGE ACNE PIPELINE**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Sarocycline, Allergan</td>
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<td>Ameluz, Bionfra AG</td>
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<td>Olumacostat glasaretil (DRM01), Dermira</td>
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<td>Topical Radezolid, Melinta Therapeutics</td>
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<td>SB204, Novan</td>
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<td>SIRS-T, Sol-Gel Technologies</td>
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<td>TWIN, Sol-Gel Technologies</td>
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<td>SNA-001, Sienna Biopharmaceuticals</td>
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<tr>
<td>XEN801, Xenon Pharmaceuticals</td>
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Data source: 2019 BioPharmCatalyst
ABOUT FACE

Navigating Neuromodulators and Injection Techniques for Optimal Results

Visit http://tinyurl.com/AboutFaceDT for online testing and instant CME/CE certificate.

RELEASE DATE: JUNE 1, 2019  EXPIRATION DATE: JUNE 30, 2020

FACULTY

Steve G. Yoelin, MD (Chair)
Joel L. Cohen, MD
Dee Anna Glaser, MD
Joely Kaufman, MD
Ava Shamban, MD

This continuing medical education activity is jointly provided by Amedco and MedEdicus LLC.

This continuing medical education activity is supported through an unrestricted educational grant from Galderma Laboratories, LP.
ACTIVITY DESCRIPTION
This activity provides a review of the properties and aesthetic uses of currently available neuromodulators, or botulinum neurotoxin type A products, through a review of the literature, real-world cases, and expert clinical perspectives. The desired results of this activity are for health care practitioners to improve their ability to provide neuromodulators appropriately to their patients for optimal patient outcomes.

TARGET AUDIENCE
This educational activity is intended for health care practitioners, including physicians, physician assistants, nurse practitioners, and nurses, with an interest in facial aesthetics.

LEARNING OBJECTIVES
Upon completion of this activity, participants will be better able to:
- Explain the conversion ratio needed for individual neuromodulators
- Use appropriate reconstitution procedures for the different neuromodulators
- Explain how to switch between neuromodulators to achieve optimal clinical outcomes
- Employ appropriate strategies for the management of complications to improve patient satisfaction
- Describe the anatomy of the face and neck that is relevant to ensure safe and effective treatment outcomes
- Illustrate the most appropriate injection strategies for a variety of patients treated with neuromodulators

SATISFACTORY COMPLETION
Learners must pass a post-test and complete an evaluation form online by going to http://tinyurl.com/AboutFaceDT. Upon passing, you will receive your certificate of completion immediately. You must score 70% or higher to receive credit for this activity, and may take the test up to 2 times. You must participate in the entire activity as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

JOINT ACCREDITATION STATEMENT
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<td>Joel L. Cohen</td>
<td>Allergan; Biopelle, Inc; Evolus, Inc; Galderma Laboratories; LP; Lutronic; Merz, Inc; Revance Therapeutics, Inc; Sciton, Inc; SENTE Inc; Sonoma Pharmaceuticals, Inc; and Swiss-American CDMO, LLC</td>
<td>Consultant</td>
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<td>Dee Anna Glaser</td>
<td>Dermira, Inc; Galderma Laboratories, LP; and OrthoDerm</td>
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<td>Joely Kaufman</td>
<td>Allergan; Atacama Therapeutics, Inc; Brickell Biotech, Inc; Dermira, Inc; Galderma Laboratories, LP; and Revance Therapeutics, Inc</td>
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<td>Ava Shamban</td>
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<td>Steve G. Yoelin</td>
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ABOUT FACE
Navigating Neuromodulators and Injection Techniques for Optimal Results

Introduction
Achieving successful outcomes and patient satisfaction with botulinum neurotoxin type A (BTX-A) injection requires that clinicians understand the properties of the individual products, along with their similarities and differences, and be knowledgeable about relevant anatomy, reconstitution, dosing, and proper injection technique. Multiple BTX-A products are commercially available for cosmetic use, but each product has unique characteristics, and the marketed products are not interchangeable. This review addresses the aforementioned topics through an evaluation of relevant literature, experts’ clinical perspectives, and case narratives.

Manufacturing and Composition
Since 2010, practitioners in the United States have had access to 3 commercially available BTX-A products with cosmetic indications: abobotulinumtoxinA (aboBTX-A), incobotulinumtoxinA (incoBTX-A), and onabotulinumtoxinA (onaBTX-A). A fourth product, prabotulinumtoxinA-xvfs (praBTX-A), was approved by the US Food and Drug Administration in February 2019. AboBTX-A, incoBTX-A, onaBTXA, and praBTX-A all contain BTX-A produced from fermentation of Clostridium botulinum type A strain, but they are produced using different manufacturing processes and vary from each other compositionally. (Note: At the time this CME/CE activity was developed, praBTX-A was not commercially available. Because of a lack of practical experience with praBTX-A, it is not discussed in detail in this activity.)

Clostridium botulinum type A produces a protein complex that contains a core neurotoxin protein, BTX-A (~150 kDa), bound to ≥ 1 nontoxic accessory proteins (NAPs). The NAPs are removed during the purification process for incoBTX-A. With the other products, the NAPs dissociate from the core neurotoxin in the vial upon reconstitution when the protein complex is exposed to the physiologic pH of normal saline.

Potency for BTX-A products is expressed in units and determined for each product with the manufacturer’s proprietary assay method and reference standard. Therefore, potency units are product specific and not interchangeable among BTX-A products.

Conversion Ratios
Preclinical and clinical studies have been conducted to determine conversion ratios among products that can be used as a guide for selecting doses that will result in similar efficacy and safety and for comparing relative treatment cost. The studies produced varying results that can be explained by their methodological inconsistencies, including differences in anatomic sites of injection, BTX-A doses, and end points to determine treatment efficacy. Several reviews of available study data, however, suggest that the conversion ratio ranges between 2:1 and 3:1 for aboBTX-A:onaBTX-A and is 1:1 for incoBTX-A:onaBTX-A. It is important to reiterate that there is no universally accepted conversion ratio among products; the topic remains open to discussion.

Experts’ Clinical Perspectives
Dr Yoelin: What conversion ratios for aboBTX-A:onaBTX-A and incoBTX-A:onaBTX-A do you use in your practice?
Dr Glasser: I find that the ratio needed to achieve similar results in terms of peak effect and durability with aboBTX-A:onaBTX-A varies among different anatomic sites. Therefore, a ratio of between 2:5:1 and 3:1 gives a good starting point, but it is not absolute. For incoBTX-A:onaBTX-A, I generally use a ratio higher than 1:1, typically between 1:2:1 and 1:5:1. I teach residents that converting from one toxin to another is like learning a foreign language in the sense
that once you become fluent in the foreign language, you no longer convert every foreign word back into English.

Dr Kaufman: I use a conversion ratio of 3:1 for aboBTXA:onaBTX and 1.5:1 for incoBTXA:onaBTX. With these ratios, I feel I can get similar results, including duration, with any of the available neuromodulators.

Dr Shamban: When trying to achieve similar results with different toxins, I consider duration of effect to be the important end point. With this in mind, I use a ratio of 3:1 for aboBTXA:onaBTX and 1.5:1 for incoBTXA:onaBTX.

Dr Cohen: I, also, use a ratio of 3:1 for aboBTXA:onaBTX.

Dr Yoelin: I use the same 3:1 ratio for aboBTXA:onaBTX. Another area of interest is how quickly the desired effects from these products can be achieved. Patients often want to see results quickly.

Do you think any of the toxins have a faster onset of action?

Dr Cohen: Results of at least 1 controlled split-face study showed a faster onset of action with aboBTX than with onaBTX, and patient diary data from clinical trials are consistent with my clinical impression that aboBTX might have a slightly faster onset than does onaBTX, but this probably does not have real clinical relevance.

Dr Kaufman: Data from the aboBTXA study I conducted with Dr Cohen suggested that increasing the volume of diluent for reconstitution results in a faster onset.

Dr Shamban: A recent study reported that onset of BTX action for treatment of forehead and glabellar lines can be accelerated by 24 hours if patients perform postinjection facial exercises.

Reconstitution

Directions for reconstitution found in both the prescribing information for the BTX products and in manufacturers’ guides list different volumes of diluent that result in different final concentrations. Table 2 provides a simplified listing of reconstitution methods that result in a final volume of 0.1 mL for each BTX. The chosen diluent volume can vary, depending on such factors as site of injection, treatment goals, and patient-specific characteristics. Practitioners might have personalized approaches derived from their clinical experience.

Table 1. BTXA Products With Cosmetic Indications

<table>
<thead>
<tr>
<th></th>
<th>OnaBTX A</th>
<th>AboBTX A</th>
<th>IncoBTX A</th>
<th>PrabTXA</th>
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<tbody>
<tr>
<td>Year of FDA approval</td>
<td>2002*</td>
<td>2009</td>
<td>2010</td>
<td>2019</td>
</tr>
<tr>
<td>Active substance (molecular weight)</td>
<td>BTXA with NAPs (900 kDa)</td>
<td>BTXA with NAPs (500-900 kDa)</td>
<td>BTXA without NAPs (150 kDa)</td>
<td>BTXA with NAPs (900 kDa)</td>
</tr>
<tr>
<td>Excipients</td>
<td>Human serum albumin, sodium chloride</td>
<td>Human serum albumin, lactose</td>
<td>Human serum albumin, sucrose</td>
<td>Human serum albumin, sodium chloride</td>
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<tr>
<td>Purification method</td>
<td>Crystallization</td>
<td>Chromatography</td>
<td>Chromatography</td>
<td>Not available</td>
</tr>
<tr>
<td>Finishing method</td>
<td>Vacuum dried</td>
<td>Freeze dried</td>
<td>Lyophilized</td>
<td>Vacuum dried</td>
</tr>
<tr>
<td>Potency testing method</td>
<td>Cell based</td>
<td>Animal based (LD50 assay)</td>
<td>Cell based</td>
<td>Animal based (LD50 assay)</td>
</tr>
<tr>
<td>Units per vial</td>
<td>50 or 100</td>
<td>300 or 500</td>
<td>50 or 100</td>
<td>100</td>
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</table>

Approved indications for cosmetic use:

- Temporary improvement in the appearance of moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity, moderate-to-severe lateral canthal lines associated with orbicularis oculi activity, and moderate-to-severe forehead lines associated with frontalis muscle activity.
- Temporary improvement in the appearance of moderate-to-severe glabellar lines associated with procerus and corrugator muscle activity in adults aged < 65 years.
- Temporary improvement in the appearance of moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

Abbreviations: aboBTX, abobotulinumtoxinA; BTXA, botulinum neurotoxin type A; FDA, US Food and Drug Administration; incoBTX, incobotulinumtoxinA; LD50, median lethal dose; NAP, nontoxic accessory protein; onaBTX, onabotulinumtoxinA; prabTXA, prabotulinumtoxinA-xvfs.

* Year of approval for cosmetic use

Table 2. Simplified BTXA Reconstitution Methods

<table>
<thead>
<tr>
<th>Units per Vial</th>
<th>Diluent, mL</th>
<th>Dose per 0.1 mL, U</th>
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<td>AboBTX A</td>
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<td>IncoBTX A</td>
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</tr>
<tr>
<td>PrabTXA</td>
<td>100</td>
<td>2.5</td>
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Abbreviations: aboBTX, abobotulinumtoxinA; BTXA, botulinum neurotoxin type A; incoBTX, incobotulinumtoxinA; onaBTX, onabotulinumtoxinA; prabTXA, prabotulinumtoxinA-xvfs.

* After adding diluent, incoBTXA must be swirled and inverted.

Experts’ Clinical Perspectives

Dr Yoelin: I typically use 2 mL of bacteriostatic saline to reconstitute the 100–U vials of onaBTX and incoBTX and the 300-U vial of aboBTX. This technique retains a 3:1 ratio of aboBTX:onaBTX and therefore makes it easy for me to do a dose conversion between toxins because I like to think about the volume injected at each site rather than the units dispensed. I believe that this strategy simplifies the injection process for someone who is a novice, intermediate, or advanced injector. In addition, I use the same reconstitution volume regardless of the intended site of injection because I believe it is helpful to reduce as many variables as possible when treating with BTXA.

What diluent volumes do you use for reconstituting vials of 300 U of aboBTX and 100 U of incoBTX and onaBTX?

Dr Cohen: I also use the same diluent volume whether I am reconstituting the 100-U vial of onaBTX or the 300-U vial of aboBTX because it makes the dose conversion of aboBTX to onaBTX mathematically easy. For most areas, I use a 1-mL dilution for the 300-U vial of aboBTX and the 100-U vial of onaBTX.

During my fellowship, Alastair Carruthers, MD, once stated that when treating glabellar lines, dilution is done for the convenience of the injector, whereas dose determines efficacy for the patient. Results of studies I have done are consistent with this idea. In a recent study
evaluating aboBTX,A, which Dr Kaufman and I conducted, efficacy, durability, and adverse events were similar when the 300-U vial was reconstituted with either 1.5 or 2.5 mL to administer a total dose of 50 U. In an earlier study in which I was involved with Alastair Carruthers, MD, and Jean Carruthers, MD, during my fellowship, we found no difference in efficacy comparing treatments performed using onaBTX reconstituted with 1, 3, 5, or 10 mL.13

Dr Kaufman: For injectors who are just starting out with BTXA injections, I recommend against using the 1-mL dilution for onaBTX. The reason is 2-fold: (1) working with the more concentrated solution makes it more difficult to achieve the desired dose precision; and (2) there is more waste if any of the preparation is lost accidentally.

I generally use 2.0 mL for onaBTX and aboBTX, and approximately 1.5 or 1.6 mL for incoBTX. As exceptions, I double the diluent volume when I am doing superficial intradermal injections for rosacea or when doing a Nefertiti lift to use in the very superficial aspect of the platysma because it wraps around the jawline. When I place the toxin superficially—for example, during Microtox procedures—I prefer to inject tiny amounts of neuromodulator, as low as 1 U per site. The goal is to treat the superficial, extremely thin muscle fibers without affecting the underlying deeper muscles. Other uses for hyperdiluted toxin could be for treating larger areas, in which the desire is to achieve even distribution of drug without reaching the end point of complete muscle paralysis. I love this approach for difficult-to-treat large foreheads, where complete paralysis might look unnatural or lead to flattened and lowered eyebrows.

Dr Shamban: I generally use 2.5 mL for onaBTX, 3.0 mL for aboBTX, and 2.0 mL for incoBTX. I like a more concentrated solution when treating the glabella in order to avoid spread into the frontalis and a splayed brow appearance. For glabellar treatments, I use just 1 mL to dilute 300 U of aboBTX or the 100-U vials of the other products.

Dr Glaser: I typically use 2.0 mL for onaBTX and incoBTX and 3.0 mL for aboBTX. I increase the amount of diluent I use when I am treating the platysma, or sometimes for the forehead, because I believe that increasing the injection volume for a given dose leads to a greater spread, or field of effect.

My advice to novice injectors is to start by choosing 1 diluent volume for all treatments and staying with it to develop expertise and understand the results. Then, they can think about tweaking the approach by experimenting with different volumes according to body location and anatomy to see what works in their hands.

Field of Effect

Movement of neurotoxin away from the site of injection has relevance for efficacy and safety of BTX,A injection, and it is discussed in the literature in various terms, such as spread, diffusion, and migration. Although these terms are sometimes used interchangeably, they are different by definition. Spread refers to rapid physical movement of toxin from the injection site and depends on injection-related variables, whereas diffusion is the slow kinetic dispersion beyond the original injection site (the toxin’s movement to receptors). Migration pertains to other mechanisms of movement, such as distal effects far from the injection point or retrograde axonal transport.

From a practical perspective, the overall area affected by injection of the neurotoxin—that is, the field of effect—is the issue of interest, regardless of the mechanism. Factors that might influence the field of effect include injection characteristics (eg, volume, speed, angle, depth, pressure, and needle gauge), dose and concentration of the neurotoxin, injection site, and postinjection massage/manipulation.17,18

Whether or not the field of effect differs among BTX,A products is controversial. There are inconsistent findings from comparative studies that investigated this question, and cross-study comparisons are hampered by a lack of standardized terminology and methodology differences among studies, including differences in treatment sites, outcome measures, conversion ratios, doses, and injection volumes. Despite differences in their molecular weight due to the presence or absence of NAPs, aboBTX, incoBTX, and onaBTX would be expected to have the same field of effect, given that NAPs are thought to dissociate from the core neurotoxin upon reconstitution. Consistent with this concept, an animal study found diffusion to adjacent muscles was similar for the 3 BTX,A products and was limited overall.19

A small pilot study evaluating patients being treated for forehead hyperhidrosis reported that aboBTX,A was associated with a greater field of anhidrotic effect than was onaBTX.A 20 Hexsel and colleagues conducted a series of comparative studies evaluating the field of effect following forehead injections of aboBTX,A and onaBTX,A using different conversion ratios and concluded that any differences between the products reflect the dose dependency of diffusion.21-23 A review of these and other studies also supports the notion that dose is the determining factor in the field of effect.24

Experts’ Clinical Perspectives

Dr Yoelin: From your experience, are there differences in field of effect with the various BTX,A products?

Dr Kaufman: I think there is no difference in spread or diffusion among the 3 BTX,A products when all other injection parameters are constant. If using a 3:1 conversion ratio for aboBTX,A:onaBTX,A, however, I might be giving a slightly higher dose of aboBTX,A vs onaBTX,A, and this might result in a slightly larger field of effect for aboBTX,A.

Dr Cohen: A study reporting similar outcomes with aboBTX,A treatment of crow’s feet, whether the dose was injected into 1 or 3 sites, might also be interpreted as evidence for spread with aboBTX,A.26 If dose and other potential variables are controlled, I do not think there is any theoretical basis or real evidence to support the idea that there might be field-of-effect differences among the BTX,A products. Having said that, however, aboBTX,A is my preferred product if I am treating patients who have a large fan-shaped arch of lateral canthal rhytides (in which the patients’ crow’s feet are extensive, often extending from the lateral orbital rim to the temple hair line, such as in endurance athletes who train and squat for long periods of time) because in my hands, it works better than the other toxins in that setting. I do not know if it is a dose-related phenomenon explained by the conversion ratio I am using or a product-related field-of-effect difference.

Immunogenicity

Because they are foreign proteins, both the 150-kDa neurotoxin and the NAPs can stimulate antibody formation.26 Antibodies to the neurotoxin that block its binding to neuronal cells might “neutralize” the neurotoxin’s activity. Antibodies to the NAPs, however, do not affect neurotoxin activity.27

According to the literature, factors associated with the development of neutralizing BTX,A antibodies include use of higher doses and a shorter interval between injections (< 2 months).29 Compared with therapeutic indications, such as for the treatment of dystonia, cosmetic BTX,A treatments use low doses, and reported rates of development of neutralizing antibodies in patients treated for cosmetic applications with any of the BTX,A products are low or absent (0% to 0.28%).28,29

Furthermore, the development of neutralizing antibodies to BTX,A does not absolutely result in lack of response, and patients might become nonresponders to BTX,A injections without evidence of developing antibodies to BTX,A.28,30 Loss of benefit in the latter situation might be explained by muscle adaptation, inadequate dosing, improper administration technique, and unrealistic patient expectations.24
Experts’ Clinical Perspectives

Dr Cohen: Anecdotally, I have heard of patients who became nonresponders after developing antibodies, but subsequently became responsive again after some period of time. I have several patients whom I treat for hyperhidrosis or a cosmetic indication (or both) using a shorter interinjection interval; in my experience, they do not seem to have any higher risk of becoming nonresponders. I think this immunogenicity risk significantly declined since onaBTXA had its protein load dramatically decreased in 1996.

Dr Glaser: It is likewise my experience using BTX-A for cosmetic treatments that shortening the injection interval does not lead to a decrease in or loss of response.

ABOUT Case: Treatment of Female Glabella

From the Files of Steve G. Yoelin, MD

A 23-year-old woman presented to reduce the appearance of glabellar rhytides. She was treated with incoBTXA. The 100-U vial of incoBTXA was reconstituted with 2.0 mL of bacteriostatic saline. Using a 33G 0.5-in syringe, a total dose of 30 U was injected across 7 sites as follows: 5 U into each medial corrugator, 5 U into each lateral corrugator, and 5 U into the procerus (Figure 1A). In addition, 2.5 U was injected into the orbicularis oculi at each lateral brow to enhance brow lifting (Figure 1B).

Manufacturers recommend dividing the BTXA dose across 5 sites when treating glabellar lines and using total doses of 20 U for incoBTXA and onaBTXA and 50 U for aboBTXA. This patient had a strong frown, so a higher dose was used to result in a greater duration of effect. In addition, it is safe to completely relax the glabellar complex. Although BTXA injection into the corrugator and procerus muscles will result in eyebrow elevation through relaxation of the depressor actions of the corrugator procerus muscle, administering 2 additional injections into the orbicularis oculi at each lateral brow results in enhanced browlifting by relaxing the depressor portion of the orbicularis oculi. Weakening of all of the depressors of the brow, central (including procerus) and lateral, will elevate the brow and can also result in reduction of lower forehead lines secondary to neurotoxin field of effect.

Eyelid ptosis can occur after BTXA treatment for glabellar lines. The risk can be minimized by keeping the injections into the corrugator muscle at least 1 cm above the brow and not lateral to the midpupillary line; applying digital pressure over the supraorbital rim during corrugator injection; and pointing the needle superiorly, away from the orbit. Eyelid ptosis is self-limiting; if treatment is required, an ophthalmic alpha-adrenergic agonist (eg, apraclonidine, 0.5%) can be used to elevate the ptotic eyelid.

ABOUT Case: Treatment of Male Glabella

From the Files of Joely Kaufman, MD

A 54-year-old man presented to the office complaining of a “weird” look to his forehead after he was treated at another office 10 days prior. He was not sure which BTXA he had received. On examination, he had elevation of the lateral brow at rest and extensive peaking on animation (Figure 2A). Two 7.5-U doses of aboBTXA were administered to normalize the frontalis activation and give him a straighter, more natural looking male brow (Figure 2B).

Figure 1. Glabellar rhytides were treated with 30 U of incobotulinumtoxinA as shown (A). A total dose of 30 U would be administered if onabotulinumtoxinA was used. A total dose of 90 U would be administered if abobotulinumtoxinA was used. Two injections of 2.5 U of incobotulinumtoxinA were injected at each lateral brow to enhance lifting (B).

Figure 2. Corrective treatment of brow arching in a male patient using 2 injections of abobotulinumtoxinA (7.5 U each) in the lateral portions of the frontalis (A) to achieve a smoother, more natural appearance (B).

Figure 3 demonstrates a 7-point injection pattern that could be followed on a male brow at the initial visit. A higher dose of neurotoxin is generally needed when treating men because they tend to have larger and stronger muscles than do women. For such injections using aboBTXA, the 300-U vial is reconstituted with 2 mL of diluent. A total aboBTXA dose would be 90 U—15 U injected at each of 5 sites in the glabellar complex and 7.5 U at each of 2 forehead sites. If using the other BTXA agents, the total dose for onaBTXA would be 30 U (5 U at each of the 5 glabellar sites and 2.5 U at each of the 2 forehead sites) and 42 U for incoBTXA (7 U for each glabellar site and 3.5 U per forehead site). If the tail of the corrugator is not strong, fewer units are injected at the lateral site.

Swelling, bruising, pain at the injection site, and headache can occur after all BTXA treatments, but these adverse events are generally mild and temporary. Complications specific to treatment of glabellar rhytides include eyebrow ptosis, upper eyelid ptosis, and eyelid sensory disorder.
ABOUT Case: Treatment for Perioral Rhytides
From the Files of Joel L. Cohen, MD

A 28-year-old woman presents for rejuvenation of perioral etch lines. She was treated with 6 U of onabotulinumtoxinA into the orbicularis oris muscle, using a 0.3-cc insulin needle with a 31G short hub (Figure 4A). Treatment with a low dose of BTX-A can help delay the development or worsening of permanent etching, and repeat treatments every few months might soften the appearance of existing lines (Figure 4B).

Figure 4. Perioral lines in the upper lip treated with 6 U of onabotulinumtoxinA as shown (A). In similar cases, total dose ranges for other botulinum neurotoxin type A agents are 10 to 22 U of abobotulinumtoxinA and 4 to 8 U of incobotulinumtoxinA. A low dose of botulinum neurotoxin type A softens the wrinkles in the upper lip without hindering function and expression (B).

Repetitive dynamic activity of the orbicularis oris muscle can lead to development of static radial perioral rhytides. BTX-A can relax the orbicularis oris, but the key is to use a low enough dose that will soften the musculature around the philtrum without significantly affecting the lateral orbicularis in a manner that will interfere with facial expressions and lip function. In a study investigating onabotulinumtoxinA treatment of hyperdynamic perioral lines, doses of 7.5 and 12.0 U were associated with similar improvement and duration, but the higher dose was associated with more adverse events, including changes in the ability to whistle, drink from a straw, purse the lips, and enunciate the letters “p” and “b.” There might also be feelings of general oral incompetence.

Appropriate patient selection is essential because of the potential for impairing muscle sphincter function. Clinicians should be very cautious about administering BTX-A in the orbicularis oris in certain patients, including wind instrument players, singers, broadcast journalists, and scuba divers. Such patients should be treated with a low dose, and only after thoroughly explaining the risks.

Optimal rejuvenation of the perioral region/lower face often requires a multimodal approach that combines BTX-A with additional procedures that address other age- or photodamage-related changes, including skin texture and laxity. According to clinician experience, the best use of BTX-A around the mouth is as an adjuvant therapy to resurfacing. Treating the orbicularis oris approximately 1 week before ablative resurfacing weakens the muscle and limits the extent to which it can contract, thereby preventing imprinting of lines in the skin during the healing process.24 Studies have also shown that pretreatment with neuromodulators before other procedures, including surgery involving skin cancer repairs, can lead to a more favorable effect on the cytokine and chemokine pathways, leading to a better result.25-27

ABOUT Case: Treatment of a Small Eye
From the Files of Ava Shamban, MD

A 52-year-old woman presented for treatment to correct eye size asymmetry. Note the smaller palpebral aperture on the left side of her face, which was thought to be at least partly hereditary; the differences in vermilion contour, which conferred a sneering appearance at rest; and the development of a dimple in the medial aspect of the upper left cheek upon animation due to synkinesis (Figures 5A and 5B). A total of 20 U of onabotulinumtoxinA (4 U/0.1 mL) was injected subcutaneously, using a 32G, 0.5-in aesthetic needle (Figure 5B). After BTX-A injection, the treated eye no longer appeared “squinty”, and its size resembled the contralateral eye (Figure 5C).

The patient was delighted with the outcome and continues to be treated every 4.5 months.

Figure 5. Eye asymmetry (A) is treated with a total of 20 U of onabotulinumtoxinA subcutaneously as shown (B). In similar cases, a total of 60 U of abobotulinumtoxinA or 20 U of incobotulinumtoxinA would be used. After the injection, the eye appeared more symmetrical (C).

Appropriate dose selection and proper placement of the neurotoxin is important to avoid complications, which can include lower lip dysfunction and change in lower lip contour. To minimize risk, the injections should be delivered into the inferior portion of the depressor anguli oris and lateral to the oral commissures. When selecting the appropriate dose of BTX-A to administer in areas of the lower face, a conservative approach is recommended in order to reduce the risk of administering toxin into the wrong muscle and to limit the field of effect that could result from administering a dose that is too high. Patient follow-up is crucial; having the patient return 2 to 3 weeks after the initial injection allows the clinician to determine if there is an optimal improvement, or to re-treat if the results are not optimal.

ABOUT Case: Treatment for Perioral and Chin Dimpling
From the Files of Dee Anna Glaser, MD

A 71-year-old man presented for lower face rejuvenation to address chin dimpling and downward turning of the oral commissures (Figure 6A). He was treated with abobotulinumtoxinA; a 300-mL vial was diluted with 3 mL of diluent. Using a 30G needle, a total of 30 U was injected in 3 equal aliquots into the depressor anguli oris muscles on either side of the face and the central mentalis muscles. When the patient returned after 2 weeks, he was pleased with the outcome (Figure 6B).

Figure 6. A total of 30 U of abobotulinumtoxinA to treat a dimpled chin and downturned corners of the mouth (A). Ten units were injected in each of the locations. To achieve similar results with other agents, 5 U of onabotulinumtoxinA or 6 U of incobotulinumtoxinA would be administered in each site. Major improvement was seen at follow-up 2 weeks after the injection (B).
ABOUT FACE Summary Points

Four BTXA products are commercially available for cosmetic use.
- They are not interchangeable.
- The products vary compositionally and in their manufacturing processes.
- Potency units are product specific.
- Differences in NAP content among products is thought to have no effect on efficacy or safety.

There is no universally accepted conversion ratio among BTXA products.
- Several reviews and experts suggest the ratio for aboBTXA:onaBTXA is between 2:1 and 3:1.
- Several reviews suggest the ratio for incoBTXA:onaBTXA is 1:1, but some experts believe it is higher (between 1:2:1 or 1:5:1).

Practitioners might vary the diluent volume used to reconstitute BTXA products, depending on site of injection, treatment goals, patient-specific characteristics, and mathematical ease of dose conversion among products.

References

Movement of BTXA away from the site of injection affects efficacy and safety outcomes.
- Field of effect, which represents the overall area affected, can vary according to injection characteristics, BTXA dose and concentration, injection site, postinjection massage, facial exercises, and manipulation.
- Some experts believe that reported differences in field of effect among products reflect differences in dose or other injection parameters rather than any product-specific characteristic.

Reported rates of neutralizing antibody development with cosmetic use of BTXA products is low or absent.

Careful dose selection and proper placement of BTXA injections is needed to achieve the desired cosmetic result and to avoid complications.
- Swelling, bruising, pain at the injection site, and headache can occur after all BTXA treatments.

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