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Clinical Analysis for Today's Skincare Specialists
March 2015 | VOL. 36, NO. 03 |

Clinical

Organizations partner on antibiotic awareness

Lisette Hilton | Senior Staff Correspondent

Advancing BCC treatment

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Organizations partner on antibiotic awareness

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The Centers for Disease Control and Prevention (CDC) is focusing efforts to promote responsible antibiotic use in dermatology. That's with good reason. Dermatologists, according to new government data, prescribe more antibiotics per provider than doctors in any other specialty, including primary care and pediatrics.

CDC's efforts to improve antibiotic use goes back to the mid-1990s, according to Lauri Hicks, D.O., an infectious

ANTIBIOTIC AWARENESS *see page* **37**

In This Issue

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+ the Art of Skin

Dermatologist sees art in histopathological images; strikes artistic chord with son

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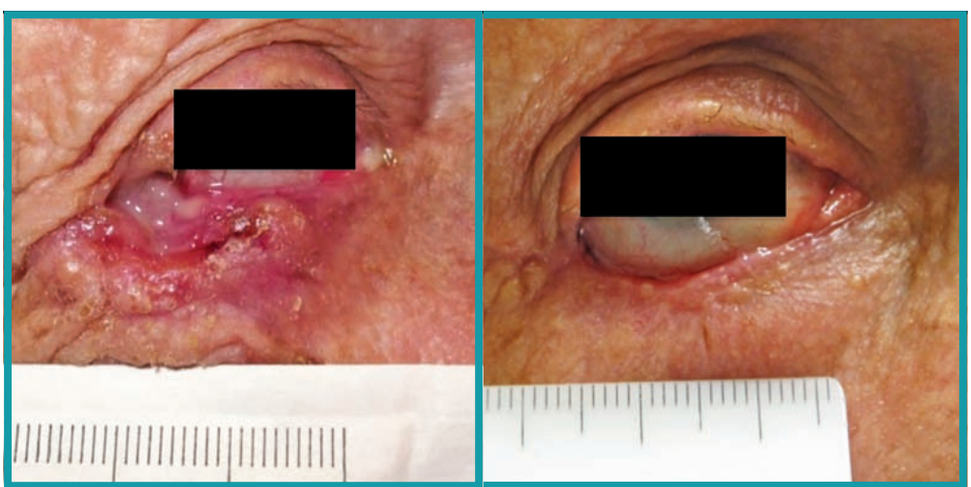
Advancing BCC treatment

New targeted agents are changing how physicians approach therapy



Neoadjuvant treatment might be the next clinical application of hedgehog inhibitors. An open-label study of 15 patients with large BCCs found that neoadjuvant vismodegib given for three to six months reduced the anticipated surgical defect size by 27% (P = 0.006).[4] Photo: Jean Y. Tang, M.D., Ph.D.

Caroline Helwick | Staff Correspondent

Recent understanding of the molecular basis of basal cell carcinoma (BCC) has propelled a fairly mundane skin cancer into the spotlight, with one targeted agent approved and another on its way for advanced, inoperable, sporadic BCCs. The success of the Hedgehog pathway inhibitors in treating BCC as well as basal cell nevus syndrome (BCNS) has changed patients' lives, according to experts who spoke at the 3rd Annual World Cutaneous Malignancies Congress (San Francisco, October 2014).

"The majority of BCCs are simple, but some become locally advanced and even metastasize. Traditionally the options were very limited for these patients, but with understanding of the Hedgehog pathway and its key role in essentially all BCCs, we can now intervene," said Aleksandar Sekulic, M.D., Ph.D., assistant professor of dermatology at the Mayo Clinic, Scottsdale, Arizona, who led the pivotal trial leading to the approval of vismodegib.

Hedgehog inhibitors are indicated for metastatic BCC (mBCC) patients or patients with locally advanced BCC (laBCC) where surgery is not considered appropriate. In the ERIVANCE clinical trial, which led to the FDA approval of vismodegib, the laBCC patients had (1) a lesion > 1 cm, (2) two or more recurrences and were considered unlikely to be cured with resection, or (3) a high likelihood that surgery will produce substantial morbidity or deformity.

EMERGING MOLECULAR LANDSCAPE

James Macdonald, M.D., dermatologist at the Central Utah Clinic in Provo (who is also a dermatopathologist), described how molecular insights revolutionized the approach to treating advanced BCC. Nearly all sporadic BCCs have mutations

BCC TREATMENT *see page* **74**

UBM

INDICATION

XEOMIN® (incobotulinumtoxinA) for injection, for intramuscular use is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

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

CONTRAINDICATIONS

XEOMIN is contraindicated in patients with a known hypersensitivity to the active substance botulinum toxin type A or to any of the components in the formulation and in the presence of infection at the proposed injection site(s), as injection could lead to severe local or disseminated infection.

WARNINGS AND PRECAUTIONS

- The potency units of XEOMIN are not interchangeable with other preparations of botulinum toxin products. Therefore, units of biological activity of XEOMIN cannot be compared to or converted into units of any other botulinum toxin products.
- Hypersensitivity reactions have been reported with botulinum toxin products (anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea). If serious and/or immediate hypersensitivity reactions occur further injection of XEOMIN should be discontinued and appropriate medical therapy immediately instituted.
- Treatment with XEOMIN and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. When distant effects occur, additional respiratory muscles may be involved. Patients may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. Dysphagia may persist for several months, which may require use of a feeding tube and aspiration may result from severe dysphagia *[See Boxed Warning]*.
- **Glabellar Lines:** Do not exceed the recommended dosage and frequency of administration of XEOMIN. In order to reduce the complication of ptosis the following steps should be taken:
  - » avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes;
  - » corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.
- Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of XEOMIN.
- XEOMIN contains human serum albumin. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and Creutzfeldt-Jakob disease (CJD). No cases of transmission of viral diseases or CJD have ever been reported for albumin.

ADVERSE REACTIONS

Glabellar Lines: The most commonly observed adverse reaction (incidence ≥ 2% of patients and greater than placebo) for XEOMIN was Headache (5.4%).

DRUG INTERACTIONS

Concomitant treatment of XEOMIN and aminoglycoside antibiotics, spectinomycin, or other agents that interfere with neuromuscular transmission (e.g., tubocurarine-like agents), or muscle relaxants, should be observed closely because the effect of XEOMIN may be potentiated. The effect of administering different botulinum toxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

USE IN PREGNANCY

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. XEOMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PEDIATRIC USE

The safety and effectiveness of XEOMIN in patients less than 18 years of age have not been established.

Please see Brief Summary of full Prescribing Information on the following pages.

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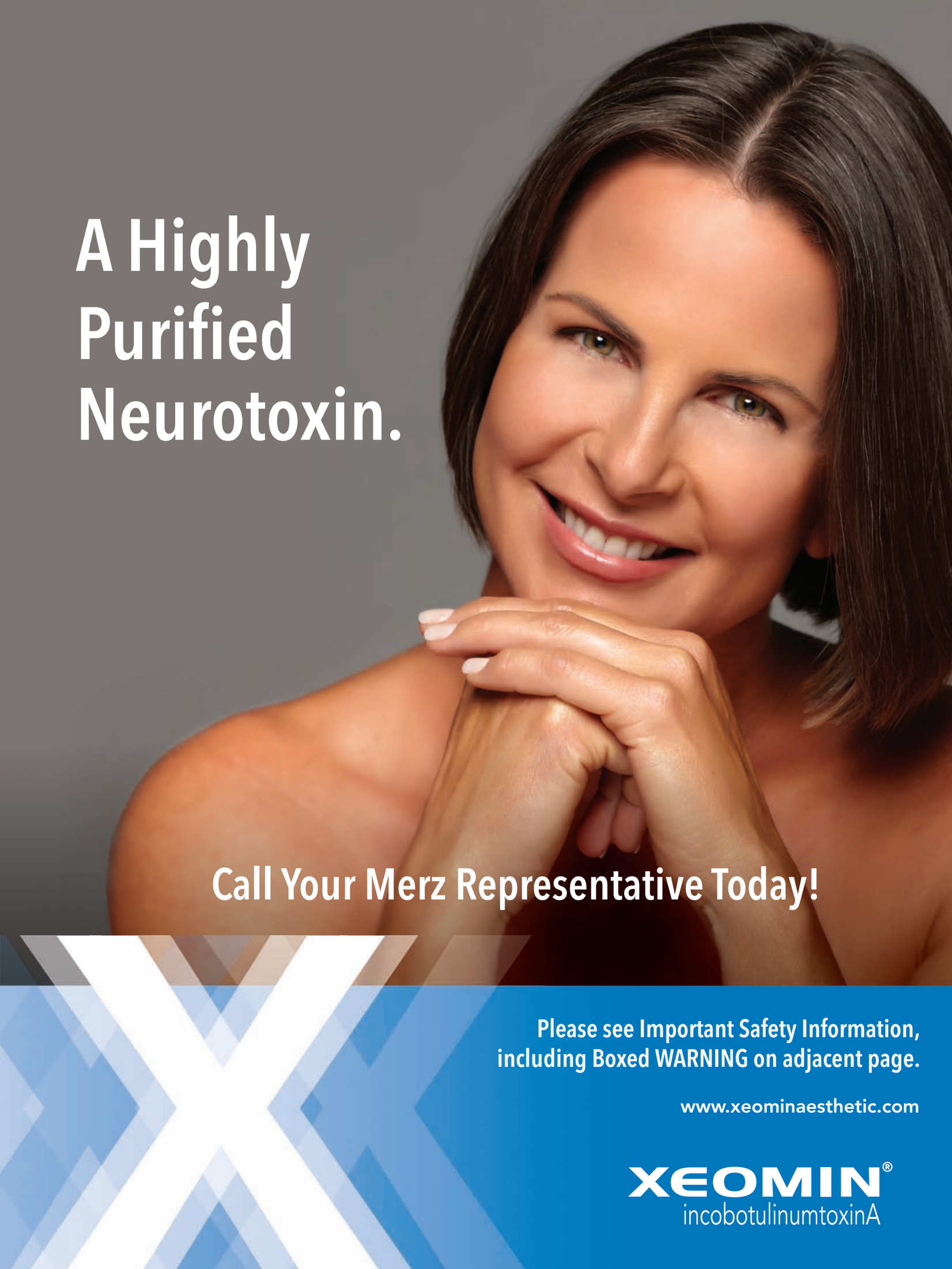
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Postmarketing reports indicate that the effects of XEOMIN and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia,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

CONTRAINDICATIONS

Hypersensitivity-Use in patients with a known hypersensitivity to the active substance botulinum neurotoxin type A, or to any of the excipients (human albumin, sucrose), could lead to a life-threatening allergic reaction. XEOMIN is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation *[see Warnings and Precautions]*.

Infection at Injection Site-Use in patients with an infection at the injection site could lead to severe local or disseminated infection. XEOMIN is contraindicated in the presence of infection at the proposed injection site(s).

WARNINGS AND PRECAUTIONS

- **Spread of Toxin Effect-**Postmarketing safety data from XEOMIN and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties *[see Boxed Warning (above)]*.
- **Lack of Interchangeability between Botulinum Toxin Products-**The potency Units of XEOMIN are specific to the preparation and assay method utilized. They are not interchangeable with the other preparations of botulinum toxin products and, therefore, Units of biological activity of XEOMIN cannot be compared to or converted into Units of any other botulinum toxin products assessed with any other specific assay method.
- **Hypersensitivity Reactions-**Hypersensitivity reactions have been reported with botulinum toxin products (anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea). If serious and/or immediate hypersensitivity reactions occur further injection of XEOMIN should be discontinued and appropriate medical therapy immediately instituted.
- **Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia-**Treatment with XEOMIN and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised. In general, limiting the dose injected into the sternocleidomastoid muscle may decrease the occurrence of dysphagia. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin *[see Warnings and Precautions and Adverse Reactions in Full Prescribing Information for more information]*.
- **Pre-existing Neuromuscular Disorders and other Special Populations-**Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of XEOMIN *[see Adverse Reactions]*.
- **Corneal Exposure, Corneal Ulceration, and Ectropion in Patients Treated with XEOMIN for Blepharospasm-**Reduced blinking from injection of botulinum toxin products in the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means. Because of its anticholinergic effects, XEOMIN should be used with caution in patients at risk of developing narrow angle glaucoma. To prevent ectropion, botulinum toxin products should not be injected into the medial lower eyelid area. Ecchymosis easily occurs in the soft tissues of the eyelid. Immediate gentle pressure at the injection site can limit that risk.
- **Risk of Ptosis in Patients Treated with XEOMIN for Glabellar Lines-**Do not exceed the recommended dosage and frequency of administration of XEOMIN. In order to reduce the complication of ptosis the following steps should be taken:
  - » Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
  - » Corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.
- **Human Albumin and Transmission of Viral Diseases-**This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

ADVERSE REACTIONS

The following adverse reactions to XEOMIN are discussed in greater detail in other sections of the labeling:

- Hypersensitivity *[see Contraindications and Warnings and Precautions]*
- Spread of Effects from Toxin *[see Warnings and Precautions]*

Glabellar Lines In three placebo-controlled trials in 803 subjects with glabellar lines, 535 subjects received a single dose of 20 Units XEOMIN and 268 subjects received placebo. XEOMIN treated subjects were 24 to 74 years old, and were predominantly female (88%). The most frequent adverse reactions in XEOMIN treated subjects were: headache 29 (5.4%), facial paresis 4 (0.7%), injection site hematoma 3 (0.6%) and eyelid edema 2 (0.4%). Four serious adverse events occurred in two placebo-treated subjects. Six XEOMIN treated subjects experienced six serious adverse events. All serious adverse events were assessed as unrelated to study drug. The adverse reactions below reflect exposure to XEOMIN with glabellar lines in placebo-controlled studies. Adverse reactions are adverse events in which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 4: Adverse Reactions in Placebo-Controlled Trials

Adverse reactions	XEOMIN (N=535) (%)	Placebo (N=268) (%)
Nervous system disorders	**33 (6.1)**	**6 (2.2)**
Headache[1]	29 (5.4)	6 (2.2)
Facial paresis (brow ptosis)	4 (0.7)	0
General disorders and administration site conditions	**5 (0.9)**	**2 (0.7)**
Injection site hematoma	3 (0.6)	0
Injection site pain	1 (0.2)	0
Facial pain	1 (0.2)	0
Injection site swelling	0	1 (0.4)
Sensation of pressure	0	1 (0.4)
Eye disorders	**5 (0.9)**	**0**
Eyelid edema	2 (0.4)	0
Blepharospasm	1 (0.2)	0
Eye disorder	1 (0.2)	0
Eyelid ptosis	1 (0.2)	0

In open label, multiple dose trials, adverse reactions were reported for 105 of the 800 subjects (13.1%). Headache was the most common adverse reaction, reported for 57 subjects (7.1%), followed by injection site hematoma in 8 subjects (1.0%). Adverse reactions reported in less than 1% of subjects were: facial paresis (brow ptosis), muscle disorder (elevation of eyebrow), injection site pain, and eyelid edema.

Immunogenicity-As with all therapeutic proteins, there is a potential for immunogenicity.

Postmarketing Experience-The following adverse reactions have been reported during post-approval use with XEOMIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: eye swelling, eyelid edema, dysphagia, nausea, flu-like symptoms, injection site pain, injection site reaction, allergic dermatitis, localized allergic reactions like swelling, edema, erythema, pruritus or rash, herpes zoster, muscular weakness, muscle spasm, dysarthria, myalgia and hypersensitivity.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with XEOMIN. Coadministration of XEOMIN and aminoglycoside antibiotics or other agents interfering with neuromuscular transmission, e.g., tubocurarine-type muscle relaxants, should only be performed with caution as these agents may potentiate the effect of the toxin. Use of anticholinergic drugs after administration of XEOMIN may potentiate systemic anticholinergic effects. The effect of administering different botulinum toxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of XEOMIN.

USE IN SPECIFIC POPULATIONS

Pregnancy-Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. XEOMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers-It is not known whether botulinum toxin type A is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XEOMIN is administered to a nursing woman.

Pediatric Use-Safety and effectiveness of XEOMIN in patients less than 18 years of age have not been established *[see Warnings and Precautions].*

Geriatric Use-Glabellar Lines There are limited clinical data with XEOMIN in subjects over 65 years of age and over in clinical studies with glabellar lines. Of the total number of subjects in the placebo-controlled clinical studies GL1 and GL2, 21 (4%) subjects were 65 and over. Efficacy was observed in 20% (3/15) of XEOMIN subjects 65 years and over. For the entire safety database of geriatric subjects, there was no increase in the incidence of adverse events related to treatment with XEOMIN.

OVERDOSAGE

Excessive doses of XEOMIN may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of the respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis *[see Warnings and Precautions].* Symptomatic treatment may be necessary. Symptoms of overdose are not likely to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis. In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 770-488-7100. More information can be obtained at http://www.cdc.gov/ncidod/srp/drugs/formulary.html#1a.

Please visit www.xeomin.com for full Prescribing Information.

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

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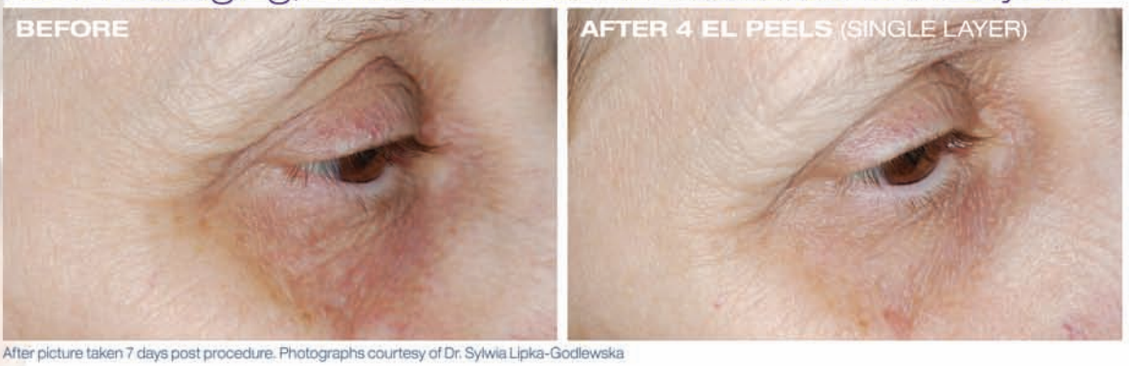

After picture taken 7 days post procedure. Photographs courtesy of Dr. Sylwia Lipka-Godlewska

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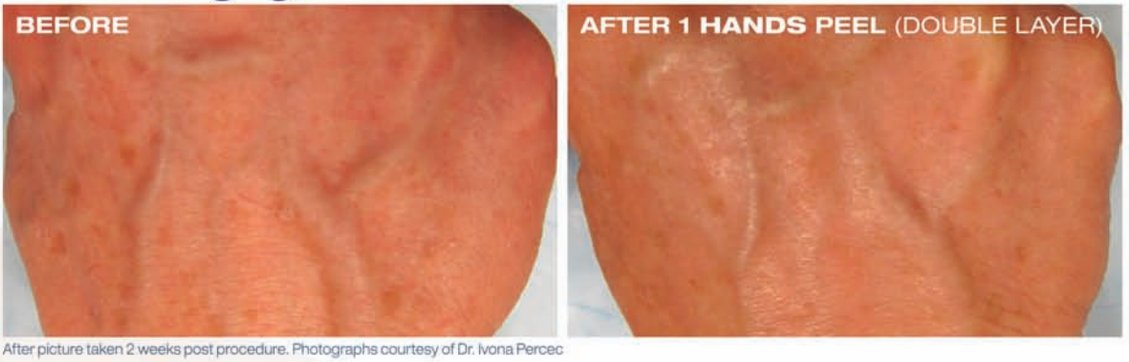

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Elaine C. Siegfried, M.D.,
is professor of pediatrics and dermatology, Saint Louis University Health Sciences Center, St. Louis, Mo.

Easy-to-remember 'isms' aid patient communication

With age and experience have come increased clinical efficiency. At some point, making medical decisions became faster and easier way before I was able to condense the time it takes to explain why. Years of repeating justifications to students, residents, and patients have honed my explanations into "isms". These are kernels of truth packed into a few easy-to-remember words, as an efficient way to communicate.

Most experienced clinicians have their own "isms". My collection includes those gleaned from my mentors as well as from esteemed colleagues. In some cases, Google helped verify the origin of an "ism". If your recognize one of yours, I welcome feedback.

PREVENTIVE CARE "ISMS"

The "isms" I use most often are about common conditions that are either best managed with preventive care or are difficult to treat. Convincing some patients (and their parents) to adhere to preventive treatment or to opt against aggressive procedures requires a good explanation. Below are several that have served me well.

For counselling parents, I use the term "anticipatory guidance." This often includes monitoring, rather than intervening. With regards to hemangiomas, Milton Waner, M.D., countered the obsolete "benign neglect" approach with, "There is nothing benign about neglect." Ilona Frieden, M.D., coined a related "ism" that she called "active non-intervention" as a more supportive approach to hemangiomas. This is also applicable to many other conditions that may benefit from close monitoring.

"There's no glory in prevention." Providing anticipatory guidance does not often receive the same degree of credit as quick-fix interventions, like a surgical procedure, because the benefits are difficult to prove. But prevention is often the best treatment. I use this phrase to encourage use of emollients and bleach baths for children with eczema, for advising children in wart-prone families to wear water shoes at public pools, and to convince parents of infants with high-risk distribution hemangioma precursors to start propranolol.

I have a few mottos for parents who are unnecessarily concerned about a skin lesion, and insist on blood tests or a painful procedure for their non-assenting child:

"Radiologists know that spots are common on bones and internal organs. People worry more about spots on the skin just because they can see them." Some are ditzels of no consequence, while others are iceberg tips. I let parents know that the visual prominence of the lesion is not necessarily proportional to its risk, and that "It's my job to know when to worry."

Sarah Jensen, M.D., (who completed her residency in my department more than a decade ago) tells patients "There are a multitude of treatments for warts, because none of them are very successful." My take: "Warts are common. If there was a uniformly effective treatment, your doctor would have offered it. And if I could guarantee that one treatment would work, no matter how difficult or uncomfortable, or if treating now would prevent a bad outcome, I would hold your child down, even kicking and screaming, to get it done."

Only after seeing thousands of patients with skin disease of similar and widely varying impact has it become obvious that, "What you have and the way you feel about it" are unrelated.

It is important to acknowledge a patient's and parents' perceptions and to help guide them to a rational decision about the risk-benefit ratio of evaluation and treatment options. So, "Never make the evaluation or treatment worse than the disease" is a valuable sequel. Several trainees reminded me about teaching them to: "Treat the patient, not the parent."

Many remembered my molluscum BOTE (Beginning of the End) sign.[1] This reflects the power of catchy phrase and Googlable publication.

ECZEMA-ISMS

Patients with eczema fill 50% of my clinic schedule, but take 80% of my time. So I have had a lot of practice in honing my eczema-isms.

"Eczema doesn't kill you, but it can ruin your life" applies to families and patients with severe eczema. I hope it communicates that I feel their pain, including the lack of a well-defined safe and effective treatment.

The cosmeceutical-industrial complex reflects the strongest incentive to produce topical products for people with sensitive skin: marketability. Explaining this to patients allows me to equate product appeal based on qualities such as packaging, odor, tactile quality, and "natural" ingredients with the qualities of other products like candy and cigarettes (rather than safety or health-related benefits). More than one resident mentioned my related "poison ivy is natural" anology.

My newly board-certified colleague, Stephanie Frisch, M.D., translated this "ism" into "What you don't use is more important than what you do use."

For patients with eczema, identifying and avoiding contact allergens is an important aspect of initial management. While patterned involvement can suggest likely topical allergens, I refer to erythroderma as "being on fire". Tinatin Gotsiridze, M.D., reminded me of waiting until "the smoke clears" to see a suggestive pattern.

I often see frustrated patients with severe eczema who have been treated for

COLLECTIVE "isms" *see page* 16

NEW

FOR THE TREATMENT OF COMEDONAL AND INFLAMMATORY ACNE

ONEXTON™

(clindamycin phosphate and benzoyl peroxide) Gel,1.2%/3.75%

For more information,
please visit **www.OnextonGel.com**

INDICATION

ONEXTON (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75% is indicated for the topical treatment of acne vulgaris in patients 12 years of age or older.

IMPORTANT SAFETY INFORMATION

- ONEXTON Gel is contraindicated in patients with a known hypersensitivity to clindamycin, benzoyl peroxide, any component of the formulation or lincomycin.
- ONEXTON Gel is contraindicated 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 or systemic clindamycin. ONEXTON Gel should be discontinued if significant diarrhea occurs.
- Orally and parenterally administered 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 burning sensation, contact dermatitis, pruritus and rash. All occurred in <0.5% of patients.
- ONEXTON Gel should not be used in combination with erythromycin-containing products because of its clindamycin component.
- Patients should be advised to avoid contact with the eyes or mucous membranes.
- Patients should avoid exposure to natural sunlight and avoid artificial sunlight (tanning beds or UVA/B treatment) while using ONEXTON Gel.

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

VALEANT®
Dermatology

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ONEXTON™
(clindamycin phosphate and benzoyl peroxide)
Gel,1.2%/3.75%

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ONEXTON Gel safely and effectively. See full prescribing information for ONEXTON Gel.

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]

WARNINGS AND PRECAUTIONS

Colitis/Enteritis

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 significant 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)

	Before Treatment (Baseline)			Maximum During Treatment			End of Treatment (Week 12)		
	Mild	Mod.*	Severe	Mild	Mod.*	Severe	Mild	Mod.*	Severe
Erythema	20	6	0	28	5	<1	15	2	0
Scaling	10	1	0	19	3	0	10	<1	0
Itching	14	3	<1	15	3	0	7	2	0
Burning	5	<1	<1	7	1	<1	3	<1	0
Stinging	5	<1	0	7	0	<1	3	0	<1

*Mod. = 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 irritancy 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/m^2, 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/m^2, 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

Carcinogenicity, 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.

Carcinogenicity 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, and 40 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, 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 keratoacanthoma 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, 4.8, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m^2, 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/m^2) revealed no effects on fertility or mating ability.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

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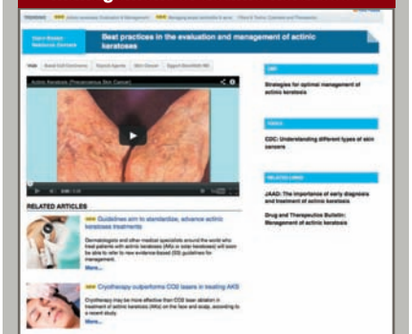
Best practices in the evaluation and management of actinic keratoses



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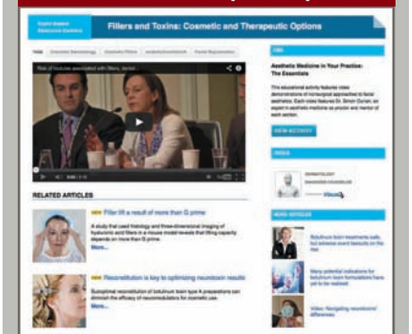

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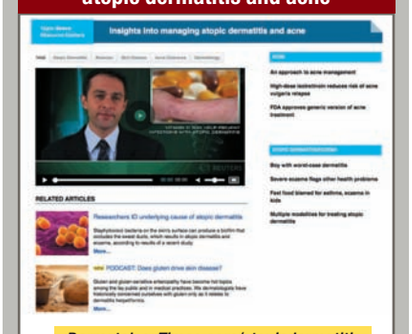

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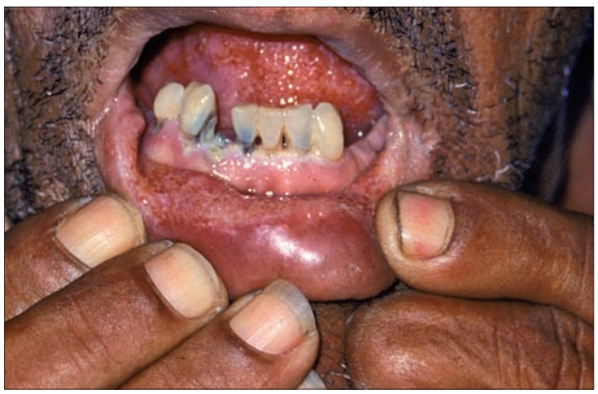
What's your diagnosis?



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A 53-year-old farmer is complaining of some rough skin on his lips and on his tongue that occasionally bleeds.

CHOOSE ONE:

- LYMPHOMA
- PARACOCCIDIOIDOMYCOSIS
- BLASTOMYCOSIS

bit.ly/marchdiagnosis

VIDEOS

E-mazing medical marketing minute

Tim Sawyer, president of Crystal Clear Digital Marketing sits down with Jacob Boeckmann, M.D., of Facial Aesthetic Concepts in Orange County, Calif. In this episode, the two discuss the value of high quality web content to inform and educate both new and existing patients and the value of embracing the benefits of social technology.

bit.ly/e-mazing-march-interview

How often do you go off-label when you use laser devices in your practice?

Vegas Cosmetic Surgery 2014 Laser Roundtable experts E. Victor Ross, M.D., Michael Gold, M.D., and David Goldberg, M.D., J.D., share their answers.

bit.ly/off-label-devices

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LAST MONTH'S DIAGNOSIS:
Coxsackievirus

Learn more at: bit.ly/februarydiagnosis

Blog

Are visual flashes related to injectable fillers around the eyes?

Jason Emer, M.D.

A recent realself.com post stated that shortly after filler injections (Restylane) under the eyes and in the glabella, the patient experienced flashes of light in their visual field with a change in vision. They inquired as to if this was possibly due to the filler injection procedure. I suggested this patient seek out immediate evaluation. Read why.

bit.ly/marchcosmeticconsiderations

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IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on 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. Body weight loss of ≥10% occurred in 2% (16/784) of patients treated with Otezla compared to 1% (3/382) 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 (eg, 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

Please turn the next page for Brief Summary of Full Prescribing Information.

References: 1. Schafer PH, Parton A, Capone L, et al. *Cell Signal*. 2014;26:2016-2029. **2.** Otezla [package insert]. Summit, NJ: Celgene Corporation; 2014. **3.** Data on file, Celgene Corporation.

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- Otezla® (apremilast) was 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 or placebo twice daily for 16 weeks, after a 5-day titration[2,3]
- Inclusion criteria: Age ≥18 years, BSA involvement ≥10%, sPGA ≥3, PASI score ≥12, candidates for phototherapy or systemic therapy[2]
- PASI-75 response at week 16 (primary endpoint)[2,3]
  - Study 1: Otezla 33% vs placebo 5% ($P < 0.0001$)
  - Similar PASI-75 response was achieved in Study 2

BSA, body surface area; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment.

IMPORTANT SAFETY INFORMATION

Contraindications

- Otezla® is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Warnings and Precautions

- Depression: Treatment with Otezla is associated with an increase in adverse reactions of depression

During clinical trials, 1.3% (12/920) of patients treated with Otezla reported depression compared to 0.4% (2/506) on placebo; 0.1% (1/1308) of Otezla patients discontinued treatment due to depression compared with none on placebo (0/506). Depression was reported as serious in 0.1% (1/1308) of patients exposed to Otezla, compared to none in placebo-treated patients (0/506). Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. One patient treated with Otezla attempted suicide; one patient on placebo committed suicide

Carefully weigh the risks and benefits of treatment with Otezla

Continued to the left

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Otezla®
(apremilast) 30mg tablets

Rx Only

OTEZLA® (apremilast) tablets, for oral use
The following is a Brief Summary; refer to Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

OTEZLA 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

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% (1/1308) of patients treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated patients (0/506). Depression was reported as serious in 0.1% (1/1308) of patients exposed to OTEZLA, compared to none in placebo-treated patients (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) 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% (96/784) of patients treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% (16/784) of patients treated with OTEZLA 30 mg twice daily compared to 1% (3/382) 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 of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended [see *Drug Interactions (7.1)* 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 trial 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 ≥1% of Patients on OTEZLA and With Greater Frequency Than in Patients on Placebo; up to Day 112 (Week 16)

Preferred Term	Placebo (N=506) n (%)	OTEZLA 30 mg BID (N=920) n (%)
Diarrhea	32 (6)	160 (17)
Nausea	35 (7)	155 (17)
Upper respiratory tract infection	31 (6)	84 (9)
Tension headache	21 (4)	75 (8)
Headache	19 (4)	55 (6)
Abdominal pain*	11 (2)	39 (4)
Vomiting	8 (2)	35 (4)
Fatigue	9 (2)	29 (3)

(continued)

Table 3: Adverse Reactions Reported in ≥1% of Patients on OTEZLA and With Greater Frequency Than in Patients on Placebo; up to Day 112 (Week 16)

Preferred Term	Placebo (N=506) n (%)	OTEZLA 30 mg BID (N=920) n (%)
Dyspepsia	6 (1)	29 (3)
Decrease appetite	5 (1)	26 (3)
Insomnia	4 (1)	21 (2)
Back pain	4 (1)	20 (2)
Migraine	5 (1)	19 (2)
Frequent bowel movements	1 (0)	17 (2)
Depression	2 (0)	12 (1)
Bronchitis	2 (0)	12 (1)
Tooth abscess	0 (0)	10 (1)
Folliculitis	0 (0)	9 (1)
Sinus headache	0 (0)	9 (1)

*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. **Pediatric use:** The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established. **Geriatric use:** Of the 1257 patients who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis patients were 65 years of age and older, including 9 patients who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly patients ≥65 years of age and younger adult patients <65 years of age in the clinical trials. **Renal Impairment:** OTEZLA pharmacokinetics were not characterized in patients with mild (creatinine clearance of 60-89 mL per minute estimated by the Cockcroft–Gault equation) or moderate (creatinine clearance of 30-59 mL per minute estimated by the Cockroft–Gault equation) renal impairment. The dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment (creatinine clearance of less than 30 mL per minute estimated by the Cockroft–Gault equation) [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*]. **Hepatic Impairment:** Apremilast pharmacokinetics were characterized in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

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.

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Are you liable for your covering physician's alleged negligence?

Dr. Skin is a dermatologic surgeon and head of a resident training program at a well-recognized academic center. He performed a surgical excision on an eyelid growth on Mrs. Smith. Mrs. Smith is a healthy 50-year-old woman and she is not on any medication. Her visual acuity, prior to the procedure, was corrected quite easily with contact lenses.

The surgical procedure went smoothly and lasted less than one hour. Mrs. Smith left the office without any difficulty at 11 a.m. in the morning. Dr. Skin called Mrs. Smith at 4 p.m. to check on her post-operative course. She reported some ecchymosis, but otherwise no difficulties. Dr. Skin called his covering physician (Dr. Ecchymosis) at 6 p.m. and signed out to him. At that time, they discussed Mrs. Smith's surgery.

Mrs. Smith called Dr. Skin's office at 8 p.m. with a concern about her surgery. Dr. Skin's answering service immediately paged Dr. Ecchymosis, the covering physician. Dr. Ecchymosis returned the page within 15 minutes. In their discussion, Mrs. Smith described the ecchymosis. She also now described significant blurring of vision in her right eye. When she tried to correct her vision with an old set of glasses, she found no improvement. Dr. Ecchymosis discussed the situation with Mrs. Smith and reassured her that such findings are not unusual. He suggested that she try to go to sleep and call Dr. Skin in the morning.

The next morning, Mrs. Smith woke to find she had no vision in her right eye. She immediately returned to Dr. Skin's office. From there, she was sent to an ophthalmologist. He noted that she had evidence of a retrobulbar hemorrhage. Although he immediately performed surgery to correct the problem, Mrs. Smith's blindness was permanent. Had Dr. Skin and/or Dr. Ecchymosis made the correct diagnosis and referred Mrs. Smith for immediate surgery, the blindness would have been prevented.

Mrs. Smith brought a negligence cause of action against both Dr. Skin and the covering physician, Dr. Ecchymosis. The basis of her case against Dr. Skin was that he was in a "joint-venture" with Dr. Ecchymosis. After all, they cover each other's practices every night. It should be noted that there are no payments made for the cross-coverage and the two practices share neither staff nor facilities.

IS DR. SKIN LIABLE?

Whether Dr. Skin is liable will generally depend on the acts of the on-call physician who allegedly committed the act of negligence, as well as applicable law. Imputing of Dr. Skin's liability in this situation will generally turn on the degree to which the actions of the on-call physician were influenced or controlled by Dr. Skin.

For example, if the on-call physician consulted with Dr. Skin and, in reliance on his judgment, injured Mrs. Smith, liability might be attached to both physicians.

However, the mere fact that at various times different physicians are on-call for the same patients, will not typically expose them to liability for the acts of a physician who was allegedly negligent during his or her on-call shift.

A joint venture is typically defined as two or more parties combining property and/or services in a joint undertaking for profit with the rights of mutual control.

All joint venturers may be held liable for actions of individual venturers. Physicians who share on-call are not usually considered to be engaged in a joint venture that would subject them to liability for each other's actions.

CONSIDERING PRECEDENT

In Rossi v. Oxley, 495 SE2d 39 (Ga 1998), a patient sued a physician who participated in an on-call arrangement with other independent physicians. Each on-call physician billed patients directly for any services provided. The Georgia Supreme Court held that a joint venture did not exist between the physicians. Liability could not be extended on the basis of a simple on-call arrangement. The court noted that the mutual control element was not satisfied since the patient's physician could not control the on-call physician's judgment in treating the patient.

In addition, the court noted, even if it could be argued that both physicians "controlled" the patient, it would reject any vicarious liability for sharing of on-call duties for public policy reasons. A finding of liability, the court noted would discourage the practice of making on-call arrangements and therefore decrease the availability of quality care, increase costs or both.

Had Dr. Skin chosen Dr. Abdomen, a general surgeon, as the on-call physician, a cause of action in negligence may have been present against Dr. Skin.

In this case, the question becomes one of Dr. Skin's duties in providing on-call coverage for his patients. Dr. Skin had a duty to provide a covering physician that understands the dermatologic surgical procedure and its potential complications. If the general surgeon would not generally be expected to understand the surgical procedure and its complications, Dr. Skin may have breached his duty of reasonable care to Mrs. Smith by providing Dr. Abdomen as a covering physician. If that breach in duty led to the blindness, then Dr. Skin would be also liable for the negligence.

A similar situation would exist in a multi-specialty group where there is often cross-coverage for on-call duty. In such a situation, Dr. Skin might have no control over

LEGAL EAGLE *see page* 16

LEGAL EAGLE:
Are you liable for your covering physician's alleged negligence? *from page* **15**

the choice of the covering physician. If the doctor on call was a vascular surgeon, Dr. Skin might not be able to escape liability for a negligent cause of action imputed to the vascular surgeon. In such a situation, Dr. Skin would be better off to follow his own patients.

RESIDENT RESPONSIBILITY

In training programs, it is not unusual to have resident or fellow physicians cover for senior faculty physicians. In that situation the resident or fellow (trainee) physician is often paid a salary during the training program. Occasionally, the trainee physician is not paid for the position. In either situation, if the trainee physician errs, the supervising physician might share liability with the trainee physician. In this situation, the laws of agency apply. The threshold question becomes one of whether the trainee physician is an agent of the supervising physician. If the trainee was performing an act that was in the scope of his "employment" as a trainee physician, and if it was in the furtherance of this employment relationship, then he is an agent of the supervising physician. In a cause of action against both physicians for negligence, both physicians might share culpability. If the trainee undertakes actions that are not in his role as an agent, then the trainee himself will have sole liability.

In the hypothetical situation described above, the fact pattern could be changed to one of Dr. Ecchymosis being a resident in training under Dr. Jones. If evaluating post-excision patients is in the scope of Dr. Ecchymosis' employment, and he performs a negligent act, then both Dr. Skin and Dr. Ecchymosis will share liability. If Dr. Ecchymosis performs an act not within the scope of his training, or his employment with Dr. Skin, then Dr. Skin will escape culpability. Dr. Ecchymosis will be solely liable.

If, in another example, an ophthalmology practice contains both general ophthalmologists and one oculoplastic surgeon, liability would rest on both the treating cosmetic surgeon and the covering general ophthalmologist if the retrobulbar hemorrhage was not recognized by the general ophthalmologist.

The same precarious situation can potentially occur in a dermatology practice. A typical group practice situation might have a cosmetic surgical dermatologist, several general dermatologists and a dermatopathologist/dermatologist. On a typical day, the surgical dermatologist might perform a liposuction procedure under general anesthesia. The "partner" dermatopathologist/dermatologist on-call that evening might know nothing about liposuction. If the patient developed complications from the procedure, the significance of which would have been minimized by early detection, then liability will be shared between both the covering dermatopathologist and the surgical dermatologist. The surgeon will not be able to suggest that it was not his turn for coverage. In such a practice, coverage for surgical procedures might be best undertaken by those with expertise in those areas. **DT**

COLLECTIVE "ISMS":
Dialogue that aids patient communication *from page* **8**

years with cycles of prednisone and antibiotics. This approach gives them quick relief followed by rebound flares. I call this the "roller coaster" when explaining my approach to "get off the roller coaster" and achieve more enduring remission.

MEDICATION USE "ISMS"

Other "isms" are related to the important issue of using an appropriate quantity of medication. These include: "If you use too much it's bad for you," and "if you use too little, it won't work".

For parents hesitant to use topical corticosteroids or calcineurin inhibitors, I remind them that too much water, sun or even food can kill you. (I have to give credit to Parcelsus for his 500 year old "ism": "All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison.") Dr. Frisch, modified this "ism" to: "It's not what you use, it's how much". She reminded me that underuse of topicals is also applicable to acne. Pearl Kwon, M.D., shifts responsibility to the patient by saying: "The M.D. after my name does stand for medical doctor, not magic doctor."

MISCELLANEOUS "ISMS"

With regard to making difficult decisions about recommending higher-risk treatment for conditions with a spectrum of severity, such as systemic therapy for eczema or intervention for disfiguring birthmarks, I equate it to pornography: "You know it when you see it."

Lesions that are not disfiguring can be considered "distinguishing" in the same category as hair color, eye color, and even piercings or tattoos. Alanna Bree, M.D., reassures patients with concerns about distinguishing features with: "Your beauty comes from the inside, not the outside."

I often try to put painful procedures into perspective for needle-phobic children by telling them that the procedure requires a little "pinch". If this elicits fright, I ask them "What do you think hurts most?" Then I tell them the answer: "feeling scared". That aphorism is too brief for some children, so I distract them with a true story about the patient that taught it to me. He was a husky 8-year-old boy who came to my clinic from the emergency room in a wheelchair because he had joint pain that made it difficult to walk. His legs were covered in giant bullae. At that time, I used the word "shot" as an acid-test to help evaluate a child's degree of anxiety. When he heard that word, he leaped off the table and ran for the door. Ultimately, the biopsy required four people to hold him down. After I injected the lidocaine and said, "There, it's done." He replied, "Was that all? Why didn't you tell me?" Courtney Tobin, M.D., says it a little simpler: "The anticipation is worse than the procedure."

My daughter offered a few of my Dr. Mom "isms": "Put petroleum jelly on it." And, "Don't worry unless it gets worse, doesn't go away, or changes." **DT**

Read more of Dr. Siegfried's discussion of others' "isms" online at: *bit.ly/dermisms*

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The irregular border

We are at an exciting time in medicine. A nearly exponential increase in the understanding of biology, chemistry, and pharmacology figuratively strains the digital shelves that hold all of this knowledge, while giant leaps in information technology mean that it is all accessible with a few taps of a smartphone. Modern medicine has more answers than ever before, and a new era of evidence-based decision-making has taken hold, bringing light and clarity to dark, unknown realms.

And yet, all is not well in this exciting new world of data and reason: there is unrest. There is increasing interest in so-called alternative medicine, which can be defined in a number of ways, but perhaps most pointedly as medicine that is simply not evidence-based. Both patients and practitioners are clearly interested in this domain and this is in striking contrast to the bright, shining edifice of evidence-based medicine. Indeed, studies indicate some 50% of dermatology patients — our patients — have tried one or more forms of alternative medicine.[1,2]

If modern medicine is so great — and it clearly is — why are people seeking these alternatives? Three major motivations seem to lie at the root of this movement:

- diseases that are not curable;
- explanations that are unsatisfying; and
- treatments that are thought to be unsafe and/or only symptomatic.

Another reason may have to do with the experience of seeing a doctor in the modern day: rushed, harried, and often more focused on the computer than on the patient. This is probably not how our forebears envisioned the art of medicine being practiced. In Dermatology — perhaps particularly so — these are all strongly represented: Many of our diseases are chronic and incurable; much of our understanding of the pathophysiology is incomplete; thus, many of our explanations fall short; and we have many treatments that only offer a temporary reprieve from a condition and yet still have many potential side effects.

Each month we hope to explore different diseases and treatments, looking into alternative approaches and their rationale. We will focus on the evidence: It may be surprising how much evidence is actually available in some areas.

Sadly, it does not seem likely that these conditions will be going away anytime soon for the majority of dermatologic diseases, which brings us to this column. Each month we hope to explore different diseases and treatments, looking into alternative approaches and their rationale. We will focus on the evidence: It may be surprising how much evidence is actually available in some areas. And, as we delve deeply, the line between alternative and mainstream may become a bit blurrier than it seemed at first blush. Above all else, we hope that it is stimulating and useful, for both skeptic and believer.

Alternatives in AD treatment

As we all know too well, atopic dermatitis is a chronic, relapsing, itchy condition that often begins in the first years of life, but may affect patients of all ages. Its etiopathogenesis is complex and still not fully understood, but the most recent research points to a combination of skin barrier dysfunction, immunologic aberrations, microflora imbalance, and abnormalities in the perception of itch.[3,4]

While intellectually stimulating, such a confusing collection of pathology defies a clear and simple explanation when patients ask: "Why do I have this disease?" And that is, unfortunately, no small number: AD affects up to 20% of children in developed countries and recent estimates are as high as 10% of adults having some form of eczema as well.[5]

The conventional approach to treatment for AD includes addressing the four main areas of dysfunction with moisturization, anti-inflammatory agents, anti-microbials, and anti-pruritic therapy. Allergen identification and avoidance of triggers is also helpful when possible.[6]

Generally speaking, most patients respond favorably to such regimens and the risks associated with conventional therapies are limited.

More recently, however, there has been increased scrutiny of topical corticosteroids: highly effective though they may be, but with a significant number of concerning side effects that make them undesirable for certain patients. This perception may lead to poor adherence to the plan, with more

ALTERNATIVES see page 21

Ivermectin: A New Player in the Rosacea Game

Published as a promotional supplement to
Dermatology Times
March 2015

By Scott Kober, MBA, CCMEP

In the most recent issue of this publication, we provided an overview of current classifications and grading systems that define rosacea, along with information on traditional therapeutic approaches for the management of inflammatory papules and pustules. In this issue, we'll focus on ivermectin 1%, the newest addition to the rosacea armamentarium, by reviewing its mechanism of action and exploring data that supported its recent approval by the FDA for the once-daily topical treatment of inflammatory lesions, or bumps and pimples associated with rosacea.

Mechanism of action

Ivermectin has been reported to have both anti-inflammatory and antiparasitic activities. It has been used orally as an antiparasitic for more than 25 years to treat conditions such as onchocerciasis, pediculosis, and scabies. A topical formulation is also FDA-approved to treat head lice.

Ivermectin's antiparasitic effects in rosacea are thought to be associated with its ability to decrease the density of mites called *Demodex folliculorum*. Although the exact cause of rosacea remains unclear, one emerging theory concerns the impact of *Demodex* mites on the exacerbation of the condition.[1] In clinical trials, *Demodex* density has been shown to be 5.7 times higher in the skin of patients with rosacea compared to healthy controls.[2] Approximately 35% to 50% of patients with rosacea have an increased load of *Demodex*.[3]

Oral ivermectin has been shown to reduce the number of *Demodex* mites in patients with blepharitis and demodicidosis. It is postulated that topical ivermectin is efficacious in reducing the inflammatory response in patients with rosacea in part due to its ability to directly eliminate these *Demodex* mites. This hypothesis, however, needs to be studied further in clinical trials.

Ivermectin has also been shown to have anti-inflammatory effects due to its ability to inhibit lipopolysaccharide-induced production of inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1β, while upregulating the anti-inflammatory cytokine IL-10 (see Figure 1 for visual representation of this process). It is important to note that ivermectin's exact mechanism of action in the treatment of rosacea is still unclear. Figure 2 includes information on readers' overall familiarity with ivermectin's primary effects in rosacea.[4]

Efficacy data

As noted in the initial article in this 2-part series, agents currently utilized to control the proliferation of inflammatory papules and pustules in patients with rosacea include topical metronidazole (twice-daily 0.75% gel, cream, or lotion, and once-daily 1% gel or cream), topical azelaic acid (AZA) twice-daily 15% gel, and modified-release doxycycline 40 mg once daily.[5,6] Although each of these agents has demonstrated efficacy in patients with rosacea, patients can expect only partial clearance without proven duration of remission. For many patients with rosacea, 50% or even 75% improvement isn't good enough—to be able to truly overcome the emotional and psychological toll of rosacea, they want to be completely clear of inflammatory lesions.

Three phase 3 clinical trials were conducted to compare the safety and efficacy of ivermectin 1% against the approved topical agents, AZA 15% gel and metronidazole.[7–9]

In the first 2 of these trials, patients with moderate-to-severe papulopustular rosacea were treated with either ivermectin or Cetaphil-derived vehicle cream for 12 weeks.[7] Patients in the ivermectin group then continued with ivermectin for an additional 40 weeks while patients in the vehicle group were switched to AZA for the remaining 40 weeks of the trial.[8]

In the initial 12-week components of these studies, 38.4% and 40.1% of patients treated with ivermectin were deemed "clear" or "almost clear" according to Inverstigator's Global Assessment compared to 11.6% and 18.8% in the vehicle arms ($P<.001$ in both studies).[7] In the 40-week extension trials, 71.1% and 76.0% of patients treated with ivermectin were deemed "clear" or "almost clear" at the end of 1 year.[8] Only 59.4% and 57.9% of patients treated with AZA met these criteria, although direct comparisons between the 2 groups cannot be made because patients in the control arm received 12 fewer weeks of active AZA treatment.[8]

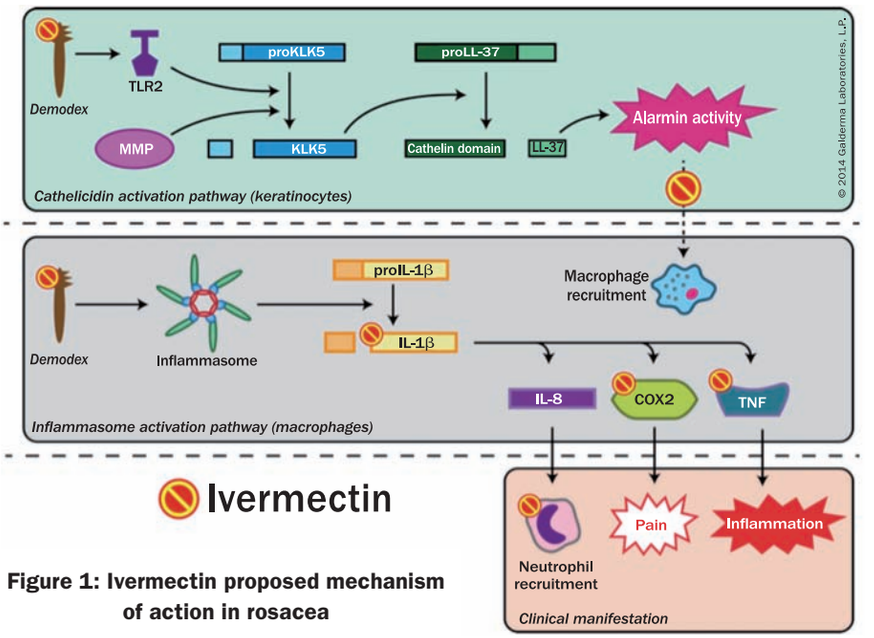

Figure 1: Ivermectin proposed mechanism of action in rosacea

It is also important to note that approximately 11% of patients in the ivermectin arm of these studies saw resolution or near resolution of their papules and pustules at week 4.[7]

The third phase 3 trial compared once-daily ivermectin to twice-daily metronidazole 0.75% cream. Patients in this trial completed 16 weeks of treatment. (Data from a 36-week extension trial have not yet been published.) At 16 weeks, 84.9% of patients in the ivermectin group were deemed "clear" or "almost clear" versus 75.4% in the metronidazole group ($P<.001$). Patients with severe rosacea at baseline saw nearly equivalent levels of improvement as patients with moderate rosacea.[9]

Safety data

Tolerability is of critical importance in any topical treatment of rosacea. In fact, in the phase 3 trial that compared ivermectin to a

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vehicle cream derived from Cetaphil, there were fewer local side effects in the ivermectin than vehicle arm (4.2% vs. 7.2%).[7]

In all 3 of the phase 3 trials, less than 2% of all patients experienced a dermatologic adverse event related to ivermectin, whereas approximately 10% to 15% of patients reported local intolerance, including stinging/burning, dryness, and itching. Rates of local intolerance for the comparator agents (AZA or metronidazole) were slightly higher in each of the studies.[7–9]

Combination therapy

Although ivermectin has demonstrated effectiveness in reducing papules and pustules associated with rosacea, it has limited, if any, effect on background erythema. Although it has not been studied in clinical trials in combination with an alpha agonist such as brimonidine, this may be an approach to consider.

Combination therapy in patients with papulopustular rosacea that includes both a topical agent (metronidazole or AZA) along with doxycycline is often a popular approach.[10] Although this again may be a consideration, there are no published data involving ivermectin to support such a regimen.

Drug holidays in rosacea

Rosacea is a lifelong condition, with an often unpredictable course. For many patients, continuous treatment is necessary. There are many patients whose condition clears up in the short term, but who then stop taking their prescribed topical or systemic therapy only to return to their previous baseline a few weeks later.

It is important from a quality-of-life standpoint to continue exploring options for drug-free holidays. A handful of recent studies have looked either at tapering or at discontinuing therapy after initial resolution of papulopustular rosacea.

One study explored a strategy of tapering from a combination of twice-daily AZA and doxycycline to once-daily AZA alone in patients who achieved ≥75% inflammatory lesion count reduction after 12 weeks on the twice-daily regimen. After 6 months of this maintenance regimen, 75% of patients remained in remission. (Loss of remission was defined as either 50% deterioration in the lesion count improvement from the initial phase of the study, increase in erythema intolerable to the subject, or maintenance therapy failure as judged by the investigator and/or the subject.)[11]

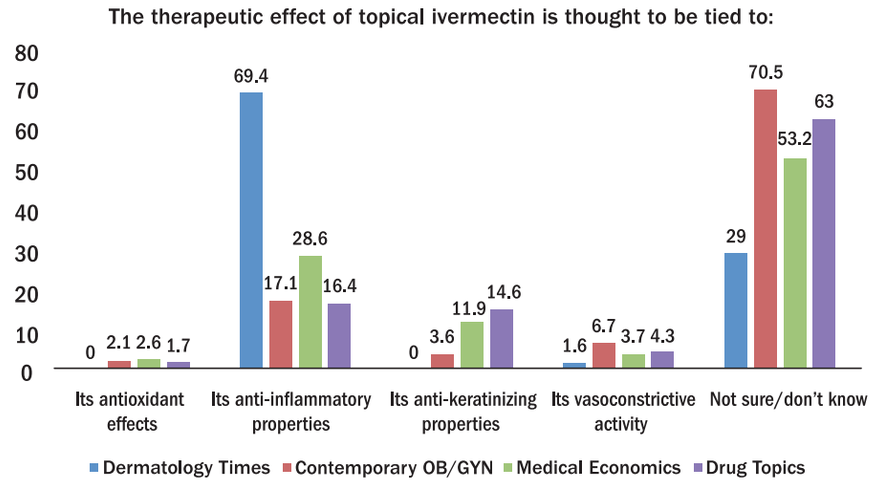

Figure 2: In a recent multidisciplinary Pulse Poll survey of readers, only *Dermatology Times* readers were mostly able to correctly identify that ivermectin is effective in rosacea largely due to its anti-inflammatory effects.

The phase 3 ivermectin study detailed earlier in this article that compared a 16-week regimen of ivermectin to metronidazole looked at a more rigid cutoff. In that study, patients who were deemed "clear" or "almost clear" stopped treatment entirely after 16 weeks. The study's primary endpoint is time to relapse after treatment cutoff. Data from this trial are expected to be presented later in 2015.

Conclusion

Once-daily ivermectin 1% provides clinicians with new opportunities to successfully improve the overall appearance and quality of life for patients with inflammatory pustules and papules associated with rosacea. Its overall efficacy, safety, and once-daily dosing offer significant improvements over currently available options that should be attractive to patients with rosacea.

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ALTERNATIVES:
Rationale behind alternative theories and approaches to AD treatment *from page* **21**

than one third of patients admitting to nonadherence to treatment in the setting of topical corticosteroid phobia in one study.[7]

Additionally, there is a perception that their effect — as well as that of the topical calcineurin inhibitors — is only symptomatic, and fails to address the "root" of the problem.

This makes for very fertile ground for alternative medicine, with many possible theories and approaches. We will limit ourselves to a few that have some decent evidence for potentially being useful, and also look at two that seem likely to be *unhelpful*, although they are frequently discussed.

SUNFLOWER SEED OIL

The skin barrier is of critical importance in AD, and is likely the primary issue in at least some types of eczema. Sunflower (*Helianthus annus*) seed oil is rich in linoleic acid, a fatty acid that can help maintain the skin barrier and decrease transepidermal water loss, both of which could be helpful for the barrier dysfunction in AD.[8]

Studies have also demonstrated anti-inflammatory properties of sunflower seed oil which would address another important aspect of AD.[8]

When put to the test, the evidence points to at least a modest effect in AD. A study of 86 children with moderate AD randomized to corticosteroids with or without a sunflower-oil-containing cream found a significant impact on lichenification and excoriation, decreased corticosteroid use, and improved quality of life compared to the control group.[9]

Another study of 19 adults randomized to receive olive oil to one arm versus sunflower seed oil to the other found that the olive oil actually caused a worsening of the barrier function and erythema. Sunflower seed oil, on the other hand, preserved skin barrier function and improved hydration.[10]

Safe and inexpensive, sunflower oil seems a reasonable consideration for any patient with AD, so long as there is not a known sunflower seed allergy.

COCONUT OIL

Bacterial infection (usually with staphylococcus) is a major issue in AD. Coconut oil (*Cocos nucifera*) has been shown to address another closely-related issue in atopic dermatitis: staphylococcal colonization. In a randomized controlled trial it was found to clear an impressive 95% of staphylococcal colonization in patients with AD.[11]

Safe and inexpensive, sunflower oil seems a reasonable consideration for any patient with AD, so long as there is not a known sunflower seed allergy.

When put to a more clinical test, it actually outperformed mineral oil in treating pediatric AD over 8 weeks in a randomized trial thus,[12] making it an interesting alternative consideration.

TOPICAL VITAMIN B12

Beyond topical corticosteroids and calcineurin inhibitors (which appear to do much of their work via anti-inflammatory pathways), there is not much in the armamentarium to combat the itch of AD. Antihistamines are often unhelpful, and a variety of over-the-counter cooling preparations offer only limited relief. Vitamin B12 (cobalamin) is a powerful scavenger of nitric oxide—which has been linked to triggering pruritus—making it a compelling consideration for treating AD. Additionally, *in vitro* studies have demonstrated that B12 suppresses the cytokine production of T lymphocytes and multiple inflammatory cytokines, also promising for AD therapy.[13]

When put to the test, a double-blinded randomized control trial of topical B12 in children with AD found significant improvement in the active group over the placebo at 2 and 4 weeks.[14]

Another randomized trial of 49 AD patients found that the B12 group had significantly better improvement in AD compared to placebo control.[13]

The concept of a safe, topically applied vitamin for AD is very attractive, even if just as an adjunctive therapy, much in the same way that niacinamide is now frequently found in moisturizers targeted towards acne and rosacea.

ACUPUNCTURE, ACUPRESSURE

Generally considered a part of Traditional Chinese Medicine, acupuncture and acupressure build upon the idea that energy meridians in the body can become unbalanced and that by stimulating certain points ("acupoints") with needles, pressure, magnets, or even lasers, the flow can be restored and rebalanced.[15]

From a conventional standpoint, there are studies that show clear changes in specific brain areas with acupuncture, and evidence that there is endorphin production with acupuncture, suggesting a neurocutaneous connection.[16]

While formal acupuncture would require a specially trained practitioner, more limited versions could be performed by nearly anyone, including patients themselves.

The study that got me excited about acupuncture was actually not in atopic dermatitis at all, but rather for the intractable itch of uremic pruritus. 40 patients with severe, refractory pruritus related to kidney failure were randomized to acupuncture at one point (Large Intestine 11, located near the antecubital fossa) three times weekly or acupuncture at a sham point for 1 month. At 1 month and 3 months, the itch was significantly lower in the actual acupuncture group ($p<0.001$), suggesting a real effect.[17]

Inspired by that study, we carried out a pilot study of acupressure—a tiny titanium bead that was massaged on that same acupuncture spot by the

ALTERNATIVES see page 92

BOTOX® Cosmetic (onabotulinumtoxinA) IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products

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

Spread of Toxin Effect

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

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

Injections In or Near Vulnerable Anatomic Structures

Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX® injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Safety and effectiveness have not been established for indications pertaining to these injection sites. Some patients had pre-existing dysphagia or significant debility. Pneumothorax associated with injection procedure has been reported following the administration of BOTOX® near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

Hypersensitivity Reactions

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

Cardiovascular System

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

Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of BOTOX® Cosmetic.

Pre-existing Conditions at the Injection Site

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

Human Albumin and Transmission of Viral Diseases

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

ADVERSE REACTIONS

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

The most frequently reported adverse event following injection of BOTOX® Cosmetic for lateral canthal lines was eyelid edema (1%).

DRUG INTERACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

Please see brief summary of full Prescribing Information on the following pages.

Actual patient treated for moderate to severe crow's feet and glabellar lines. ***Results may vary.***

BOTOX® Cosmetic
onabotulinumtoxinA injection

There's only one BOTOX® Cosmetic

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The one that brought her here.

The one that brings her back.

Give her the one
she asks about by name.

BOTOX® Cosmetic
onabotulinumtoxinA injection

Indications

Glabellar Lines

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

Lateral Canthal Lines

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

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

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

Please see additional Important Safety Information about BOTOX® Cosmetic on opposite page.

BOTOX® Cosmetic (onabotulinumtoxinA)
for injection
(Brief summary of full prescribing information)

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan, Inc. 2525 Dupont Dr., Irvine, CA 92612

WARNING: DISTANT SPREAD OF TOXIN EFFECT

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products

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

Spread of Toxin Effect

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

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

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

Injections In or Near Vulnerable Anatomic Structures

Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received **BOTOX®** injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus, and stomach. Safety and effectiveness have not been established for indications pertaining to these injection sites. Some patients had pre-existing dysphagia or significant debility. Pneumothorax associated with injection procedure has been reported following the administration of **BOTOX®** near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

Hypersensitivity Reactions

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

Cardiovascular System

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

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX® Cosmetic** *(see Warnings and Precautions).*

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with **BOTOX®** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved *(see Warnings and Precautions).*

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

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

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

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

Pre-existing Conditions at the Injection Site

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

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

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

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

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

Human Albumin and Transmission of Viral Diseases

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

ADVERSE REACTIONS

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

- Spread of Toxin Effects *(see Warnings and Precautions)*
- Hypersensitivity *(see Contraindications* and *Warnings and Precautions)*
- Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia *(see Warnings and Precautions)*

Clinical Trials Experience

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

BOTOX® and **BOTOX® Cosmetic** contain the same active ingredient in the same formulation, but have different labeled Indications and Usage. Therefore, adverse events observed with the use of **BOTOX®** also have the potential to be observed with the use of **BOTOX® Cosmetic**.

In general, adverse reactions occur within the first week following injection of **BOTOX® Cosmetic** and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

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

Glabellar Lines

Table 2 lists selected adverse reactions reported by ≥1% of **BOTOX® Cosmetic** treated subjects (N=405) aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of **BOTOX® Cosmetic** in the improvement of the appearance of glabellar lines.

Table 2: Adverse Reactions Reported by ≥1% of the BOTOX® Cosmetic treated Patients and More Frequent than in Placebo-treated Patients in Double-blind, Placebo-controlled Clinical Studies of Treatment of Glabellar Lines

Adverse Reactions by System Organ Class	BOTOX® Cosmetic (N=405)	Placebo (N=130)
General Disorders and Administration Site Conditions Facial pain	6 (1%)	0 (0%)
Nervous System Disorders Facial paresis	5 (1%)	0 (0%)
Eye Disorders Eyelid ptosis	13 (3%)	0 (0%)
Musculoskeletal and Connective Tissue Disorders Muscular Weakness	6 (1%)	0 (0%)

Lateral Canthal Lines

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

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

Adverse Reactions by System Organ Class	BOTOX® Cosmetic 24 Units (N=526)	Placebo (N=530)
Eye disorders Eyelid edema	5 (1%)	0 (0%)

Immunogenicity

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

In three Lateral Canthal Line trials, 916 subjects (517 subjects at 24 Units and 399 subjects at 44 Units) treated with **BOTOX® Cosmetic** had specimens analyzed for antibody formation. Among the 916 **BOTOX® Cosmetic** treated subjects, 14 subjects (1.5%) developed binding antibodies and no subjects (0%) developed the presence of neutralizing antibodies.

The data reflect the subjects whose test results were considered positive or negative for neutralizing activity to **BOTOX® Cosmetic** in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to **BOTOX® Cosmetic** with the incidence of antibodies to other products may be misleading.

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

Post-marketing Experience

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

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *(see Warnings and Precautions).*

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events.

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

Ear and labyrinth disorders
Hypoacusis; tinnitus; vertigo

Eye disorders
Diplopia; strabismus; visual disturbances; vision blurred

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

General disorders and administration site conditions
Denervation; malaise; pyrexia

Metabolism and nutrition disorders
Anorexia

Musculoskeletal and connective tissue disorders
Muscle atrophy; myalgia

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

Respiratory, thoracic and mediastinal disorders
Aspiration pneumonia; dyspnea; respiratory depression and/or respiratory failure

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

DRUG INTERACTIONS

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

Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

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

Anticholinergic Drugs

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

Other Botulinum Neurotoxin Products

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

Muscle Relaxants

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

Glabellar Lines

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

Lateral Canthal Lines

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

OVERDOSAGE

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

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

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

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm.

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STUDY EXAMINES MELANOMA CELLS' INFLUENCE ON KERATINOCYTES

Molecular Cancer
January 2015

A team of researchers from the Czech Republic reports new understanding of the complexity of tumor biology.

After morphometrical and immunohistochemical analyses of epidermis surrounding nodular melanoma were performed, the data were compared to results of transcriptome profiling of *in vitro* models, in which human primary keratinocytes (HPK) were co-cultured with melanoma cells (MC), normal human melanocytes and nonmalignant cells also originating from neural crest (NCSC), respectively. Differentially expressed candidate genes were verified, and biological activity of candidate proteins was assessed on cultured HPK.

90 PERCENT of the cases, the epidermis surrounding nodular melanoma exhibited hyperplastic features

The researchers found that in 90% of the cases, the epidermis surrounding nodular melanoma exhibited hyperplastic features, which exhibited aberrant suprabasal expression of keratin 14 and loss of keratin 10. They found that MC and NCSC can increase expression of keratins 8, 14, 19 and vimentin in the co-cultured HPK, and note that this *in vitro* finding partially correlates with pseudoepitheliomatous hyperplasia observed in melanoma biopsies. The researchers also observed evidence of basic fibroblast growth factor (FGF-2), chemokine ligand (CXCL-1), interleukin-8 (IL-8) and vascular endothelial growth factor (VEGF-A) participation in the activity of melanoma cells on keratinocytes.

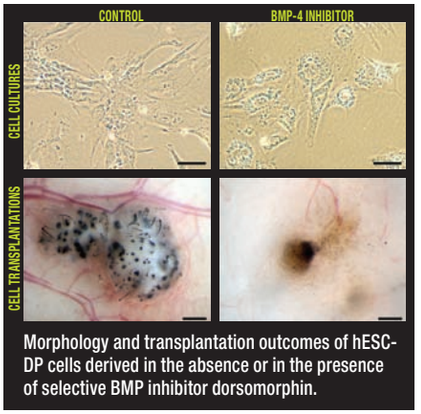
"Our data support the hypothesis of the importance of the microenvironment in melanoma biology, but our understanding of these mechanisms is still limited." study author Ondrej Kodet, M.D., of Charles University in Prague, Czech Republic, tells *Dermatology Times*. **DT**

—Bill Gillette

Read the study
bit.ly/cellinfluence

STEM CELLS GENERATE HUMAN HAIR GROWTH

PLOS One
January 2015



Morphology and transplantation outcomes of hESC-DP cells derived in the absence or in the presence of selective BMP inhibitor dorsomorphin.

Researchers have developed a way to generate new human hair growth using pluripotent stem cells, according to a study published online in *PLOS One*, January 21. The study, according to its researchers at the Sanford-Burnham Medical Research Institute, La Jolla, Calif., is the first step toward creating a cell-based hair loss treatment.

The researchers' protocol encourages human pluripotent stem cells to differentiate into dermal papilla cells. Dermal papillae are mesenchymal cells that regulate hair follicle formation and growth cycle. However, in adults, these cells cannot be readily amplified outside the body and they quickly lose their hair-inducing properties, according to Alexey Terskikh, Ph.D., associate professor in the Development, Aging and Regeneration Program at Sanford-Burnham.

"We developed a protocol to drive human pluripotent stem cells to differentiate into dermal papilla cells and confirmed their ability to induce hair growth when transplanted into mice," he says. "Our next step is to transplant human dermal papilla cells derived from human pluripotent stem cells back into human subjects."

Boca Raton, Fla., hair transplant surgeon Alan J. Bauman, M.D., tells *Dermatology Times* that the possibility that Dr. Terskikh's work could be a real step toward hair follicle multiplication is exciting. The keys to clinical success in the long and short term would be the resulting follicles' ability to resist the effects of dihydrotestosterone, or DHT, a primary trigger for hair loss, as well as the ability of the hair to maintain adequate diameter, length via normal hair cycles, and other qualities in order to produce cosmetically significant hair. **DT**

—Lisette Hilton

Read the study
bit.ly/stemcellhair

NEW ANTIBIOTIC MAY HELP TREAT ACNE, MRSA INFECTIONS

A NEW ANTIBIOTIC called teixobactin kills serious infections in mice with no detectable resistance, according to a recently released study in the journal *Nature*. The finding could pave the way to more effective treatments for drug-resistant infections caused by methicillin-resistant Staphylococcus aureus (MRSA).

The new antibiotic also might eventually be used to treat certain dermatologic disorders, according to Kim Lewis, Ph.D., a professor at Northeastern University and co-founder of NovoBiotic Pharmaceuticals, which has patented teixobactin.

"Teixobactin is highly active against *propionibacterium acnes* and other skin pathogens," Dr. Lewis tells *Dermatology Times*, "and given the lack of resistance development to this compound, it is a potential therapeutic to treat acne."

The World Health Organization has issued warnings about the developing risk of basic healthcare due to infections occurring during routine operations unless something drastic is done to prevent it. Dr. Lewis and his colleagues are attempting to address the problem by tapping into new potential sources of antibiotics. To date they've collected about 50,000 strains of uncultured bacteria and discovered 25 new antibiotics, of which teixobactin is the most recent.

Dr. Lewis says he hopes to start human testing on the drug in two years. **DT**

—Bill Gillette

Read the study
bit.ly/newantibiotic

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Dermatology Times

Secondary infections in AD

JOHN JESITUS | STAFF CORRESPONDENT

OFTEN AT MEDICAL MEETINGS, "people like to talk about fascinating, juicy infectious diseases" most dermatologists never see, says Sheila Fallon Friedlander, M.D., professor of clinical pediatrics and medicine (dermatology) at the University of California, San Diego.

Challenges that dermatologists face almost daily include secondary infections in atopic dermatitis (AD). In such cases, says Dr. Friedlander, it can be difficult to distinguish whether a patient is simply flaring or suffering secondary infection.

Dr. Sheila Fallon Friedlander, M.D.

To resolve this conundrum, "We look for the classic signs of infection: honey-colored crust and oozing. But often, a patient won't have classic findings. In such situations, utilizing appropriate dry skin care and topical corticosteroids may be enough to clear the patient, even if *S. aureus* is cultured from the site. If that doesn't work, empiric antibiotic therapy may be the next best step."

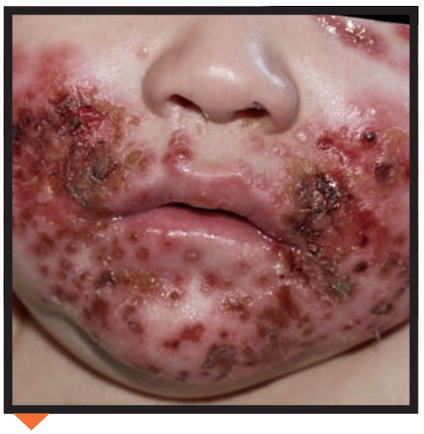
QUICK READ

Everyday infectious-disease challenges include secondarily infected eczema in all its permutations.

Research in this regard is "very interesting," she says. A large meta-analysis[1] and several experts have stated that there is insufficient evidence to show a benefit of oral antibiotics in managing infected or uninfected eczema. However, says Dr. Friedlander, "This doesn't mean that antibiotics are ineffective. Many studies that have been performed are small and/or poorly designed."

Accordingly, says Dr. Friedlander, "When we treat patients, we try to use our head. We know that it's important, when in doubt and before instituting therapy, to obtain cultures because of the high incidence of MRSA nationwide, and to help guide appropriate therapy. It's equally important to use oral antibiotics only when you believe they are appropriate."

While awaiting culture results, she says, "If your community has a very high incidence of MRSA, as in Texas,



Eroded, crusted ovoid papules most marked in the perioral area. This child has eczema herpeticum, but could also be secondarily infected with *S. aureus*.

Photos: Sheila Fallon Friedlander, M.D.

use either clindamycin or Bactrim (sulfamethoxazole, trimethoprim; Roche). However, if you're in San Diego, where MRSA incidence is lower, particularly in patients with AD, we often start with a cephalosporin." Some physicians use clindamycin empirically, she says. But if a patient has no history of recurrent infections, and particularly no evi-

SECONDARY INFECTIONS *see page* **31**

Quotable

"We don't know what we don't know — over confidence can be a problem."

Stephen Helms, M.D.
Jackson, Miss.

on tools to reduce medical errors

See story page 42

DTExtra

Two measles-containing vaccines are unlikely to result in adverse effects, a 12-year cohort study has found. Researchers evaluated the effects of 123,200 doses of measles-mumps-rubella-varicella (MMRV) vaccine and 584,987 doses of measles-mumps-rubella and varicella (MMR+V) vaccines (given separately on the same day) in children aged 12 to 23 months from 2000 to 2012 to determine whether MMRV posed more risk that MMR+V. Risks for the seven main study outcomes didn't differ significantly. Researchers didn't discover any new safety concerns for either vaccine course.

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SECONDARY INFECTIONS:
Staph, strep, and MRSA *from page* **28**

dence of MRSA in any family contacts, "We'll start out empirically with cephalosporins."

In one case Dr. Friedlander presented, a boy was treated with sulfamethoxazole-trimethoprim for possible MRSA, but the next day, his mother reported that his skin looked worse. Cultures taken from his lesional skin grew Group A Streptococcus. In one review of children with AD who underwent skin cultures, investigators found that 16 percent had Group A strep, and 14 percent had evidence of both staph and strep.[2]

"A couple things are important here. First, the kids who have strep are more likely to be febrile, to have facial and perioral involvement and to be hospitalized, versus those with *S. aureus* alone." Second, Dr. Friedlander says, sulfamethoxazole-trimethoprim is ineffective against Group A strep.

"That's why we generally don't use Bactrim as first-line therapy in children who look well, unless I'm certain or highly suspicious that it's MRSA." Conversely, she says that clindamycin and cephalosporins cover both strep and most staphylococcal infections. "Some MRSA strains won't be covered by clindamycin, but many will."

BLEACH BATH EFFICACY DATA

For patients with eczema who have chronic or recurrent staph infections, Dr. Friedlander says, many recent publications tout the benefits of bleach baths (lasting approximately 10 minutes) and other hygienic measures such as mupirocin ointment to the nares to help eliminate nasal carriage. In one study, twice-weekly bleach baths for three months led to a 20 percent decrease in staph infections.[3] For teens who refuse bathing, she suggests bleach body washes and gels.

There's controversy about the right concentration, however. "Many people use half a cup in a full 40-gallon tub, for a concentration of .0005 percent." Whether to rinse off the solution also is controversial. "I generally have kids rinse off, but this makes more work for mom. And no one has documented that it makes a difference. But one thing is clear: you'll want to grease them up with moisturizers when they get out."

Regarding bleach's mechanism of action, Dr. Friedlander says, "We know that bleach is antiviral, antifungal and antimicrobial." But a recent study shows that bleach also can inhibit inflammatory processes within the skin.[4] "So it may be that these soaks are not only killing off bacteria, but also helping to decrease the inflammation."

In another common scenario, she says, an infant with a skin infection

SECONDARY INFECTIONS *see page* **34**

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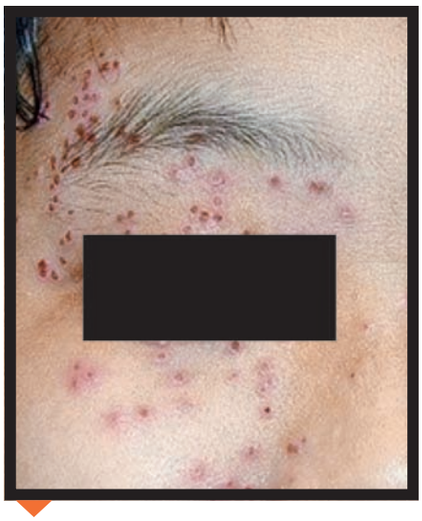
SECONDARY INFECTIONS:
Biofilms may be pivotal in development of AD *from page* **31**

treated empirically with clindamycin may return two days later with homogenous-looking, highly erythematous lesions clustered mainly in the perioral area. "In this case, we must consider a virus. In fact, if we were to do a Tzanck stain of one of this child's lesions, we might see multinucleate giant cells," a hallmark of eczema herpeticum.



Unilateral periocular involvement with monomorphic ovoid crusted papules. Though a more subtle presentation, this case also is eczema herpeticum.

"If we think a child has eczema herpeticum, we don't usually have time in clinic to do Tzanck stains. But I would suggest, if you can, that you obtain cultures or direct fluorescent antibody, which you can send off to a lab. A pearl that helps indicate you're dealing with a virus is that the lesions are almost always very monomorphic – like punched-out, crusted papules of similar size. Often, there is facial involvement."

Afflicted children need acyclovir (20 mg/kg four times daily; she uses the liquid formulation), Dr. Friedlander says. Usually, "These children are well enough to be treated as outpatients. When in doubt, cover for bacteria as well."

Meanwhile, dermatologists' understanding of the role of *S. aureus* in AD keeps evolving. A recent study showed that *S. aureus* can elaborate a biofilm that obstructs eccrine ducts, resulting in miliaria.[5] Dr. Friedlander says, "Some investigators now believe that may play a crucial role in the development of AD. Usually, we think of staph as a secondary phenomenon. But there's now some evidence that staph may have the ability to obstruct sweat glands, and this may be a pivotal event in the development of AD."

Regarding other conditions associated with AD, Dr. Friedlander says a recent case-control study provides early evidence of a link with molluscum contagiosum. Dermatologists have long suspected such a link, she says, but the evidence was very weak. "Now we have a somewhat better study that was performed in American Indians. It showed that molluscum contagiosum was more likely to have a prior or co-occurring diagnosis of eczema, scabies or some form of dermatitis compared to controls."[6] Treatment options for patients with molluscum include cantharidin, cimetidine, and cryotherapy, she says. **DT**

Dr. Friedlander reports no relevant financial interests. This article was assembled from presentations at MauiDerm, January 26-30, 2015, and supplemental interviews.

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MRSA 300 presents unique challenges

New antibiotics are available to help combat MRSA, including the particularly troublesome MRSA 300.

Among methicillin-resistant *Staphylococcus aureus* (MRSA) strains, MRSA 300 is proving particularly widespread and hardy, says Theodore Rosen, M.D., professor of dermatology at Baylor College of Medicine. MRSA 300 has grown particularly problematic in the United States, says Dr. Rosen. Typically presenting as abscesses and cellulitis, it is the most common MRSA strain found in the general population, as well as in athletes, soldiers, IV drug users, the homeless, and men who have sex with men.

"Unlike hospital-acquired MRSA," Dr. Rosen adds, "MRSA 300 is uniquely capable of colonizing extra-nasal sites such as the oropharyngeal and anogenital areas, and can survive on fomites." MRSA 300 is also increasingly drug (including mupirocin) resistant, he says. Sources of contamination range from raw meats – often derived from animals given unnecessary antibiotics – to frequently handled household objects such as landline phones, bathroom fixtures, and hair brushes.

Clinicians should consider MRSA 300 particularly if infections occur in areas such as the groin, buttocks, penis, vulva and suprapubic skin, Dr. Rosen says. Fortunately, he adds, the IV antibiotics oritavancin, dalbavancin and tedizolid earned FDA approval for MRSA in 2014. The longer half-life of these drugs means that they require fewer administrations per course than previously available IV antibiotics, he says. Dosing recommendations are as follows:

- Oritavancin – single 1,200 mg dose
- Dalbavancin – 1,000 mg; 500 mg one week later
- Tedizolid – 200 mg QD. **DT**

Disclosure: Dr. Rosen reports no relevant financial interests.
For more information: www.mauiderm.com

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IMPORTANT RISK INFORMATION

Contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria, or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the LEVULAN KERASTICK for Topical Solution.

The most common adverse events include scaling/crusting, hypo/hyperpigmentation, itching, stinging and/or burning, erythema and edema. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of patients at some time during treatment. However, these effects are temporary and should completely resolve by 4 weeks after treatment.

*At 8 weeks, 77% of patients treated with LEVULAN KERASTICK PDT experienced 75% clearance of AK lesions vs 23% of the control group. 83% of the patients treated with LEVULAN KERASTICK PDT had 75% clearance of face lesions and 60% of the patients had 75% clearance of scalp lesions. 66% of patients treated with LEVULAN KERASTICK PDT experienced 100% clearance of AK lesions vs 13% of the control group. 70% of the patients treated with LEVULAN KERASTICK PDT had 100% clearance of face lesions and 55% of the patients had 100% clearance of scalp lesions.

*Results from two identical, randomized, multi-center, two-arm Phase 3 studies with a total of 243 patients. Patients who were not complete responders at week 8 had a retreatment of the persistent target lesions. All patients returned at week 12 after initial treatment.

† Patients treated with LEVULAN KERASTICK PDT should avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. Most common adverse events are temporary and should completely resolve by 4 weeks after treatment.

** LEVULAN KERASTICK PDT is a 2-part treatment procedure that can be completed within a 24 hour period. LEVULAN KERASTICK must be applied by a qualified healthcare professional.

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INDICATIONS AND USAGE

The LEVULAN KERASTICK for Topical Solution, a porphyrin precursor, plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses of the face or scalp.

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The LEVULAN KERASTICK for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the LEVULAN KERASTICK for Topical Solution.

WARNINGS AND PRECAUTIONS

Photosensitivity

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

Application of LEVULAN KERASTICK Topical Solution to perilesional areas of photodamaged skin of the face or scalp may result in photosensitization. Upon exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, such photosensitized skin may produce a stinging and/or burning sensation and may become erythematous and/or edematous in a manner similar to that of actinic keratoses treated with LEVULAN KERASTICK Photodynamic Therapy. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK should be used by a qualified health professional to apply drug only to actinic keratoses and not perilesional skin. If for any reason the patient cannot return for blue light treatment during the prescribed period after application of LEVULAN KERASTICK Topical Solution (14 to 18 hours), the patient should call the doctor. The patient should also continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. If stinging and/or burning is noted, exposure to light should be reduced.

Irritation

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

Coagulation Defects

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

ADVERSE REACTIONS

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

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

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

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

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

TABLE 1 Post-PDT Cutaneous Adverse Events - ALA-018/ALA-019

	FACE				SCALP			
	LEVULAN (n=139)		Vehicle (n=41)		LEVULAN (n=42)		Vehicle (n=21)	
Degree of Severity	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe
Scaling/Crusting	71%	1%	12%	0%	64%	2%	19%	0%
Pain	1%	0%	0%	0%	0%	0%	0%	0%
Tenderness	1%	0%	0%	0%	5%	0%	0%	0%
Itching	25%	1%	7%	0%	14%	7%	19%	0%
Edema	1%	0%	0%	0%	0%	0%	0%	0%
Ulceration	4%	0%	0%	0%	2%	0%	0%	0%
Bleeding/Hemorrhage	4%	0%	0%	0%	2%	0%	0%	0%
Hypo/hyper-pigmentation	22%		20%		36%		33%	
Vesiculation	4%	0%	0%	0%	5%	0%	0%	0%
Pustules	4%	0%	0%	0%	0%	0%	0%	0%
Oozing	1%	0%	0%	0%	0%	0%	0%	0%
Dysesthesia	2%	0%	0%	0%	0%	0%	0%	0%
Scabbing	2%	1%	0%	0%	0%	0%	0%	0%
Erosion	14%	1%	0%	0%	2%	0%	0%	0%
Excoriation	1%	0%	0%	0%	0%	0%	0%	0%
Wheal/Flare	2%	1%	0%	0%	2%	0%	0%	0%
Skin disorder NOS	5%	0%	0%	0%	12%	0%	5%	0%

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

OVERDOSAGE

LEVULAN KERASTICK Topical Solution Overdose

LEVULAN KERASTICK Topical Solution overdose has not been reported. In the unlikely event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 40 hours after ingestion. The consequences of exceeding the recommended topical dosage are unknown.

BLU-U Light Overdose

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

Information for Patients:

LEVULAN KERASTICK Photodynamic Therapy for Actinic Keratoses.

- The first step in LEVULAN KERASTICK Photodynamic Therapy (PDT) for actinic keratoses is application of the LEVULAN KERASTICK Topical Solution to actinic keratoses located on the patient's face or scalp.
- After LEVULAN KERASTICK Topical Solution is applied to the actinic keratoses in the doctor's office, the patient will be told to return the next day. During this time the actinic keratoses will become sensitive to light (photosensitive). Care should be taken to keep the treated actinic keratoses dry and out of bright light. After LEVULAN KERASTICK Topical Solution is applied, it is important for the patient to wear light-protective clothing, such as a wide-brimmed hat, when exposed to sunlight or sources of light.
- Fourteen to eighteen hours after application of LEVULAN KERASTICK Topical Solution the patient will return to the doctor's office to receive blue light treatment, which is the second and final step in the treatment. Prior to blue light treatment, the actinic keratoses will be rinsed with tap water. The patient will be given goggles to wear as eye protection during the blue light treatment.
- The blue light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, the patient will experience sensations of tingling, stinging, prickling or burning of the treated lesions. These feelings of discomfort should improve at the end of the light treatment.
- Following treatment, the actinic keratoses and, to some degree, the surrounding skin, will redden, and swelling and scaling may also occur. However, these lesion changes are temporary and should completely resolve by 4 weeks after treatment.

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LAB-1442AW Rev B

The pendulum is swinging

Industry is responding to the need for antibiotic-free treatment options. Galderma's Epiduo gel, an antibiotic free acne treatment, is the number one topical prescription drug for acne in the world, according to Humberto C. Antunes, Galderma's president and chief executive officer. Galderma no longer produces topical acne products containing antibiotics and is focused on developing antibiotic-free acne options, according to Antunes.

"The long-term use of antibiotics for the treatment of acne will contribute to the problem of antibiotic resistance," he says. "I think, by joining the CDC, we've demonstrated our commitment to dermatology patients ...."

But there's much more work to do. After all, it's not easy to change long-term prescribing behaviors. The shift in thinking about antibiotic use should start in medical schools and dermatology training, says Diane S. Berson, M.D., associate clinical professor of dermatology, Weill Medical College of Cornell University New York-Presbyterian Hospital and a founding member of the American Acne and Rosacea Society.

"I think it's important to teach our residents and medical students about this because, when I was training, I was taught that it was fine to use both topical antibiotics and oral antibiotics simultaneously," Dr. Berson says.

SPAUD plans to provide clinicians with updated recommendations on optimal antibiotic prescribing and is focused on monitoring patient information on antibiotic resistance and its significance in dermatology, according to Lawrence F. Eichenfield, M.D., president of AARS and professor of pediatrics and medicine (dermatology), University of California, San Diego School of Medicine. The forthcoming AARS SPAUD publication will include a wide range of information on antibiotic resistance and its significance to dermatologists, he says. DT

(http://acneandrosacea.org/education/news/3rd_spaud)

ANTIBIOTIC AWARENESS:
Panels and partnerships join forces *from page* 1

disease doctor and medical director of the CDC's Get Smart: Know When Antibiotics Work campaign. Historically, the government has partnered primarily with pediatricians, internists, and family practitioners because they commonly prescribe antibiotics for upper respiratory infections. But a recent data analysis turned CDC's attention to dermatology and dentistry, because of those specialties' high antibiotic prescribing rates.


Dr. Hicks

"Dermatologists came out on top in terms of the frequency of providing per provider across the U.S. Dermatologists prescribed 724 prescriptions per provider in 2011," Dr. Hicks says.

The next highest prescriber by specialty was family practice, at 667 prescriptions per provider in 2011, followed by pediatrics at 598, according to Dr. Hicks.

JOINING FORCES

To get a handle on antibiotic use in dermatology and to promote responsible prescribing, the Get Smart: Know When Antibiotics Work campaign has joined forces with Galderma Laboratories and the American Acne and Rosacea Society (AARS).

The first step is to analyze what leads to prescribing, Dr. Hicks says. "We're also actively reaching out the American Acne and Rosacea Society. What we would like to do is to work with the folks in the dermatology field who are already interested in this topic... and better understand what would help dermatologists improve their prescribing practices."

Lawrence F. Eichenfield, M.D., president of AARS and professor of pediatrics and medicine (dermatology), University of California, San Diego School of Medicine, says dermatologists' high antibiotic prescribing rates make sense given that dermatologists may see more patients and new patients each year than family practice physicians or pediatricians.

There are important reasons for dermatologists' prescribing rates, he notes. "In dermatology, many of the conditions treated with antibiotics are chronic and the antibiotics are being used both for their influence on bacterial colonization and quantity, as well as for direct antiinflammatory effects," Dr. Eichenfield says.

The dermatology community is interested in becoming more conscious about the relevance to dermatology practice of antibiotic resistance, as well as about the broader ecologic influences of antibiotic use and its impact to antibiotic resistance, according to Dr. Eichenfield. AARS's partnership with CDC will help to educate dermatologists about resistance and encourage appropriate, judicious use of antibiotics. That includes minimizing the overuse of antibiotics, minimizing extended courses of oral antibiotics when not necessary, and minimizing overuse of topical antibiotics if not necessary for disease control, according to Dr. Eichenfield, who is AARS president.

"The Scientific Panel on Antibiotic Use in Dermatology (SPAUD) is a group that is dedicated to addressing antibiotic use in dermatology. The third meeting of this group was held in September of 2014 and put together a superb panel of experts in dermatology, microbiology, pharmacology and a representative of CDC," Dr. Eichenfield says.

ANTIBIOTIC AWARENESS *see page* 38

Interventions

CDC needs to gather information before trying to intervene, according to Lauri Hicks, D.O., an infectious disease doctor and medical director of the CDC's campaign.

"There are many different types of possible interventions. I think the first one would just be education efforts and outreach and collaboration with the professional societies that reach dermatologists," Dr. Hicks says.

Other interventions include providing feedback on provider performance relative to certain syndromes.

The goal, she says, is to work with dermatologic societies to better understand how to introduce quality metrics related to prescribing for common dermatologic conditions that lead to antibiotic overuse. DT

ANTIBIOTIC AWARENESS:
Acne and cuteaneous considerations *from page* **37**

AN ACNE FOCUS

Opportunities to improve antibiotic stewardship are clear when one looks at the treatment of acne. Acne, which affects from 40 to 50 million Americans[1] is the most common skin disorder in U.S. and the most common condition dermatologists treat, according to Diane S. Berson, M.D., associate clinical professor of dermatology, Weill Medical College of Cornell University New York-Presbyterian Hospital and a founding member of the American Acne and Rosacea Society.

"Traditionally, dermatologists have treated acne with antibiotics, both topically and orally. It is now known that P. acnes, which is involved in the development of acne, has developed a resistance to topical and now some oral antibiotics," Dr. Berson says.

Dr. Berson says she thinks dermatologists are beginning to appreciate the problem of antibiotic overuse.

"Dermatologists are often the first physicians to treat patients with MRSA," she says.

acne, according to a study published in late 2013 in Pediatric Dermatology. Researchers who combed information about the leading therapies for children diagnosed with acne, collected from the National Ambulatory Medical Care Survey (NAMCS) from 1993 to 2009, found that pediatricians and dermatologists had different prescribing patterns.[2]

"The leading medications were topical treatments, including adapalene (14.4%), benzoyl peroxide (12.8%), and tretinoin (12.5%). Treatment of this age group differed substantially between specialties, with dermatologists frequently prescribing topical retinoids and primary care physicians preferring antibiotics, particularly oral antibiotics," according to the study's abstract.

CUTANEOUS INFECTIONS

Another consideration about the high antibiotic prescribing rates in dermatology is that cutaneous infections are quite common, according to Dr. Eichenfield.

> In dermatology, many of the conditions treated with antibiotics are chronic and the antibiotics are being used both for their influence on bacterial colonization and quantity, as well as for direct anti-inflammatory effects."
>
> Lawrence F. Eichenfield, M.D.
> San Diego School of Medicine

The message seems to be getting through to dermatologists about using oral antibiotics less often and for shorter durations, Dr. Berson says.

"I think the message we need to get through to dermatologists is that we should not be using topical antibiotics as a monotherapy," she says. "We have lots of great topical options now including medications that contain both retinoids and benzoyl peroxide. And if you're using retinoids and benzoyl peroxide, you really don't need to add a topical antibiotic."

Dermatologists may, in fact, have a leg up on other specialties when it comes to prescribing non-antibiotic options for

"One of the manifestations of antibiotic resistance has been the emergence of MRSA, which can commonly present as cutaneous infection," he says. "The management of MRSA and other staph infections in dermatologic disease, for instance atopic dermatitis, where there are high colonization rates of staph as part of the disease process, put dermatologists in the situation where they are managing skin infections and complications of the infections—many times with appropriate use of antibiotics."

Dermatologists have been at the forefront of the use of other antimicrobial approaches, such as the use of bleach baths for chronic skin infections. These approaches may appropriately control cutaneous skin infection without the use of oral antibiotics, according to Dr. Eichenfield. **DT**

1 Acne Facts. Retrieved from: https://www.aad.org/media-resources/stats-and-facts/conditions/acne
2 Davis SA, Sandoval LF, Gustafson CJ, Feldman SR, Cordoro KM. Treatment of preadolescent acne in the United States: an analysis of nationally representative data. Pediatr Dermatol. 2013 Nov-Dec;30(6):689-94. Epub 2013 Jul 22

Beyond monotherapy

AVOID ORAL antibiotics as monotherapy in the treatment of acne. "… for moderate/severe acne patients, oral antibiotics should not be used as monotherapy, but should be used in concert with topical retinoids and with antimicrobial products, such as benzoyl peroxide, that may limit the emergence of bacterial resistance," according to Lawrence F. Eichenfield, M.D., president of AARS and professor of pediatrics and medicine (dermatology), University of California, San Diego School of Medicine. Limit the use of oral antibiotics. If you need to use them, consider shortening duration of use, according to Dr. Berson.

Avoid topical antibiotics as monotherapy in the treatment of acne, according to Berson, M.D., associate clinical professor of dermatology, Weill Medical College of Cornell University, New York-Presbyterian Hospital and a founding member of the American Acne and Rosacea Society. Consider using combinations that include a retinoid and benzoyl peroxide, such as Epiduo (adapalene and benzoyl peroxide gel 0.1%/2.5%, Galderma) instead of, or in order to diminish topical antibiotic use, according to Dr. Berson. The consensus recommendation on topical antibiotics in the Evidence-Based Recommendations for the Diagnosis and Treatment of Pediatric Acne, published in Pediatrics[1], puts it this way: "Topical antibiotics (clindamycin, erythromycin) are not recommended as monotherapy because of slow onset of action and predictable emergence of antibiotic-resistant bacterial organisms. (SOR: C). If topical antibiotic treatment is to be prolonged for more than a few weeks, topical [benzoyl peroxide] should be added, or used in combination products." **DT**

1 Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics.* 2013;131 Suppl 3(Supplement 3):S163-86.

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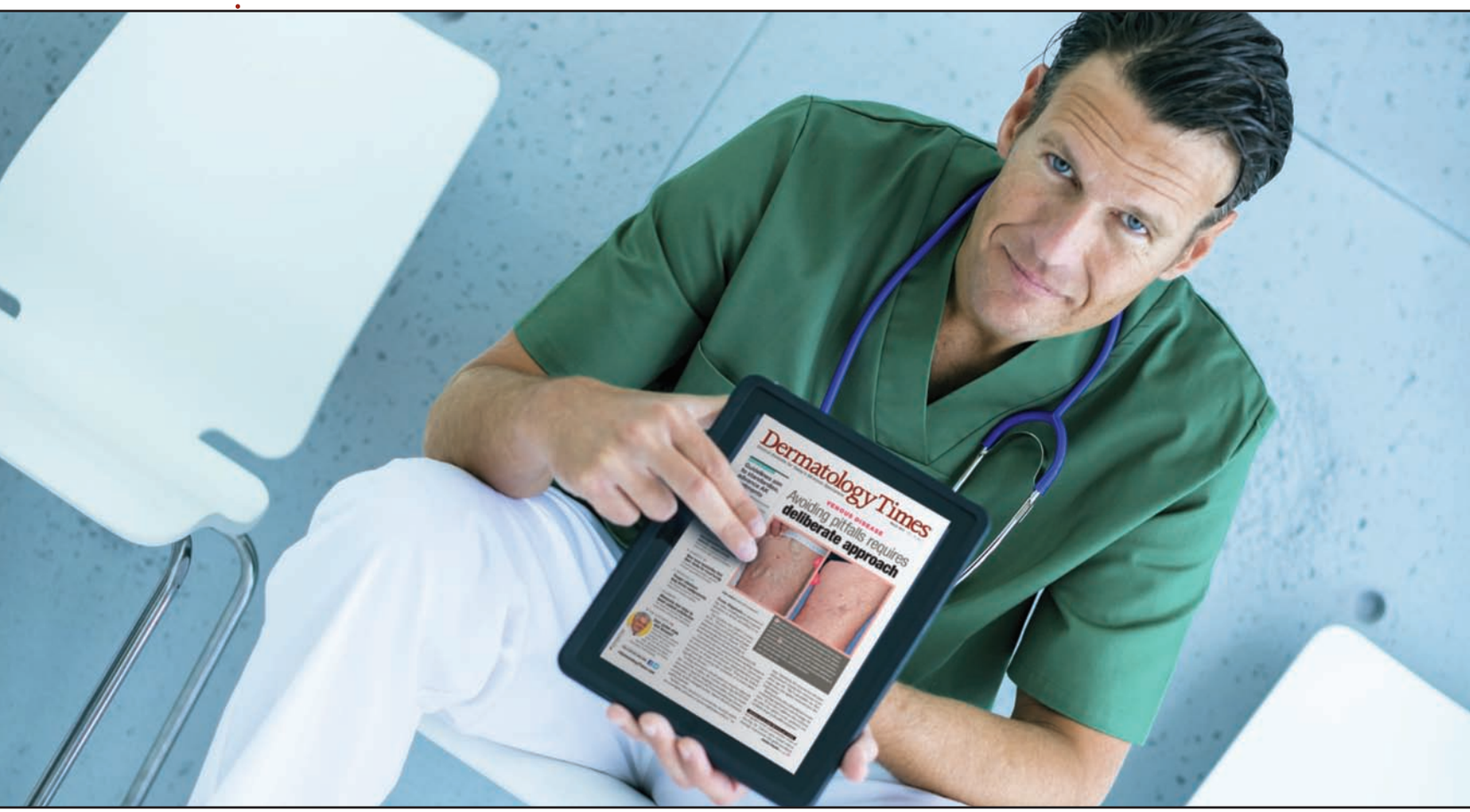

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Genetic clues to pigmentation disorders

LOUISE GAGNON | STAFF CORRESPONDENT

GENETICS EXPLAINS why the administration of a drug like imatinib produces a vitiligo-like appearance in patients, according to Jean Bolognia ,M.D., professor of dermatology at Yale School of Medicine, Yale University in New Haven, CT.

"When you give a drug that decreases the activity of KIT, then your patients can develop areas that look like vitiligo," according to Dr. Bolognia, who discussed inherited disorders of depigmentation at the 89th annual meeting of the Canadian Dermatology Association (June 2014, Toronto).

"Just like the child with piebaldism who has a reduction in KIT receptor function, if you decrease the activity of the KIT receptor via a drug such as imatinib, you will get patches of leukoderma. Both disorders can mimic vitiligo. Being aware of this phenomenon can assist in making the correct diagnosis," she says.

Mutations in the same gene can lead to different disorders. For example, activating mutations that lead to an increase in KIT activity are seen in patients with mastocytosis while mutations that lead to a decrease in KIT activity result in the autosomal disorder piebaldism.

QUICK READ

Knowledge of the genetics of pigmentation and disorders of pigmentation is growing.

GENETIC OF HAIR COLOR

Dr. Bolognia noted that blonde hair is linked to a polymorphism in the regulatory portion of the gene that encodes the KIT ligand gene.

"Upstream in the regulatory region of the KIT ligand gene, you see a base-pair change in the DNA in individuals with blonde hair. This alteration leads to decreased binding by the LEF1 transcription factor and the latter is WNT-activated," she says.

An individual's hair color is related to the amount of brown-black melanin versus yellow-red pheomelanin in his or her hair. For example, individuals with red hair harbor polymorphisms in the gene that encodes the melanocortin 1 receptor (MC1R). As a result, when MSH binds to its receptor on the melanocytes, there is minimal, if any, production of cyclic AMP and as a result, decreased production of tyrosinase. Formation of pheomelanin requires less tyrosinase activity than formation of eumelanin. The formation of pheomelanin can be thought of as a default pathway.

Experiments in mice with the equivalent of red hair have shown that the reduced production of eumelanin can be circumvented via the topical application of forskolin (which increases intracellular cyclic AMP). Application of forskolin led to the production of eumelanin within the skin of the treated mice. In the future, perhaps a similar approach could be taken for patients with red hair and the inability to tan.

In addition to polymorphisms in the KIT ligand and MC1R genes, physiologic variation in pigmentation is also related to polymorphisms in the genes that are involved in oculocutaneous albinism (OCA) including those that encode tyrosinase (OCA1), the P protein (OCA2), tyrosinase-related protein 1(OCA3), and members of the solute carrier families 24 and 45 (OCA4, OCA6).

Patients with OCA harbour mutations experience markedly reduced or absent enzyme (OCA1, OCA3) or transporter activity (OCA2, OCA4, OCA6). It is important to remember that in addition to pigmentary dilution of the skin, hair and eyes, there are ocular abnormalities in these patients, e.g. strabismus, nystagmus, photophobia, reduced visual acuity.

One interesting form of OCA1 is the temperature-sensitive subtype in which a temperature-sensitive tyrosinase leads to white hairs in the axillae and groin and pigmented hairs on the distal arms and legs. The explanation for this phenomenon is that the enyzme has some activity at 35 degrees Celsius and minimal to no activity at 37 degrees Celsius. As a result, cooler areas of the body have pigmented hairs. This same phenotype is seen in Siamese cats.

The future holds promise for patients who are at increased risk of developing skin carcinomas because of their inability to make eumelanin as more discoveries lead to a better understanding of the physiology of pigmentation. **DT**

Study: CME improves psoriasis care

WHILE RESEARCH looking at the impact of the Performance Improvement (PI) CME format on dermatology has been lacking, a new study sheds some light on the topic. It suggests dermatologists completing a PI CME on psoriasis significantly improved in important patient care aspects.

The American Academy of Dermatology offers eight PI CMEs in a variety of areas. For this study, researchers assessed physician practice patterns after completing the AAD's psoriasis PI CME. The psoriasis PI CME was created by the AAD in part to assist dermatologists in fulfilling Part IV of their Maintenance of Certification requirements.

Study participants self-audited patient charts, which met inclusion criteria in stage A, and reflected on their results, benchmarked against peers. They reviewed educational materials in stage B, developed improvement plans, and completed the CME by self-auditing a different set of patient charts after the plan's implementation, according to the study.[1]

The biggest improvements were noted in the areas of cardiovascular disease counseling. Less than a third of dermatologists completing stage A reported they had counseled psoriasis patients about their increased cardiovascular disease and cardiovascular risk factors, compared to nearly 80 percent of stage C completers. The improvement was as dramatic (at 47.2%) in dermatologists documenting recommendations that psoriasis patients should see their primary care practitioners for cardiovascular risk assessments. Persistent gaps, however, remained in counseling patients about smoking, alcohol use and obesity.

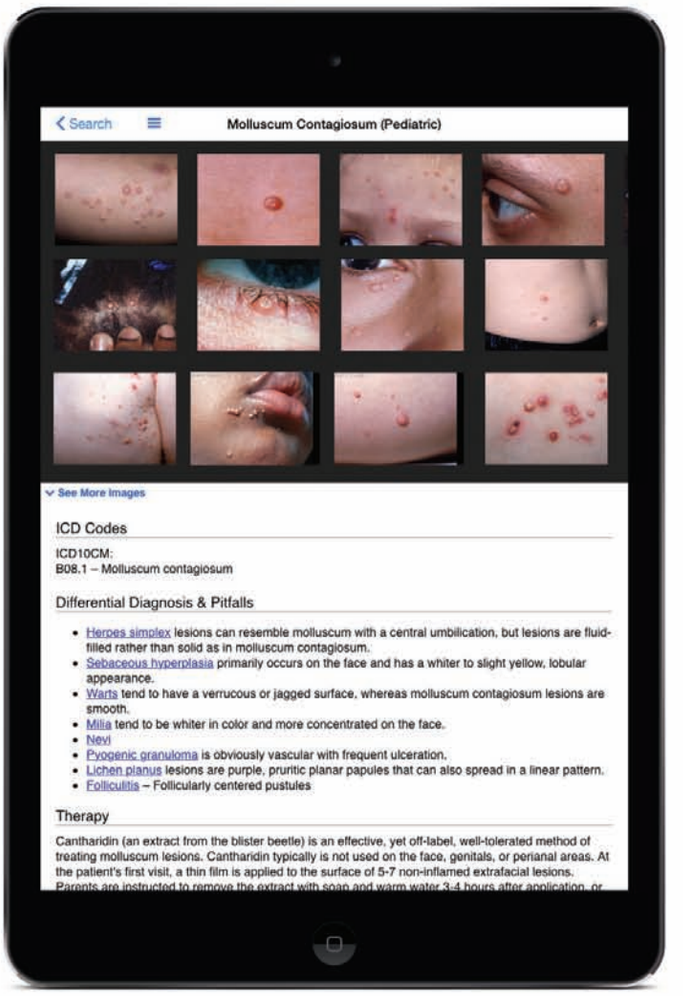
"Well done education, not only enhances knowledge for dermatologists but can change their practice patterns to improve patient outcomes. The first step is to appreciate that practice gaps exist and then find and use appropriate tools to address these gaps," the study's senior author Robert S Kirsner, M.D., Ph.D., tells *Dermatology Times*.

The overriding goal of education is to change physicians' practice patterns and, ultimately, improving patient care, according to Dr. Kirsner, who is interim chairman and professor of dermatology and cutaneous surgery at the University of Miami Miller School of Medicine, Miami, Fla. **DT**

— Lisette Hilton

1 Gist DL, Bhushan R, Hamarstrom E, Sluka P, Presta CM, Thompson JS, Kirsner RS. Impact of a Performance Improvement CME activity on the care and treatment of patients with psoriasis. J Am Acad Dermatol. 2015 Jan 7.

Precisely.



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Communication, checklists improve patient safety

JOHN JESITUS | STAFF CORRESPONDENT

CLEAR COMMUNICATION and well-constructed checklists might be the most powerful tools in the battle against medical errors, experts say.

As the complexity of medicine in general has increased in recent decades, says Stephen Helms, M.D., so has the potential for errors. A recent book estimates that approximately 6,000 drugs — and 4,000 medical and surgical procedures — are in use worldwide.[1]

"The numbers are staggering," says Dr. Helms, who is a professor in the Department of Dermatology at the University of Mississippi Medical Center in Jackson, Mississippi.

QUICK READ

Reducing medical errors requires a structured approach that includes teamwork, communication, and tools to help eliminate bias and oversights.

> "Think about your day – what are all the steps that happen, and can you create a map showing potential problem areas where you can intervene?"
>
> Eliot Mostow, M.D., M.P.H.
> **Rootstown, Ohio**

Meanwhile, adds Eliot Mostow, M.D., the number of medical diagnoses has mushroomed to a level approaching "diagnostic overload." And with the number of publications and electronic communication generated in the medical field, he adds, "There's a medical literature overload." Dr. Mostow is professor and chair of dermatology, Northeast Ohio Medical University, and associate clinical professor of dermatology, Case Western Reserve University School of Medicine.

TARGETING TROUBLE SPOTS

In this context, Dr. Mostow says, preventing medical errors begins with identifying their potential sources. Specifically, he and Dr. Helms suggest using a process analysis approach like that of the military and airline industries. In the latter area, they say, the discovery during the 1980s that up to 80% of commercial airline accidents stemmed from human error led to the development of an approach called Crew Resource Management (CRM). The concept didn't take off in the commercial airline industry, however, until pilots overcame their resistance to accepting tools such as checklists, which they initially considered to be "beneath them," Dr. Helms says.

In dermatology, Dr. Mostow recommends taking a similar systematic approach in identifying potential error sources, incorporating not only your practice, but also those practices who refer to you. Within this system, he says, anything from a misdiagnosis to a misspelled phone message can have minimal to disastrous consequences.

To prevent such problems, Dr. Mostow says, "Think about your day — what are all the steps that happen, and can you create a map showing potential problem areas where you can intervene? For example, your practice gets a phone call. A patient walks in the door. Who's greeting them? Who brings the patient back" to an examination room and takes the patient's history?

Just as any point of patient contact can introduce errors, so can mishandling of any materials related to a patient, Dr. Mostow says. For example, Dr. Helms says, surgeons at Columbus Children's Hospital have noted significantly poorer results if prophylactic antibiotics are given more than one hour before or after a procedure.[1]

"This is a simple slipup that may make a difference — it has nothing to do with training of nurses, anesthesiologists or other providers. It does, however, highlight a lack of communication between team members," Dr. Helms says.

CRACKING COGNITIVE CODE

Technical errors often make headlines, Dr. Helms says, but, according to expert analysis, the majority of errors are in physician thinking. In one study of medical mistakes, 80% stemmed from cognitive errors.[2] Dr. Mostow says that "cognitive errors are much harder to wrap our heads around"

Dr. Helms says that "Sometimes we don't know the diagnosis, or maybe what the best treatment is. Maybe we don't know new tests are available that we should do. It's very easy to jump to conclusions" or to misread something in a moment of haste. "We have perceptions, judgments and biases that affect our approach to the patient and how we make a diagnosis. And we don't realize what our biases are." Dr. Helms adds, "We don't know what we don't know — overconfidence can be a problem."

The main forms of cognitive bias that impact medicine include the following:[2]

- **ANCHORING –** Latching on too quickly and firmly to a single diagnosis. Dr. Helms likens it to prematurely closing the investigation without considering multiple diagnoses and forming a differential diagnosis. If other diagnoses are considered properly, he says, bedside tests or laboratory investigations may be critical.

- **ATTRIBUTION –** Failing to consider all possible sources of a problem and thereby attributing it to factors or conditions that have been influenced by one's biases. "This happens very commonly," says Dr. Helms. While taking a thorough patient history, he explains, medical professionals might formulate a dozen ways to ask a patient with eczema, 'What are you using on your

PATIENT SAFETY *see page* 45

JUBLIA®
(efinaconazole)
Topical Solution 10%

TACKLE ONYCHOMYCOSIS*
AT THE SITE OF INFECTION[1]

*For the treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

Rx Only

INDICATION

JUBLIA (efinaconazole) topical solution, 10% is indicated for the topical treatment of onychomycosis (tinea unguium) of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

IMPORTANT SAFETY INFORMATION

- JUBLIA is for topical use only and is not for oral, ophthalmic, or intravaginal use.
- Patients should be instructed to contact their health care professional if a reaction suggesting sensitivity or severe irritation occurs.
- The most common adverse reactions (incidence >1%) were (vs vehicle): ingrown toenail (2.3% vs 0.7%), application-site dermatitis (2.2% vs 0.2%), application-site vesicles (1.6% vs 0%), and application-site pain (1.1% vs 0.2%).
- JUBLIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and should be used with caution in nursing women. The safety and effectiveness in pediatric patients have not been established.

Please see Brief Summary of full Prescribing Information on the adjacent page.

Reference: 1. JUBLIA [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2014.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use JUBLIA safely and effectively. See full prescribing information for JUBLIA.

JUBLIA® (efinaconazole) topical solution, 10%

For topical use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

JUBLIA (efinaconazole) topical solution, 10% is an azole antifungal indicated for the topical treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

DOSAGE AND ADMINISTRATION

Apply JUBLIA to affected toenails once daily for 48 weeks, using the integrated flow-through brush applicator. When applying JUBLIA, ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered.

JUBLIA is for topical use only and not for oral, ophthalmic, or intravaginal use.

CONTRAINDICATIONS

None.

ADVERSE REACTIONS

Clinical Trials Experience

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

In two clinical trials, 1227 subjects were treated with JUBLIA, 1161 for at least 24 weeks and 780 for 48 weeks. Adverse reactions reported within 48 weeks of treatment and in at least 1% of subjects treated with JUBLIA and those reported in subjects treated with the vehicle are presented in Table 1.

Table 1: Adverse Reactions Reported by at Least 1% of Subjects Treated for up to 48 Weeks

Adverse Event, n (%)	JUBLIA N = 1227	Vehicle N = 413
Ingrown toenail	28 (2.3%)	3 (0.7%)
Application site dermatitis	27 (2.2%)	1 (0.2%)
Application site vesicles	20 (1.6%)	0 (0.%)
Application site pain	13 (1.1%)	1 (0.2%)

DRUG INTERACTIONS

In vitro studies have shown that JUBLIA, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

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

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 2, 10 and 50 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-16) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal deaths, decreased number of live fetuses, and placental effects) was noted at 50 mg/kg/day [559 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD based on AUC comparisons). No malformations were observed at 50 mg/kg/day (559 times the MRHD based on AUC comparisons).

Subcutaneous doses of 1, 5, and 10 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rabbits. In the presence of maternal toxicity, there was no embryofetal toxicity or malformations at 10 mg/kg/day (154 times the MRHD based on AUC comparisons).

In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day efinaconazole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (17 times the MRHD based on AUC comparisons). No effects on postnatal development were noted at 25 mg/kg/day (89 times the MRHD based on AUC comparisons).

Nursing Mothers

It is not known whether efinaconazole is excreted in human milk. After repeated subcutaneous administration, efinaconazole was detected in milk of nursing rats. Because many drugs are excreted in human milk, caution should be exercised when JUBLIA is administered to nursing women.

Pediatric Use

Safety and effectiveness of JUBLIA in pediatric subjects have not been established.

Geriatric Use

Of the total number of subjects in clinical trials of JUBLIA, 11.3% were 65 and over, while none were 75 and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and the younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year dermal carcinogenicity study in mice was conducted with daily topical administration of 3%, 10% and 30% efinaconazole solution. Severe irritation was noted at the treatment site in all dose groups, which was attributed to the vehicle and confounded the interpretation of skin effects by efinaconazole. The high dose group was terminated at week 34 due to severe skin reactions. No drug-related neoplasms were noted at doses up to 10% efinaconazole solution (248 times the MRHD based on AUC comparisons).

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one in vivo genotoxicity test (mouse peripheral reticulocyte micronucleus assay).

No effects on fertility were observed in male and female rats that were administered subcutaneous doses up to 25 mg/kg/day efinaconazole (279 times the MRHD based on AUC comparisons) prior to and during early pregnancy. Efinaconazole delayed the estrous cycle in females at 25 mg/kg/day but not at 5 mg/kg/day (56 times MRHD based on AUC comparisons).

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

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PATIENT SAFETY

Structured approach can help reduce medical errors *from page* **42**

skin?' In such cases, "We might not be asking the right questions." In one such case, Dr. Helms says, a male patient's contact dermatitis proved difficult to diagnose because he was reacting to benzocaine in a medication he had applied to his wife's skin.

- **AVAILABILITY –** Overemphasizing the most likely diagnosis or the easiest one to recall. In one case, a patient presented with cheilitis but no apparent oral cavity symptoms. Because the patient was a young female, says Dr. Helms, "I honed right in on what kind of lipstick, gloss or balm she was using," as well as toothpaste and other potentially allergenic products. "I'm so into contact dermatitis, it's easy for me to go down that road. But fortunately I did a KOH exam," which showed that the patient had an unusual candidiasis presentation.

Many errors combine cognitive and technical components, Dr. Mostow says. "I think of it as a continuum. Some items may overlap — there may be action items you assign to the wrong lesion, or there was a typo — left versus right, malignant or nonmalignant."

Other errors can stem from inaction. In this regard, Dr. Mostow says, "The largest basal cell carcinoma I ever found — 8 cm – was under an elderly female patient's breast. Over the course of several years, no one looked." In other instances, a laboratory may lose or simply fail to report back regarding a specimen. "There's lots of potential for issues we loosely call 'errors.' But it's not all black and white."

CHECKING IT TWICE

To minimize cognitive and technical errors, Drs. Helms and Mostow recommend applying root cause analysis – the Plan, Do, Check, Act (PDCA) cycle. Once you've identified a problem, Dr. Mostow says, devise and test a solution. If it fails, "Come up with another plan and do it again."

Such an approach can deliver stellar results, even though it seems simple. A pioneering paper showed more than 100 hospital intensive care units in Michigan reduced catheter-related bloodstream infection rates 66 percent after implementing an infection-control checklist.[3] The checklist included only five steps, Dr. Helms says, "and if they skipped one step, the statistics were affected. They made everybody do the exact same thing."

A good checklist functions as a cognitive safety net. Yet even the best checklists require revision and frequent updating, Dr. Mostow says. "Every checklist is terrible the first time." According to Atul Gawande, M.D., M.P.H., a good checklist is usually revised 15 to 18 times.[1]

> **"There's lots of potential for issues we loosely call 'errors.' But it's not all black and white."**
>
> Eliot Mostow, M.D., M.P.H.
> **Rootstown, Ohio**

The checklist development process begins with identifying clear, concise objectives, Dr. Helms says. At this stage, he also recommends adding items to improve communication among team members, and involving all team members in the checklist creation process.

To draft the checklist, he suggests:

- Use natural breaks in workflow as pause points
- Use simple sentences and basic language
- Make sure the checklist fits on one page, avoiding potentially distracting extraneous language.

To validate the checklist, ensure that it fits the actual workflow and detects errors while they're still correctable, Dr. Helms says, adding that the final step is to test the checklist with frontline users so that you can modify it in response to their feedback.

The result should be both thorough and simple. For example, Dr. Helms' practice has devised a checklist that goes beyond the iPLEDGE requirements to help minimize isotretinoin-related risks. Beyond logging a patient's childbearing status and birth control regimen, "For medicolegal reasons as well as good medical care, we made sure we made mention of any GI complaints, and we always want to ask about neurological history, to monitor for depression as well as to not miss pseudotumor cerebri. Additionally, we keep a log of total isotretinoin dose and all applicable lab results."

In surgical situations, Dr. Mostow adds, checklists increasingly include a 'timeout.' Before any procedure, "You say, 'Timeout — do I have everything right?' I do it especially for laser procedures — do we have the right spot? Is everybody in agreement regarding what we're doing? Do we have the right personnel? Does everyone have their goggles on? Then we go forward."

Dr. Helms says much of the public believes that, as a dermatologist, "You treat acne and warts. That's your day. They don't realize how many times we pick up significant problems related to internal disease," or solve a baffling bout of contact dermatitis. When confronted with a pruritic patient, "Just give a steroid — it doesn't matter which one. Betamethasone diproprionate and clotrimazole 'cures' everything, and we don't have to worry" about potential allergies or contraindications.

However, Dr. Helms concludes, the subtleties of modern medicine demand that dermatologists continue refining systems and strategies to keep critical information from falling through the cracks. **DT**

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Drs. Mostow and Helms report no relevant financial interests.

DT **For more** information: **www.aad.org**
http://asq.org/learn-about-quality/project-planning-tools/overview/pdca-cycle.html

Researchers isolate psoriasis triggering proteins

CASE WESTERN Reserve researchers have identified four proteins likely to contribute to psoriasis, bringing them closer to developing treatments that target the causes of the disease.


Dr. Ward

Photo: Billy Delfs

Senior author, Nicole L. Ward, Ph.D, associate professor of dermatology and neurosciences, Case Western Reserve University School of Medicine, and colleagues took skin tissue samples from Dr. Ward's psoriasis transgenic mouse model, called the KC-Tie2 mouse, and compared it with skin tissue samples of normal mice. They then examined the proteins they identified in human psoriasis skin cells and human psoriasis skin tissue samples to confirm the increased presence of these proteins in human disease.

"We used an unbiased in-gel label-free proteomics approach to identify more than 1,000 proteins that were either increased or decreased in our psoriasis mouse model, the KC-Tie2 mouse. We then identified four specific proteins: KLK6, Slc25A5, Serpinb3b (called SerpinB1 in humans) and Stefin A1 (called Cystatin A in humans), that we further validated as being increased in the mouse but more importantly, we confirmed these same proteins were increased in psoriasis patient skin," Dr. Ward says.

While researchers know that some trigger initiates a series of events leading to the disease, the cause of psoriasis remains unknown, according to Dr. Ward.

"Targeting key molecules active in this cycle have been proven to elicit clinical resolution; however, there is still no cure," she says.

Today's psoriasis therapies focus on symptomatic relief. The goal of this work, according to Dr. Ward, is not only to better understand what these proteins are doing in the context of psoriasis inflammation, but also to determine whether targeting them could reverse or prevent the disease.

"The importance of these proteins in initiating psoriasis can now be studied. We are already generating novel transgenic mouse models that overexpress or don't express these proteins at all in the skin; and believe that our future studies over the next several years will provide novel insight into the contributions of each of these molecules in psoriasis pathogenesis," Dr. Ward says. "If we discover that eliminating one of these molecules under the context of psoriasis-like skin inflammation prevents the disease from developing, our next step will be to determine whether therapies developed around targeting this protein could be effective for treating the disease." **DT**

Outcomes of the 2014 SPAUD meeting

A PUBLICATION based on the information presented and discussed at SPAUD is in progress. The following are a few top line highlights from the meeting.

The use of antibiotics in livestock feed comprises almost 80% of total antibiotic use in the US.[1] Antibiotic resistant bacterial strains as well as antibiotics themselves gain access to wastewater from livestock and poultry farms.

The addition of antibiotics to livestock feed may alter the microbial ecology, can contribute to emergence of infections in humans, and can increase carriage of resistant bacteria. For example, 30% of workers employed at farms using tetracycline in animal feed were positive nasal carriers of tetracycline-resistant MRSA nasal colonization as compared to 2% of workers employed at antibiotic-free farms.[2] In addition, a specific MRSA strain induced in hogs fed with tetracycline has subsequently been recovered from human infection, and has been found in 30% of tested supermarket beef and pork (30%), and on 10% of shopping cart handles.[3]

Human use of antibiotics represents 19.1% of annual antibiotic use in the US.[1] The most commonly prescribed oral antibiotics among all US clinicians in 2010 were azithromycin (166 Rx per 1000 persons), amoxicillin (166 Rx per 1000 persons), amoxicillin-clavulanate (70 Rx per 1000 persons), ciprofloxacin (66 Rx per 1000 persons), and cephalexin (65 Rx per 1000 persons).[4,5] When prescribing patterns of a specific antibiotic lead to a high prevalence of emergence of an antibiotic-resistant pathogenic bacteria, studies have shown that altering prescribing of the antibiotic can reduce the antibiotic resistance rate.[6,7]

Much of the data evaluating the sensitivity of Propionibacterium acnes to various antibiotics such as the tetracyclines and clindamycin is based on studies that were completed ten to fifteen years ago. More recent data shows increasing levels of less sensitive strains to commonly used antibiotics, with geographic variations correlating with the frequency of use of specific antibiotics.[8-11] Over time, some strains of P. acnes have become much less sensitive to clindamycin, which appears reduce efficacy in patients with acne vulgaris who harbor a high population of these less sensitive organisms.

Oral isotretinoin induces cutaneous changes that alter the microbial flora. The microbial effects include reduction in P. acnes, decrease in surface Gram-negative bacteria, and increase in S. aureus colonization.[12]

MRSA continues to be a common cause of cutaneous infection encountered in outpatient clinics, including dermatology. Updated practice guidelines for the management of skin and soft tissue infections from the Infectious Disease Society of America have been published in 2014.[13] **DT**

Reprinted from the SPAUD website

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Dermatologists, pharmacists partner for prescribing

LISETTE HILTON | STAFF CORRESPONDENT

DERMATOLOGISTS can partner with pharmacists to promote responsible antibiotic prescribing, experts say.

"I think pharmacists are a very important partner in the effort to improve antibiotic use, whether we're talking about prescribing for dermatologic conditions or respiratory infections," says Lauri Hicks, D.O., an infectious disease doctor and medical director of the CDC's Get Smart: Know When Antibiotics Work campaign. "... pharmacists are very accessible to the general public. I think in terms of dermatologists and pharmacists working closely together, the pharmacists can be a great resource for providing over-the-counter recommendations to the general public regarding treatment of skin conditions. Many pharmacists are also very knowledgeable about the issue of antibiotic overuse and can help identify opportunities to improve antibiotic use and limit unnecessary use," she says.

Kevin Snell, R.P.H., B.S., pharmacist in charge, ShopRite, Flanders, NJ, says that where he thinks pharmacists would have the greatest impact is in navigating formularies. Mr. Snell relays a perfect example of a missed opportunity: He was off for the weekend; another pharmacist received a script for Epiduo [adapalene and benzoyl peroxide, Galderma], which was not on the patient's plan. The pharmacist left a message for the prescribing doctor to change the prescription to something that was on the patient's formulary.

"There was an opportunity there, where if the pharmacist had said, 'We can use the generic adapalene and combine it with a benzoyl peroxide,' that would be on the formulary and still be non-antibiotic...," Mr. Snell says. "But the pharmacist just said we just have to change it to something on formulary. So, the doctor faxed me back on Monday and said to change it to Duac, which is a topical antibiotic."

OPPORTUNITIES FOR INTERACTION

The opportunity for pharmacists to interact with dermatologists happens often, he says.

"A lot of dermatologic products are expensive or non-formulary or they require prior authorization. We do have a lot of cases where we have to call the derms back. If we were to make an impact, that's where it would be," Mr. Snell says.

Helen Kizler, PharmD, a compounding pharmacist and owner of Great Earth Compounding Pharmacy in Los Angeles, Calif., says she and her staff help prevent antibiotic overuse by customizing antibiotic dosages.

"This way the patient only takes the dosage needed for their body weight and symptoms and are not limited to what is commercially available," Dr. Kizler says. "We work with dermatologists to monitor patient's usage of antibiotics and recommend alternatives to antibiotics for patients needing longer duration of treatment. By working closely with dermatologist, we can customize ingredients to help treat the cause of the problem not just mask the symptoms." **DT**

Helpful references on antibiotic use

Lisette Hilton

For the latest guidelines on the diagnosis and treatment of pediatric acne:

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Centers for Disease Control and Prevention. Get Smart: Know When Antibiotics Work. Antibiotic resistance questions and answers:

http://www.cdc.gov/getsmart/antibiotic-use/antibiotic-resistance-faqs.html#acne-medication.

American Acne and Rosacea Society: http://acneandrosacea.org/

SPAUD: http://acneandrosacea.org/education/news/3rd_spaud

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Dermatology Times

Disgruntled patients require access, attention

JOHN JESITUS | STAFF CORRESPONDENT

AVOIDING PATIENTS who report complications is perhaps the quickest path to litigation, said panelists at the annual Cosmetic Surgery Forum (Las Vegas, 2014). Instead, they advised setting personal feelings aside and lavishing such patients with TLC. Should a lawsuit arise, they added, addressing the accompanying stress may well save one's sanity and practice.

OPEN DOOR POLICY

Any dermatologic or aesthetic surgeon who says they've never had a side effect is either lying or denying — or else the affected patient never returned, according to Heidi Waldorf, M.D., director of laser and cosmetic dermatology and associate clinical professor of dermatology, Mount Sinai.

Every dermatologist has seen patients who present with complications created elsewhere, she says. When you ask the patient if she returned to the doctor, the patient says, "No, I never want to see that doctor again."

"When something bad happens, make sure that you and your staff provide a comfortable setting for your patients to return," she says. In fact, Dr. Waldorf says, some of her "complication" patients become her most loyal patients because of the way her practice treats them.

Suneel Chilukuri, M.D., says that when a patient reports a problem, his strategy is to see that patient every day.

"You want to make that patient get tired of seeing you," he says. Once the complication is under control, he gradually increases the between-visit interval to one day, two days and so on. "Work with them. They will be your best patient and your best referral source after that." He is a Houston-based cosmetic and Mohs surgeon in private practice.

Julie Woodward, M.D., adds that when a complaint surfaces, "Try not to take it personally." If you know the patient's identity, "Do whatever you can to make these patients happy." Rather than avoid them, she says, you have them return immediately, and continue to see them every week until they're satisfied. She is chief of the Oculofacial and Reconstructive Surgery Service in the Duke University Health System.

It's also important to ensure that your staff knows which patients require urgent handling. For example, Dr. Waldorf says, overly polite patients in pain may be willing to wait two weeks to be seen — unless a receptionist asks if they're concerned about a medical issue. If they are, "I want to get that call to the nurses," who perform triage using specific questions designed to uncover potential problems such as vascular necrosis. "And if you're

DISGRUNTLED *see page* **54**

QUICK READ

In dealing with complications, experts advise being responsive and accessible to affected patients — and remembering to take care of oneself in the event of a lawsuit.

Quotable

"Many of the histopathological images seen in a skin biopsy are pleaseing to the eye because they have a recognizable pattern to them, and therefore, represent a diagnosis to us..."

Hector L. Franco, M.D.
El Paso, Texas

on his son's artistic renderings

See story page 56

DTExtra

Cosmetic surgeons today are more frequently conducting virtual consultations, engaging with potential patients and managing patients postoperatively with telemedicine. Stephen S. Park, M.D., president of the American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS) uses telemedicine in two ways: To engage (or not) with people who reach out to him by email; and as a service to existing patients, where for practical purposes, he can conduct such things as wound checks, post-op visits or allay patients' concerns.

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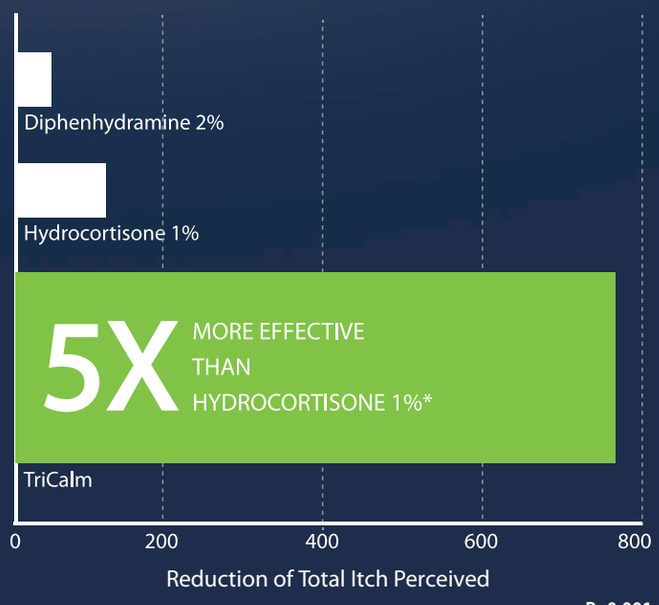

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* Head-to-head comparison of Topical Hydrocortisone 1%, Topical Diphenhydramine 2% and TriCalm® in a cowhage-induced itch model. Data on file.

DISGRUNTLED:
Patients with complications need to be given personal attention *from page* **52**

worried that someone's angry," she adds, "have the patient come in before hours, or during lunch break, so they're not sitting in the waiting room getting angrier."

In one case presented, Dr. Chilukuri learned that six weeks had passed between the time a patient injected with hyaluronic acid (HA) by a nurse at another practice began complaining of pain, and the time the patient reached his office. By then, the patient had rock-hard subcutaneous nodules in both cheeks, with an abscess that required drainage of 6.4 cc of purulent fluid.

HANDLING UNPLEASANT SURPRISES

Some complaints seemingly come from nowhere. For example, Dr. Woodward received a letter from Ipsen in late 2014 because a patient had complained to the Food and Drug Administration about lumps in the lip following a Dysport (abobotulinum toxin A, Ipsen) injection. The patient was an 86-year-old female who had undergone Dysport and Juvederm (HA, Allergan) injections on the same day.

However, Dr. Woodward says, her staff found no record of phone calls from the woman, except a complaint about her bill two months before the letter arrived.

"I remember the conversation, and we adored (the patient)," she says. "Nothing went off on our radar" suggesting she should not undergo treatment.

Nevertheless, Dr. Woodward says this patient slipped through her filter.

"I didn't do a good job of counseling her," she says.

Armed with the particulars of the case, Dr. Woodward called her Allergan representative, who provided hyaluronidase to treat the woman promptly.

In another case, a female patient returned to Dr. Waldorf with a hard white nodule above the left corner of her upper lip six weeks after undergoing calcium hydroxylapatite injection above the lip.

Originally, she says, "I'd put a little strut in the cutaneous lip across the nasolabial fold. This was the early days, when I would tell patients when they got home that if something feels bumpy, massage it down."

The patient initially loved her results. But when Dr. Waldorf asked her about any problems, she showed her the bump, a result of repeated massages the week after treatment.

"As she was massaging the swelling, she shoved this material down," she explains.

Dr. Waldorf removed the bump with a punch excision under local anesthesia.

Additionally, "I tell patients now for all fillers except Sculptra (poly-L-lactic acid, Merz/BioForm): No manipulation for one to two weeks. No facials, no rubbing — nothing."

Another patient developed biofilm after multiple HA injections performed by other physicians. "This patient had seen multiple doctors. She had HAs without a problem, then after two years suddenly started getting draining cysts and deeper cysts and abscesses across her face," Dr. Waldorf says.

Other physicians had tried steroid injections to treat these problems, resulting only in skin atrophy. Dr. Waldorf performed a punch biopsy and confirmed it was a granuloma. Routine cultures were negative, she says.

"As we know, with biofilms, you don't necessarily see organisms" under the microscope.

Accordingly, "We injected her with triamcinolone and 5-fluorouracil, in the same ratio (1:9) I use for keloids. If you don't use 5-FU, get some," she says. "It's fantastic, inexpensive and bactericidal. Plus it reduces inflammation."

Dr. Waldorf says she also gave the patient three (sequential) courses of Zithromax (azithromycin, Pfizer) and Avelox (moxifloxacin, Bayer), followed by intralesional hyaluronidase, injected with a needle because the lesions were too hard to break up with a cannula. "Ultimately, she got better," she says.

To avoid biofilms, Dr. Waldorf says, "I cleanse the heck out of people. I have my staff cleanse them," using makeup remover pads, because regular cleansers are no match for today's long-lasting makeups and tinted moisturizers.

Next, "I cleanse them with chlorhexidine, then alcohol — in that order because I don't want the chlorhexidine dripping by their eyes. Even though I'm wiping it off, it has a longer-lasting effect than alcohol." Drs. Waldorf and Chilukuri also tell patients to avoid the dentist two weeks before and two weeks after injectable treatments out of concern for bacteremia. Additionally, Dr. Waldorf says, "I now ask people about chronic periodontal disease." If someone has this problem or similar issues, "I consider giving them some doxycycline."

REPUTATION MANAGEMENT

If complaints come anonymously online, Dr. Woodward suggests hiring a reputation management firm. "Sadly, there are many of these companies popping up to deal with this repeated issue."

Should a complication spawn a lawsuit, you must take care of yourself she says. The stress can lead to a condition called medical malpractice distress syndrome. Doctors facing lawsuits can feel humiliated, embarrassed, and angry. And although the suit is often frivolous, and there is no negligence, she says, a significant amount of time and money are still required to deal with the situation. In any given year, she says, one in 20 dermatologists gets sued. Even if the suit is dismissed or withdrawn, it can be emotionally devastating.

Amy Forman Taub, M.D., says that the first time she was sued by a patient, it was devastating.

"I actually thought about changing professions," she says.

One thing she found helpful was a one-day malpractice seminar offered by her insurance company. The retreat featured talks by attorneys. It helped her understand the legal process and take the lawsuit less personally, she says.

"You can't win the case by reviewing the chart 5,000 times," Dr. Taub says. "You have to continue to provide the best care possible to the patients you see each day, and this can't be done if you are second-guessing yourself. It's important to turn to your family for reassurance and focus on the good outcomes." **DT**

Disclosures: Dr. Waldorf is a speaker and consultant for Allergan, Merz, Valeant and Galderma. Dr. Chilukuri is a speaker and consultant for Allergan, Galderma and Cynosure Lasers and a consultant for Theravant Lasers. Dr. Woodward is a speaker for SkinCeuticals, NeoCutis, Lutronic and Merz. Dr. Taub reports no relevant financial interests.

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The Art of Skin

Dermatologist sees art in histopathological images; strikes artistic chord with son

LISETTE HILTON | STAFF CORRESPONDENT

El Paso, Texas, dermatologist Hector L. Franco, M.D., looks at images of skin biopsies for histopathological changes that might indicate skin disease.

But there's more to those images than their diagnostic value, he says.

Dr. Franco

"...one finds that many of these images contain patterns and colors that offer potential artistic value," Dr. Franco says. "Many of the histopathological images seen in a skin biopsy are pleasing because they have a recognizable pattern to them and, therefore, represent a diagnosis to us, as dermatologists. On the other hand, some histopathological images are just pleasing unto themselves because, whether you know what the diagnosis is or not, they are pleasing to the mind's eye. In essence, that is what abstract art does, it pleases the eye without necessarily giving you a recognizable image."

Dr. Franco's son, Nick Franco, an artist living in Chicago, has brought his father's thinking to life in a collection he calls "inskin."

An abstract artist in his late 30s, Franco graduated from the School of the Art Institute of Chicago and has a master's in art education. He has exhibited his paintings Colorado, Texas, Arizona and Illinois.

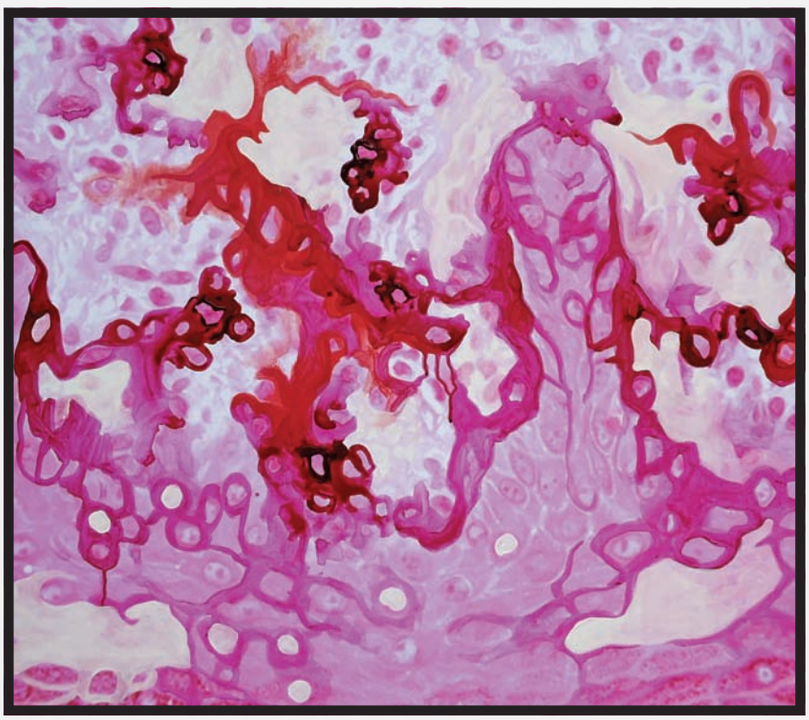
Nick had been working on his previous collection, the Thread Paintings, for more than a decade and was ready for a change. His father's recent suggestion struck an artistic chord, bringing back memories from when he was a kid and looked through Dr. Franco's journals and dermatology books.

"They're quite beautiful, as far as the color, patterns and overall design. The imagery effect is actually quite interesting to look at, especially for an abstract artist," Nick says.

ART OF SKIN see page 60

"The digital print (above) is of the diagnosis dermoepidermal junction. Layers of a fluid acrylic paint have been applied to areas of the canvas — some in a very thick application, others very thin to allow the original print to show through. For the title, I likened dermoepidermal to living outside the norm, and junction to a bond between people." — Nick Franco

Photo: Union of Outsiders, 2014. Acrylic & digital print on canvas, 1 ft 8 in x 2 ft.



"The digital print is of the diagnosis for mastocytosis. This work is gestural, with fluid acrylic outlining the cells in burgundy and layers of white creating new shapes within the composition. Like the other inskin paintings that incorporate a digital print, the image for the diagnosis has been altered digitally. The hues have been changed and the original composition turned upside down and cropped. For the title, I considered the condition: too many mast cells in the body. The term "mast" made me think of ships. When I looked at the finished piece, it reminded me of a storm at sea, with ships crashing into each other. I began to see various objects, possibly cargo, floating in the water." — Nick Franco

Photo: Too Many Ships at Sea, 2015. Acrylic & digital print on canvas, 2 ft 6 in x 3 ft 4 in.

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References: 1. SOLODYN Tablets Package Insert. Scottsdale, AZ: Valeant Dermatology; February 2012.
2. Data on file, Valeant Pharmaceuticals.

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SOLODYN®
(MINOCYCLINE HCl, USP)
EXTENDED RELEASE TABLETS

BRIEF SUMMARY
(see package insert for full prescribing information)

SOLODYN®
(minocycline HCl, USP) Extended Release Tablets

Rx Only
KEEP OUT OF REACH OF CHILDREN

INDICATIONS AND USAGE

Indication
SOLODYN is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

Limitations of Use
SOLODYN did not demonstrate any effect on non-inflammatory acne lesions. Safety of SOLODYN 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, SOLODYN should be used only as indicated *(see Warnings and Precautions)*.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS AND PRECAUTIONS

Teratogenic Effects

A. MINOCYCLINE, LIKE OTHER TETRACYCLINE-CLASS DRUGS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS.

SOLODYN should not be used during pregnancy or by individuals of either gender who are attempting to conceive a child *(see Nonclinical Toxicology & Use in Specific Populations)*.

B. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD UP TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED DURING TOOTH DEVELOPMENT.

C. All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated early in pregnancy *(see Use in Specific Populations)*.

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against Clostridium difficile colitis.

Hepatotoxicity
Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with minocycline use in the treatment of acne.

Metabolic Effects
The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

Central Nervous System Effects
Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually rapidly disappear when the drug is discontinued.

Benign Intracranial Hypertension
Pseudotumor cerebri (benign intracranial hypertension) in adults and adolescents has been associated with the use of tetracyclines. Minocycline has been reported to cause or precipitate pseudotumor cerebri, the hallmark of which is papilledema. Clinical manifestations include headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. Although signs and symptoms of pseudotumor cerebri resolve after discontinuation of treatment, the possibility for permanent sequelae such as visual loss that may be permanent or severe exists. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. If visual disturbance occurs during treatment, patients should be checked for papilledema. Concomitant use of isotretinoin and minocycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause pseudotumor cerebri.

Autoimmune Syndromes
Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis. Sporadic cases of serum sickness have presented shortly after minocycline use. Symptoms may be manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, liver function tests, ANA, CBC, and other appropriate tests should be performed to evaluate the patients. Use of all tetracycline-class drugs should be discontinued immediately.

Photosensitivity
Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using minocycline. If patients need to be outdoors while using minocycline, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician.

Serious Skin/Hypersensitivity Reaction
Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with minocycline use in patients with acne. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported. If this syndrome is recognized, the drug should be discontinued immediately.

Tissue Hyperpigmentation
Tetracycline-class antibiotics are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as over sites of scars or injury.

Development of Drug Resistant Bacteria
Bacterial resistance to the tetracyclines may develop in patients using SOLODYN, therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of SOLODYN, it should be used only as indicated.

Superinfection
As with other antibiotic preparations, use of SOLODYN may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, SOLODYN should be discontinued and appropriate therapy instituted.

Laboratory Monitoring
Periodic laboratory evaluations of organ systems, including hematopoietic, renal and hepatic studies should be performed. Appropriate tests for autoimmune syndromes should be performed as indicated.

ADVERSE REACTIONS

Clinical Trial Experience
Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not reflect the rates observed in practice.

The following table summarizes selected adverse reactions reported in clinical trials at a rate of ≥1% for SOLODYN.

Selected Treatment-Emergent Adverse Reactions in at least 1% of Clinical Trial Subjects

Adverse Reactions	SOLODYN (1 mg/kg) N=674 (%)	PLACEBO N=364 (%)
At least one treatment-emergent event	379 (56)	197 (54)
Headache	152 (23)	83 (23)
Fatigue	62 (9)	24 (7)
Dizziness	59 (9)	17 (5)
Pruritus	31 (5)	16 (4)
Malaise	26 (4)	9 (3)
Mood alteration	17 (3)	9 (3)
Somnolence	13 (2)	3 (1)
Urticaria	10 (2)	1 (0)
Tinnitus	10 (2)	5 (1)
Arthralgia	9 (1)	2 (0)
Vertigo	8 (1)	3 (1)
Dry mouth	7 (1)	5 (1)
Myalgia	7 (1)	4 (1)

Postmarketing Experience
Adverse reactions that have been reported with minocycline hydrochloride use in a variety of indications include:

Skin and hypersensitivity reactions: fixed drug eruptions, balanitis, erythema multiforme, Stevens-Johnson syndrome, anaphylactoid purpura, photosensitivity, pigmentation of skin and mucous membranes, hypersensitivity reactions, angioneurotic edema, anaphylaxis, DRESS syndrome *(see Warnings and Precautions)*.

Autoimmune conditions: polyarthralgia, pericarditis, exacerbation of systemic lupus, pulmonary infiltrates with eosinophilia, transient lupus-like syndrome.

Central nervous system: pseudotumor cerebri, bulging fontanels in infants, decreased hearing.

Endocrine: brown-black microscopic thyroid discoloration, abnormal thyroid function.

Oncology: thyroid cancer.

Oral: glossitis, dysphagia, tooth discoloration.

Gastrointestinal: enterocolitis, pancreatitis, hepatitis, liver failure.

Renal: reversible acute renal failure.

Hematology: hemolytic anemia, thrombocytopenia, eosinophilia.

Preliminary studies suggest that use of minocycline may have deleterious effects on human spermatogenesis *(see Nonclinical Toxicology)*.

DRUG INTERACTIONS

Anticoagulants

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Penicillin

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

Methoxyflurane

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Antacids and Iron Preparations

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium and iron-containing preparations.

Low Dose Oral Contraceptives

In a multi-center study to evaluate the effect of SOLODYN on low dose oral contraceptives, hormone levels over one menstrual cycle with and without SOLODYN 1 mg/kg once-daily were measured. Based on the results of this trial, minocycline-related changes in estradiol, progestinic hormone, FSH and LH plasma levels, of breakthrough bleeding, or of contraceptive failure, cannot be ruled out. To avoid contraceptive failure, female patients are advised to use a second form of contraceptive during treatment with minocycline.

Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy category D (see Warnings and Precautions)

SOLODYN should not be used during pregnancy. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and stop treatment immediately.

There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class drugs, crosses the placenta and may cause fetal harm when administered to a pregnant woman.

Rare spontaneous reports of congenital anomalies including limb reduction have been reported with minocycline use in pregnancy in post-marketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established.

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits in doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (resulting in approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients as a result of use of SOLODYN). Reduced mean fetal body weight was observed in studies in which minocycline was administered to pregnant rats at a dose of 10 mg/kg/day (which resulted in approximately the same level of systemic exposure to minocycline as that observed in patients who use SOLODYN).

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats from day 6 of gestation through the period of lactation (postpartum day 20), at dosages of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (resulting in approximately 2.5 times the systemic exposure to minocycline observed in patients as a result of use of SOLODYN). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

Nursing Mothers

Tetracycline-class antibiotics are excreted in human milk. Because of the potential for serious adverse effects on bone and tooth development in nursing infants from the tetracycline-class antibiotics, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother *(see Warnings and Precautions)*.

Pediatric Use

SOLODYN is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years and older. Safety and effectiveness in pediatric patients below the age of 12 has not been established.

Use of tetracycline-class antibiotics below the age of 8 is not recommended due to the potential for tooth discoloration *(see Warnings and Precautions)*.

Geriatric Use

Clinical studies of SOLODYN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Minocycline is not removed in significant quantities by hemodialysis or peritoneal dialysis.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis—Long-term animal studies have not been performed to evaluate the carcinogenic potential of minocycline. A structurally related compound, oxytetracycline, was found to produce adrenal and pituitary tumors in rats.

Mutagenesis—Minocycline was not mutagenic *in vitro* in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic *in vitro* using human peripheral blood lymphocytes or *in vivo* in a mouse micronucleus test.

Impairment of Fertility—Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (which resulted in up to approximately 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN) adversely affected spermatogenesis. Effects observed at 300 mg/kg/day included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

Limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis.

SOLODYN should not be used by individuals of either gender who are attempting to conceive a child.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

SOLODYN (minocycline HCl, USP) Extended Release Tablets are supplied as aqueous film coated tablets containing minocycline hydrochloride equivalent to 55 mg, 65 mg, 80 mg, 105 mg or 115 mg minocycline, are supplied as follows.

The 55 mg extended release tablets are pink, unscored, coated, and debossed with “DYN-055” on one side. Each tablet contains minocycline hydrochloride equivalent to 55 mg minocycline, supplied as follows:

NDC 99207-465-30 Bottle of 30

The 65 mg extended release tablets are blue, unscored, coated, and debossed with “DYN-065” on one side. Each tablet contains minocycline hydrochloride equivalent to 65 mg minocycline, supplied as follows:

NDC 99207-463-30 Bottle of 30

The 80 mg extended release tablets are dark gray, unscored, coated, and debossed with “DYN-080” on one side. Each tablet contains minocycline hydrochloride equivalent to 80 mg minocycline, supplied as follows:

NDC 99207-466-30 Bottle of 30

The 105 mg extended release tablets are purple, unscored, coated, and debossed with “DYN-105” on one side. Each tablet contains minocycline hydrochloride equivalent to 105 mg minocycline, supplied as follows:

NDC 99207-467-30 Bottle of 30

The 115 mg extended release tablets are green, unscored, coated, and debossed with “DYN-115” on one side. Each tablet contains minocycline hydrochloride equivalent to 115 mg minocycline, supplied as follows:

NDC 99207-464-30 Bottle of 30

Storage

Store at 25ºC (77ºF); excursions are permitted to 15º-30ºC (59º-86ºF) [See USP Controlled Room Temperature].

Handling

Keep out of reach of children

Protect from light, moisture, and excessive heat.

Dispense in tight, light-resistant container with child-resistant closure.

U.S. Patents 5,908,838; 7,790,705; 7,919,483; and Patents Pending*
*90 mg is also covered by U.S. Patents 7,541,347 and 7,544,373

Manufactured for:
Medicis, The Dermatology Company
Scottsdale, AZ 85256

02/2012

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ART OF SKIN:
Artistic perspective combines art and medicine *from page* **56**

SKIN MEETS EXPRESSIONISM

His inskin collection includes a handful of paintings that combine abstract expressionism with dermatology.


Nick Franco

It all starts with a search for the right image—one which Nick says offers something that can be brought out or emphasized. Once he finds the image, he'll alter it slightly, digitally. That might mean changing color or tone, or turning the image to a different angle. Nick then sends the digitally enhanced image to a printing company, which puts it on canvas. That's when Nick reaches for his paintbrushes, using acrylics to manipulate the image into a work of art.

"I want to be respectful of the image that I have digitally displayed on the canvas. I don't want it to look like paint on top of a digital print. I don't want the two to read as separate. I want them to read as this cohesive design," Nick says. "So, what I'll do is really examine the style, the composition, the patterns as a design on the digital print, and also the colors. [I'll] use acrylic paints to mimic it, to bring out some areas and maybe push some areas back or take them out altogether, just to create a new design."

"The digital print is of the diagnosis parathyroid adenoma. Blue-green acrylic stains multiple areas of the print, with thicker color applications for the circles and organic shapes. For the title, I began to see an aerial view of a battle. Shields are paired, or joined together, but they are doing little to protect their soldiers." — Nick Franco

Photo: Pairing Shields without Protection, 2014. Acrylic & digital print on canvas, 2 ft 6 in x 1 ft 8 in.

PHYSICIAN PARTNERSHIP

Chicago dermatologist Ron Berne, M.D., hired Nick, who also designs websites, to redo the practice website and create a practice logo. The logo is an artistic three-dimensional cross-section of skin.

"I wanted a clean, simple logo that left no doubt that we are all about skin health," Dr. Berne tells *Dermatology Times*.

The staff was so pleased with the logo's image that staff members recommended a larger, more detailed mural for the office. The result is a canvas painting of an anatomically precise three-dimensional cutaway of typical skin anatomy.

"...much like the famous drawings of the medical artist Frank Netter, the lighter blue surrounding the cube makes the detailed anatomic version 'float'!" says Dr. Berne.

Patients and staff have only had positive feedback about the painting, according to Dr. Berne.

The image in Dr. Berne's office and those of histopathology are different from an artistic perspective, however. Painting the cross-section of skin requires that Franco remain specific and true to the original design. He can play more in the paintings originating from histopathology, Franco says.


Dr. Berne

AN EYE FOR SKIN

Nick says he likes the idea of collaborating with dermatologists on pieces.

"When you're an artist and are working in your studio, you're really operating off your own inspiration, but, by incorporating the histopathologies and especially the input of other doctors, it would be interesting to reach this collaboration between the two," Nick says.

The paintings range in size from small (about a foot by a foot) to larger images. Prices in the collection he has now range from $700 for a smaller painting to $1,400 for one that's larger.

Nick says his focus for the foreseeable future is on inskin.

"I would like to keep pursuing this because it's really a challenge for me to have to work into something that has kind of already been created," he says. "I like the idea of combining these mediums. In the Chicago area, as far as the art scene is concerned, I haven't seen a whole lot of that — where there's something that combines art and medicine."

Dr. Franco says his son has successfully taken an image that is simply clinical and transformed it into something pleasing and artistic.

"It is something that can be admired on a wall," Dr. Franco says. "When a dermatologist or dermatopathologist looks at these paintings, it can feel a little bit like double dipping.... On the one hand, they can recognize the mast cell infiltrate of mastocytosis or the derma-epidermal clefting and epidermal necrosis of T.E.N. On the other hand, they can sit back and simply appreciate the colors and patterns that the artist has put on canvas." **DT**

To see the inskin collection visit Nick Franco's website at **www.nickfrancoart.com**

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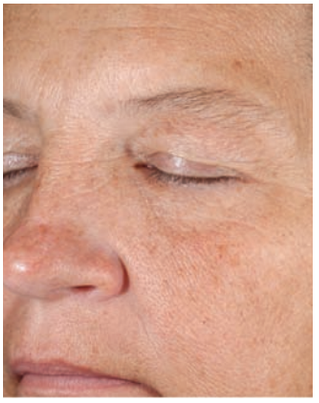
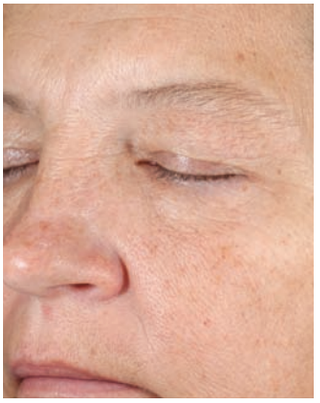


After 12 weeks*



*Data on file. Results may vary.

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Joshua Freedman, M.D., M.S., has a background in electrical and biomedical engineering. He is currently a resident physician at the University of Miami, Department of Dermatology & Cutaneous Surgery.

Jeremy B. Green, M.D. and Joely Kaufman, M.D., are in private practice at Dr. Brandt Dermatology Assoc., and voluntary assistant professors, University of Miami, Department of Dermatology & Cutaneous Surgery.

Fractionated bipolar radiofrequency devices rejuvenate skin

THE CLINICAL utility of radiofrequency (RF) devices is to deliver various morphologies of energy to biologic tissue, with objectives ranging from destruction to denaturing and rejuvenation. In the context of dermatology, three fundamental types of RF devices exist: monopolar, unipolar and bipolar, which are differentiated by the configuration of electrodes and corresponding electromagnetic fields.

Fractionated RF is a variant of bipolar RF, wherein an electrode array is patterned to divide the treatment field into multiple RF thermal zones (RFTZs) with intervening areas of untreated tissue. The application of these technologies include tightening of the skin, rhytid reduction, striae reduction, as well as heating of adipose tissue used in body contouring and cellulite reduction.

Fractionated bipolar RF creates superficial RFTZs, and it is most commonly used today for rejuvenation of the skin. Because RF devices function independent of chromophores, they can be used on all skin types with little to no risk of pigment alteration.

Radiofrequency refers to oscillating electromagnetic waves within the range of 3 kHz to 300 GHz. To provide perspective, cellular telephone signals operate from 800 MHz to 2.69 GHz, and there is rarely a moment a person in the industrialized world is not being infinitesimally irradiated by one source or another such as these cellular carrier signals, WiFi or Bluetooth. These signals are typically distant from the transmitter and have low power density, and thus a presumed negligible biological effect. At higher power densities, achieved adjacent to an RF emitter, plentiful physical interactions can occur.

DERMATOLOGIC APPLICATIONS

In dermatological applications, RF devices produce dielectric heating of organic matter; at higher frequencies the dominant mechanism may be due to molecular dipole rotation of water, which rotates rapidly to align itself with the rapidly alternating electromagnetic field (EMF). These rotating molecules in turn locally impart electric forces to neighboring molecules generating collisions that translate to kinetic energy, or heat. At lower frequencies, alternate mechanisms such as ion drag may be the predominant mechanism translating the EMF energy into thermal energy.

The conductivity of the material determines the response; for example, in RF devices the dry epidermis might be vaporized while the dermis experiences a lesser degree of heating, which is one reason cooling devices are needed. The EMF pattern is determined by the geometry of the electrodes, their size, shape, placement and metal can be designed to optimize fields for a specific application, and the voltage, current, frequency are parameters which modify the effect on tissue.

Monopolar RF devices use a single electrode with a distant ground pad or plate connected to the patient. The most common use in dermatology historically has been electrosurgery; however, in recent years devices with cosmetic applications have been cleared for tightening of lax skin, wrinkle reduction, improvement in the appearance of cellulite and body contouring via thermal effects on adipocytes.

Thermage (Solta Medical) was the first device the Food and Drug Administration cleared for RF skin contraction in 2002, followed by periocular wrinkles (2004) and body contouring (2006). Exilis (BTL), Cutera (Trusculpt) and Ellman (Pelleve) are other monopolar RF devices. What these devices have in common is the capacity to treat a range of depths from superficial dermis to subcutaneous fat.

UNIPOLAR VERSUS BIPOLAR

Unipolar RF devices have a single electrode without a ground, wherein current is driven solely by the voltage difference between the electrode and the organic tissue. These devices radiate omnidirectionally, much the way a light bulb does and may also reach the subcutaneous tissue similar to monopolar devices. Common applications include noninvasive skin-tightening treatment of larger tissue areas such as abdomen, thighs, arms, cellulite reduction and body contouring. These devices can also be used for sagging jowls and wrinkle reduction. The Accent (Alma Lasers) uses both unipolar RF for volumetric heating of adipose tissue and bipolar RF for more superficial, non-volumetric heating.

The bipolar modality of RF delivery utilizes two electrodes, a positive and negative; alternating current flows back and forth between these points. The effective field depth, and thus the depth of tissue heated, is determined by the distance of electrodes in relation to one another, although the degree of heating is still determined by the electrical parameters of the EMF.

Several incarnations of this modality are seen in clinical use: arrays of flat electrodes placed on the epidermis (eMatrix, e2, Syneron); needle electrodes mechanically inserted

FRACTIONATED *see page* **64**

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Studies conducted on patients 2 months to 65 years of age.

** Eczema Area Severity Index*

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1. Data on file.

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FRACTIONATED:
Bipolar RF delivers alternating current between two electrodes *from page* **62**

into the skin (ePrime, Syneron), (Infini, Lutronic) an array with electrodes at varied distances to achieve different depths of penetration (Endymed PRO, Endymed), and bipolar devices combined with other optical energy delivery modalities such as diode laser, or intense pulsed light (IPL; Polaris, Syneron).

Some bipolar devices utilize vacuum technology, which may enhance the depth of heating achieved. These include TiteFx (Invasix), Reaction and Vtouch (Viora). Velashape II (Syneron) combines bipolar RF with vacuum as well as infrared light. Venus Freeze (Venus Concept) uses an array of bipolar electrodes they call "multipolar," along with a magnetic pulse. Other bipolar devices on the market include Accent Elite (Alma) and Apollo-Tripolar (Pollagen).

PRACTICAL DIFFERENCES

Fractionated bipolar RF techniques migrate the concept of fractional photothermolysis (FP) from lasers to RF technologies, with some practical differences. Fractional photothermolysis was initially introduced in 2003 based on a conceptual shift from treating a continuous plane of tissue to using an array of microscopic columns of spatially confined thermal injury.[1]

The concept that untreated areas of tissue provide reservoirs which fuel a more rapid dermal remodeling process was later demonstrated histologically.[2, 3]

The observation of skin tightening in fractionated bipolar RF was strongly supported by a histological study of fractionated RF (FRF), which demonstrated significant neoelastogenesis and neocollagenesis.[4]

This study used microneedle electrodes implanted in abdominal skin; tissue temperature was held at 72 degrees Celsius for four seconds. Analysis demonstrated in the reticular dermis zones of denatured collagen they termed RF thermal zones (RFTZ) with interspersed unaltered dermis. RFTZs persisted at 28 days, but had been replaced by new tissue at 10 weeks.

The reticular dermis demonstrated increased volume, cellularity, hyaluronic acid and elastin content. Immediate increases in IL-1B, TNF-A and MMP-13 were noted and followed by increases in MMP-1, HSP72, HSP47 and TGF-B by two days. There were marked increases in tropoelastin, fibrillin and procollagen 1 and 3 by day 28.

A major difference between bipolar FRF tissue injury patterns and those created from FP is the shape of the RFTZ. Where FP creates thermal injury in dermal columns that taper as they descend; FRF creates a different pattern that depends on the electrode configuration. Arrays of surface electrodes create zones of dermal injury narrowest at the epidermis, which enlarge conically as they descend until the pattern is truncated by attenuation.

Some bipolar devices utilize vacuum technology, which may enhance the depth of heating achieved.

Using fixed electrode placement, the depth of penetration is energy dependent, with maximal depths of 450 µm attained by 10 J to 20 J power setting with a bipolar device.[5]

This pattern of thermal injury has been termed by some as "sublative" referring to its effect beneath the ablated zone at the epidermis, with only 5% of the epidermis affected (using eMatrix 64 electrode array). In contrast, microneedle FRF systems generate ovoid or cocoon-shaped areas of dermal coagulation. Depth of injury in these systems is reported to depend on microneedle depth and RF conduction times, but not energy levels, while the width of these RFTZs is dependent on conduction times[6].

STUDY RESULTS

The majority of studies using bipolar FRF devices report clinical improvement in photoaging, skin laxity and rhytids, gauged by photographic assessment after three treatments, and patient satisfaction, assessed by periodic questionnaire. Hruza et al. found more than half of 33 patients, skin types II-IV, experienced greater than 40% improvement in texture and 80% of patients were satisfied.[5]

Seung Lee et al. reported moderate (26 to 50%) and incremental improvement in 26 Asian women in skin tightness, brightness and overall appearance.[7]

Man and Goldberg reported significant improvement in most of 15 patients with darker skin types V-VI, without any postinflammatory pigmentary alteration.[8]

Numerous other small studies not detailed here echo the findings of moderate clinical improvement following a regimen of three treatments, majority patient satisfaction, safety in Asian and African-American patients and no significant adverse events. The 50 W bipolar RF system (Infini, Lutronic) with 49 proximally insulated needles was found in a pig model to induce cocoon-shaped zones of thermal coagulation, which increased in volume with increasing energy levels and increasing RF conduction times.[6]

Another study utilizing this same device found a sebosuppressive effect of a single treatment at 1.5 mm depth on Korean patients.[7]

Acne scars have also been the target of research. Ramesh et al. found 10 to 50% and 20 to 70% improvement in acne scars at the end of two and six, months respectively.[9]

Gold and Biron reported improvement in acne scars in 10 patients, skin types I-V, accompanied by high patient satisfaction.[10]

Particularly regarding acne scarring, several efforts to utilize this modality synergistically with laser and light devices have been reported.

Radiofrequency devices have become an important contributor to the

FRACTIONATED *see page* **67**

Corticosteroid DUAL ACTION Vitamin D_3 analog

Experience the combined efficacy and safety of 2 active ingredients with Taclonex® Topical Suspension[1,2]

See the difference that dual action can make at www.taclonex.com

*Also indicated for both scalp and body plaque psoriasis in adults ages 18 and older.

INDICATION AND USAGE

Taclonex® Topical Suspension is indicated for the topical treatment of plaque psoriasis of the scalp and body in patients 18 years and older and for plaque psoriasis of the scalp in patients 12 to 17 years. Patients 18 years and older should not use more than 100 g per week and patients 12 to 17 years should not use more than 60 g per week.

IMPORTANT SAFETY INFORMATION

Taclonex® Topical Suspension is not for oral, ophthalmic, or intravaginal use and should not be applied to the face, axillae, or groin. Do not use if atrophy is present at the treatment site. Do not use with occlusive dressings unless directed by a physician.

If hypercalcemia or hypercalciuria develop, discontinue until parameters of calcium metabolism normalize. Taclonex® can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent steroid. Cushing's syndrome and hyperglycemia may also occur in adults. Pediatric patients are at a greater risk than adults of systemic toxicity, HPA axis suppression and adrenal insufficiency.

The most common adverse reactions (≥1%) are folliculitis and burning sensation of skin.

Patients who apply Taclonex® to exposed skin should avoid excessive exposure to either natural or artificial sunlight. There are no adequate and well-controlled studies of Taclonex® Topical Suspension in pregnant women. Safety and effectiveness of the use of Taclonex® Topical Suspension in pediatric patients under the age of 12 years have not been established.

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

References: 1. Taclonex® Topical Suspension [package insert]. Parsippany, NJ: LEO Pharma Inc.; August 2014. **2.** Segaert S, Ropke M. The biological rationale for use of vitamin D analogs in combination with corticosteroids for the topical treatment of plaque psoriasis. *J Drugs Dermatol.* 2013;12(8):e129-e137.

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LEO®

Taclonex®

(calcipotriene and betamethasone dipropionate)
Topical Suspension, 0.005%/0.064%

Rx Only

BRIEF SUMMARY (See Package Insert for full Prescribing Information).

INDICATIONS AND USAGE: Taclonex® Topical Suspension is indicated for the topical treatment of:

- Plaque psoriasis of the scalp and body in patients 18 years and older
- Plaque psoriasis of the scalp in patients 12 to 17 years

WARNINGS AND PRECAUTIONS: Hypercalcemia and Hypercalciuria:
Hypercalcemia and hypercalciuria have been observed with use of Taclonex® Topical Suspension. If hypercalcemia or hypercalciuria develop, discontinue treatment until parameters of calcium metabolism have normalized. The incidence of hypercalcemia and hypercalciuria following Taclonex® Topical Suspension treatment of more than 8 weeks has not been evaluated. **Effects on Endocrine System:** Taclonex® Topical Suspension can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age. Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test. In a trial evaluating the effects of Taclonex® Topical Suspension and Taclonex® Ointment on the HPA axis, 32 adult subjects were treated with both Taclonex® Topical Suspension on the scalp and Taclonex® Ointment on the body. Adrenal suppression was identified in 5 of 32 subjects (16%) after 4 weeks of treatment and in 2 of 11 subjects (18%) who continued treatment for 8 weeks. In another trial of 43 subjects treated with Taclonex® Topical Suspension on body (including the scalp in 36 out of 43 subjects) adrenal suppression was identified in 3 out of 43 subjects (7%) after 4 weeks of treatment and in none of the 36 subjects who continued treatment for 8 weeks. In a trial evaluating the effects of Taclonex® Topical Suspension on the HPA axis, 31 subjects aged 12 to 17 years were treated with Taclonex® Topical Suspension on the scalp. Adrenal suppression was identified in 1 of 30 evaluable subjects (3.3%) after 4 weeks of treatment. If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. Cushing's syndrome and hyperglycemia may also occur due to the systemic effects of the topical corticosteroid. These complications are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids. Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure. **Allergic Contact Dermatitis with Topical Corticosteroids:** Allergic contact dermatitis to a topical corticosteroid is usually diagnosed by observing a failure to heal rather than a clinical exacerbation. Such an observation should be corroborated with appropriate diagnostic patch testing. **Allergic Contact Dermatitis with Topical Calcipotriene:** Allergic contact dermatitis has been observed with use of topical calcipotriene. Such an observation should be corroborated with appropriate diagnostic patch testing. **Eye Irritation:** Avoid eye exposures. Taclonex® Topical Suspension may cause eye irritation. **Risks of Ultraviolet Light Exposures:** Patients who apply Taclonex® Topical Suspension to exposed skin should avoid excessive exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc. Physicians may wish to limit or avoid use of phototherapy in patients who use Taclonex® Topical Suspension.

CONTRAINDICATIONS: None.

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 directed compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. *Clinical Trials Conducted in Subjects 18 years and older with Scalp Psoriasis:* The rates of adverse reactions given below were derived from randomized, multicenter, prospective vehicle- and/or active controlled clinical trials in adult subjects with scalp psoriasis. Subjects applied study product once daily for 8 weeks, and the median weekly dose was 12.6 g.
Adverse reactions that occurred in ≥1% of subjects treated with Taclonex® Topical Suspension and at a rate higher than in subjects treated with vehicle are presented in Table 1:

Table 1

Number and Percentage with Adverse Reactions in Scalp Psoriasis Trials (Events Reported by ≥1% of Subjects and for Which a Relationship is Possible)				
	Taclonex® Topical Suspension N=1,953	Betamethasone dipropionate in vehicle N=1,214	Calcipotriene in vehicle N=979	Vehicle N=173
Event	# of subjects (%)			
Folliculitis	16 (1%)	12 (1%)	5 (1%)	0 (0%)
Burning sensation of skin	13 (1%)	10 (1%)	29 (3%)	0 (0%)

Other less common adverse reactions (<1% but >0.1%) were, in decreasing order of incidence: acne, exacerbation of psoriasis, eye irritation, and pustular rash. In a 52-week trial, adverse reactions that were reported by >1% of subjects treated with Taclonex® Topical Suspension were pruritus (3.6%), psoriasis (2.4%), erythema (2.1%), skin irritation (1.4%), and folliculitis (1.2%). *Clinical Trials Conducted in Subjects 18 years and older with Psoriasis on the Body:* In randomized, multicenter, prospective vehicle- and/or active controlled clinical trials in adult subjects with plaque psoriasis on non-scalp areas, subjects applied study product once daily for 8 weeks. A total of 824 subjects were treated with Taclonex® Topical Suspension and the median weekly dose was 22.6 g.
There were no adverse reactions that occurred in ≥1% of subjects treated with Taclonex® Topical Suspension and at a rate higher than in subjects treated with vehicle. Other less common adverse reactions (<1% but >0.1%) were, in decreasing order of incidence: rash and folliculitis. *Clinical Trials Conducted in Subjects 12 to 17 years with Scalp Psoriasis:* In two uncontrolled prospective clinical trials, a total of 109 subjects aged 12-17 years with plaque psoriasis of the scalp were treated with Taclonex® Topical Suspension once daily for up to 8 weeks. The median weekly dose was 40 g. Adverse reactions included acne, acneiform dermatitis and application site pruritus (0.9% each).

USE IN SPECIFIC POPULATIONS: Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Animal reproduction studies have not been conducted with Taclonex® Topical Suspension. Taclonex® Topical Suspension contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically. There are no adequate and well-controlled studies in pregnant women. Taclonex® Topical Suspension should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. **Nursing Mothers:** Systemically administered corticosteroids appear in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topically administered calcipotriene or corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Taclonex® Topical Suspension is administered to a nursing woman. The patient should be instructed not to use Taclonex® Topical Suspension on the breast when nursing. **Pediatric use:** Safety and effectiveness of the use of Taclonex® Topical Suspension in pediatric patients under the age of 12 years have not been established. The safety and effectiveness of Taclonex® Topical Suspension for the treatment of plaque psoriasis of the scalp have been established in the age group 12 to 17 years. Two prospective, uncontrolled trials (N=109) were conducted in pediatric subjects age 12 to 17 years with scalp psoriasis, including assessment of HPA axis suppression in 30 subjects. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity when treated with topical drugs. They are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency upon the use of topical corticosteroids. Rare systemic toxicities such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids. Local adverse reactions including striae have also been reported with use of topical corticosteroids in pediatric patients. **Geriatric use:** Clinical studies of Taclonex® Topical Suspension in plaque psoriasis on non-scalp areas included 124 subjects who were 65 years of age or over, and 36 were 75 years of age or over. Clinical studies of Taclonex® Topical Suspension in scalp psoriasis included 334 subjects who were 65 years or over and 84 subjects who were 75 years or over. No overall differences in safety or effectiveness of Taclonex® Topical Suspension were observed between these subjects and younger subjects, and other reported clinical experience has not identified any differences in response between elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

DOSAGE AND ADMINISTRATION: Instruct patients to shake bottle prior to using Taclonex® Topical Suspension and to wash their hands after applying the product. Apply Taclonex® Topical Suspension to affected areas once daily for up to 8 weeks. Therapy should be discontinued when control is achieved. Patients 18 years and older should not use more than 100 g per week and patients 12 to 17 years should not use more than 60 g per week. Taclonex® Topical Suspension should not be used with occlusive dressings unless directed by a physician. Taclonex® Topical Suspension is not for oral, ophthalmic, or intravaginal use. Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

NONCLINICAL TOXICOLOGY: Calcipotriene may enhance the effect of UVR to induce skin tumors. Long-term animal studies have not been performed to evaluate the carcinogenic potential of betamethasone dipropionate.

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling (Patient Information and Instructions for Use)
Inform patients of the following:

- Instruct adult patients (18 years and older) not to use more than 100 g per week.
- Instruct pediatric patients (12 to 17 years) not to use more than 60 g per week.
- Discontinue therapy when control is achieved unless directed otherwise by the physician.
- Do not apply Taclonex® Topical Suspension to the scalp in the 12 hours before or after any chemical treatments to the hair. Since hair treatments may involve strong chemicals, talk with physician first.
- If applied to the scalp, do not wash hair or take a bath or shower right after application.
- Avoid use of Taclonex® Topical Suspension on the face, underarms, groin or eyes. If this medicine gets on face or in eyes, wash area right away.
- Do not occlude the treatment area with a bandage or other covering unless directed by the physician.
- Note that local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids.
- Wash hands after application.
- Instruct patients not to use other products containing calcipotriene or a corticosteroid with Taclonex® Topical Suspension without first talking to the physician.
- Instruct patients who use Taclonex® Topical Suspension to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.).

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International study reveals benefits of lower-body liposculpting

BILL GILLETTE | STAFF CORRESPONDENT

A TEAM of plastic surgeons on opposite sides of the world says they are getting excellent results and low complication rates with liposculpture of the hips, flanks and thighs.

Yixin Zhang, M.D., of Shanghai JiaoTong University, and Manuel Francesco Castello, M.D., of Clinica Villa Salaria in Rome, and their respective colleagues in China and Italy reviewed 4,000 charts of patients who had undergone lower-body liposuction sculpting. The results showed limited complications, including 50 patients experienced a postsurgical seroma that was resolved after syringe aspirations. One patient developed a major mycobacterial infection that was resolved after antibiotic therapy. Twenty patients complained of minor asymmetries that were corrected six months later under local anesthesia, while 18 experienced minor skin irregularities that improved after lipofilling.

Also, there were six cases of transient hyperpigmentation before suction drainage in the removal of large adiposities in patients with light skin, and two cases of transient paresthesia. No skin necrosis or deep vein thrombosis occurred, and no one died.

The authors stress that a key aspect of the technique is to promote and guide skin retraction after fat removal. This includes careful thinning of the skin so it can better retract and adapt to the new shape.

"The main implication of our finding is that liposculpture should not any longer be considered a method of simple fat aspiration but a very sophisticated method that allows the surgeon to modify the shape of the body and re-contour the profile," Dr. Zhang tells *Cosmetic Surgery Times*. "Indeed, the remodeling properties of superficial liposculpture should be used to reduce fat volumes and for promoting skin retraction, and the skin should no longer be considered a passive element during superficial liposuction but instead as an active, structural and dynamic constituent."

Dr. Castello says he thinks the most significant finding is the procedure's durability: "The long-term results in terms of body contouring and skin retraction have also been maintained in those patients who had pregnancies and weight losses or increases after the surgery." **DT**

The study was published in *PRS-Global Open*, the American Society of Plastic Surgeons' open-access journal.

FRACTIONATED:
Bipolar RF delivers alternating current between two electrodes *from page* **64**

armamentarium of devices available for the treatment of photoaging. The possibility for skin tightening and rejuvenation both on and off the face, in all skin types, ensures a prominent position for these devices in the aesthetic arena. **DT**

Disclosures: Drs. Kaufman and Green have served as consultants for Lutronic.

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Q&A EMU OIL, EMOLLIENTS AND COSMECEUTICALS

Zoe Diana Draelos, M.D., is a *Dermatology Times* editorial adviser and consulting professor of dermatology, Duke University School of Medicine, Durham, N.C. Questions may be submitted via email to zdraelos@northstate.net

COSMETIC CONUNDRUMS

Q. What is Emu oil?

A: Many hair care products and skincare products are featuring Emu oil as their hero active ingredient. Emu oil is obtained from the Emu bird that is native to Australia. It has a rich history in Aboriginal folk medicine for the treatment of cuts, scars, and dry skin. Emu oil is unique in that it contains 70% unsaturated fatty acids (mainly omega-9), 20% linoleic acid (omega-6), and 1-2% linolenic acid (omega-3). Linoleic and linolenic acid are the essential fatty acids necessary to maintain the skin barrier with deficiency resulting a condition resembling eczema.

Essential fatty acids are most like the protective oily coating that is physically bound to the hair shaft. With chemical hair processing involving permanent dyeing, permanent waving, and permanent straightening, this physically bound sebum-like layer is removed. Emu oil is high in essential fatty acids and is used in hair care products to improve hair appearance by increasing shine. Argan oil is another substance rich in essential fatty acids that is also used for this purpose.

Essential fatty acids are most like the protective oily coating that is physically bound to the hair shaft.

Q. What is an emollient?

A: An emollient is an oily substance that fills in the spaces between the desquamating corneocytes, thus creating a smooth skin surface. This emolliency is perceived by the consumer as smoothness and softness and can be immediately appreciated after application. In addition, the smooth surface increases light reflection improving appearance by making the skin luminous and radiant, which are two good cosmetic terms without medical meaning. Emolliency can be achieved through three methods:

- Placing a naturally occurring oily substance over skin surface (petrolatum, mineral oil, vegetable oil)
- Placing a synthetic oily substance over the skin surface (dimethicone, amodimethicone, cyclomethicone, cetyl alcohol, stearyl alcohol, octyl octanoate
- Placing a polymer film over the skin surface (vinyl acetate, polyvinyl pyrrolidone)

Basically, an emollient is a film-forming substance that makes the skin feel and look smooth.

An emollient is a film-forming substance that makes the skin feel and look smooth.

Q. What are the goals of a cosmeceutical?

A: Patients sometimes feel that cosmeceuticals are magic substances that make old skin look like young skin. In the skin care industry, a successful cosmeceutical is designed to deliver these three benefits:

- Make the skin feel smooth and soft
- Reduce transepidermal water loss thereby creating an environment for barrier repair
- Provide an added skin benefit through a novel ingredient technology

The first benefit of making the skin feel smooth and soft is an aesthetic, not functional, benefit.

The second benefit is better known as moisturization and represents a functional benefit.

The third benefit may or may not be hype based on the technology employed.

Thus, cosmeceuticals, which are classified by the FDA as cosmetics, are moisturizers with excellent aesthetics and an advertised ingredient. Since the cosmeceutical marketplace is crowded, cosmeceuticals are differentiated based on their advertised ingredient, which is the least important aspect of their formulation. **DT**

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Therapy offers hope for advanced melanoma

LOUISE GAGNON | STAFF CORRESPONDENT

NIVOLUMAB, A newly developed checkpoint protein inhibitory antibody directed against programmed death-1 (PD-1) with significant clinical activity against melanoma, can treat other malignancies outside of melanoma and renal cell carcinoma, which is one of the big advances with the treatment, according to Jeffrey Weber M.D., Ph.D., senior member of the H. Lee Moffitt Cancer Center, and director, Donald A. Adam Comprehensive Melanoma Research Center in Tampa Bay, Fla.


Dr. Weber

"For the first time, it shows activity/benefit in cancers like non-small-cell lung cancer," Dr. Weber says in an interview with *Dermatology Times*. "It is very effective in melanoma, but it appears to have efficacy in other histologies."

QUICK READ

Nivolumab is a promising treatment for metastatic melanoma and has not produced the same adverse events as have been observed with ipilimumab.

Another progressive step with the administration of nivolumab is that it is producing responses in patients who have not experienced success with ipilimumab therapy, Dr. Weber points out.

"Patients who were previously treated with multiple regimens, including those who failed ipilimumab, which is the established immunotherapy, had benefit," Dr. Weber says.

In a phase 1 study of 90 patients with unresectable stage 3 or 4 melanoma, nivolumab, administered with or without a vaccine, was well-tolerated and induced responses lasting up to 140 weeks.[1]

"Our goal is to enrich the response rate," Dr. Weber says. "It is now one out of three (patients who respond). If we can increase the response rate to two out of three, it would save a lot of healthcare dollars."

Dr. Weber notes that there was no difference between patients in the study who were administered the vaccine and those who were not, pointing out that the vaccine was intended as an immunological marker and not a therapeutic intervention.

PREDICTIVE BIOMARKERS

To increase the response rate, Dr. Weber and colleagues are on the hunt for appropriate biomarkers that would assist in predicting response.

"We noticed that high pre-treatment myeloid suppressor cell levels were associated with poor outcomes," Dr. Weber explains.

"Another important point is that we didn't see the same toxicity that occurred with the use of ipilimumab," he says. "You can safely administer

NIVOLUMAB *see page* **73**

Quotable

"We used to think that the defects within the Hedgehog signaling pathway were the primary or even the only driver in carcinogenesis."

James Macdonald, M.D.
Provo, Utah

on molecular insights advancing BCC tx

See story page 1

DTExtra

In a two-year study, researchers at the UCLA Jonsson Comprehensive Cancer Center took 43 tumor samples from 15 patients before they were prescribed the new BRAF+MEK inhibitor combo drugs and again after they relapsed when the melanoma developed resistance. The biopsied tumors were analyzed for genetic material. The researchers found that the melanoma cells developed highly unusual genetic changes in certain key cancer genes to resist the combo inhibitors. These changes not only mark the presence of drug resistant melanoma cells but also can lead to potential ways to shut them off.

READ MORE: BIT.LY/MELANOMARESISTANCE

DO YOUR PATIENTS HAVE ATHLETE'S FOOT BETWEEN THE TOES?

WTF?

What the Foot?

For tinea pedis due to *Trichophyton rubrum* and *Epidermophyton floccosum* in adult patients

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LUZU has the strength to clear fungus and relieve signs and symptoms of interdigital tinea pedis.* LUZU is the only topical azole antifungal approved to treat interdigital tinea pedis with once-daily, 2-week dosing. Efficacy demonstrated at 4 weeks post-treatment. **Treat it fast with LUZU.**

*The complete clearance rates (primary efficacy outcome) in the two trials, assessed at 4 weeks post-treatment following two weeks of double-blind once-daily treatment, were 26% vs 2% (N=209) and 14% vs 3% (N=214) for LUZU vs vehicle, respectively. Complete clearance was defined as achieving both clinical cure (absence of erythema, scaling, and pruritis) and mycological cure (negative KOH and negative fungal culture).

If your patients are asking WTF? What the Foot? Tell them about LUZU.
Visit LuzuRx.com for more information.

Indication

LUZU (luliconazole) Cream, 1% is indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum* in patients 18 years of age and older.

Important Safety Information

LUZU is indicated for topical use only and is not indicated for ophthalmic, oral or intravaginal use.

LUZU should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised when LUZU is prescribed for nursing mothers.

The most common adverse reactions in clinical trials were application site reactions, which occurred in less than 1% of subjects in both LUZU and vehicle arms. Most adverse reactions were mild in severity.

Please see Brief Summary of Prescribing Information for LUZU on next page.

Reference: 1. LUZU [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals; 2014.

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION FOR LUZU (luliconazole)
This Brief Summary does not include all the information needed to use LUZU safely and effectively. See full Prescribing Information for LUZU.

LUZU (luliconazole) Cream, 1% for topical use
Initial U.S. Approval: 2013

Rx Only

INDICATIONS
LUZU (luliconazole) Cream, 1% is an azole antifungal indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older.

DOSAGE AND ADMINISTRATION
For topical use only. LUZU Cream, 1% is not for ophthalmic, oral, or intravaginal use.
When treating interdigital tinea pedis, a thin layer of LUZU Cream, 1% should be applied to the affected area and approximately 1 inch of the immediate surrounding area(s) once daily for two (2) weeks.
When treating tinea cruris or tinea corporis, LUZU Cream, 1% should be applied to the affected area and approximately 1 inch of the immediate surrounding area(s) once daily for one (1) week.

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

In three Phase 3 clinical trials, 616 subjects were exposed to LUZU Cream, 1%: 305 with interdigital tinea pedis and 311 subjects with tinea cruris. Subjects with interdigital tinea pedis or tinea cruris applied LUZU Cream, 1% or vehicle cream once daily for 14 days or 7 days, respectively, to affected and adjacent areas. During clinical trials with LUZU Cream, 1% the most common adverse reactions were application site reactions which occurred in less than 1% of subjects in both the LUZU and vehicle arms. Most adverse reactions were mild in severity.

Post-Marketing Experience
The following adverse reactions have been identified during postmarketing use of luliconazole cream, 1%: contact dermatitis and cellulitis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS
The potential of luliconazole to inhibit cytochrome P-450 (CYP) enzymes 1A2, 2C9, 2C19, 2D6, and 3A4 was evaluated *in vitro*. Based on *in vitro* assessment, luliconazole at therapeutic doses, particularly when applied to patients with moderate to severe tinea cruris, may inhibit the activity of CYP2C19 and CYP3A4. However, no *in vivo* drug interaction trials have been conducted to evaluate the effect of luliconazole on other drugs that are substrates of CYP2C19 and CYP3A4.

Luliconazole is not expected to inhibit CYPs 1A2, 2C9 and 2D6 based on *in vitro* assessment. The induction potential of luliconazole on CYP enzymes has not been evaluated.

USE IN SPECIFIC POPULATIONS
Pregnancy: Pregnancy Category C.
There are no adequate and well-controlled studies of LUZU Cream, 1% in pregnant women. LUZU Cream, 1% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The animal multiples of human exposure calculations were based on daily dose body surface area (BSA) comparisons (mg/m^2) for the reproductive toxicology studies described in this section and in Section 13.1 of the prescribing information. The Maximum Recommended Human Dose (MRHD) was set at 8 g 1% cream per day (1.33 mg/kg/day for a 60 kg individual which is equivalent to 49.2 mg/m^2/day).

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered during the period of organogenesis (gestational days 7-17) to pregnant female rats. No treatment related effects on maternal toxicity or malformations were noted at 25 mg/kg/day (3 times the MRHD based on BSA comparisons). Increased incidences of skeletal variation (14^{th} rib) were noted at 25 mg/kg/day. No treatment related effects on skeletal variation were noted at 5 mg/kg/day (0.6 times the MRHD based on BSA comparisons).

Subcutaneous doses of 4, 20 and 100 mg/kg/day luliconazole were administered during the period of organogenesis (gestational days 6-18) to pregnant female rabbits. No treatment related effects on maternal toxicity, embryofetal toxicity or malformations were noted at 100 mg/kg/day (24 times the MRHD based on BSA comparisons).

In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered from the beginning of organogenesis (gestation day 7) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (0.6 times the MRHD based on BSA comparisons). No treatment effects on postnatal development were noted at 25 mg/kg/day (3 times the MRHD based on BSA comparisons).

Nursing Mothers
It is not known whether luliconazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LUZU Cream, 1% is administered to women who are breastfeeding.

Pediatric Use
The safety and effectiveness of LUZU Cream, 1% in pediatric patients have not been established. The number of pediatric patients ≥12 years of age were too small to adequately assess safety and efficacy.

Geriatric Use
Of the total number of subjects in clinical studies of LUZU Cream, 1%, 8 percent were 65 and over, while 1.4 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies to evaluate the carcinogenic potential of LUZU Cream, 1% have not been conducted.

Luliconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster lung cell chromosomal aberration assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus test).

In a fertility study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered prior to and during mating and through early pregnancy. Treatment related effects on reproductive function were noted in females (decreased live embryos and decreased corpus luteum) at 5 and 25 mg/kg/day and males (decreased sperm counts) at 25 mg/kg/day. No treatment related effects on fertility or reproductive function were noted at 1 mg/kg/day (0.1X MRHD based on BSA comparisons).

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

Inform patients that LUZU Cream, 1% is for topical use only. LUZU Cream, 1% is not intended for intravaginal or ophthalmic use.

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Bridgewater, NJ 08807

VALEANT
Pharmaceuticals North America LLC

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Product of Japan

Issued: 8/2014
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DM/LUZ/15/0007

voice of the dermatologist

The majority of BCCs are simple, but some become locally advanced and even metastasize ... with understanding of the Hedgehog pathway and its key role in essentially all BCCs, we can now intervene.

Aleksandar Sekulic, M.D., Ph.D., Arizona

On advancements in BCC therapy; see story, page 1

NIVOLUMAB:
Dermatologists, oncologists can collaborate to control allergic skin eruptions *from page* **70**

the PD-1 inhibitor with a patient who had toxicity with ipilimumab, even if it was severe. There is not really any cross-reactive toxicity."

The most recent data from the second line phase 3 trial CA209-037, which evaluated nivolumab compared to dacarbazine or carboplatin/paclitaxel in patients with unresectable or metastatic melanoma who had been previously treated, suggest greater responses (32% vs. 11%) favouring nivolumab. A complete response was seen in 3% of nivolumab patients and 0% of chemotherapy patients.

Of 405 patients, 272 received nivolumab, and the balance received chemotherapy. The co-primary endpoints of the investigation were objective response rates in the first 120 subjects assessed after at least 24 weeks of follow-up, and overall survival. Of 38 who did respond, 36 continued to respond at six months, with most responders to the monoclonal antibody still in remission.

Investigators also found grade 3/4 adverse events were much more frequent in the chemotherapy arm compared to the nivolumab arm (31% vs. 9%).

Overall data on survival are pending but the phase 3 data that have emerged should definitively exclude single-agent chemotherapy as an option for treating advanced melanoma, according to Dr. Weber.

TOXICITY OF NIVOLUMAB

Patients taking agents such as nivolumab, may rarely develop serious dermatological toxicities, according to a medical oncologist involved in clinical trials where the therapy has been administered.

> **"You can safely administer the PD-1 inhibitor with a patient who had toxicity with ipilimumab, even if it was severe. There is not really any cross-reactive toxicity."**
>
> Jeffrey Weber M.D., Ph.D.
> **Tampa Bay, Fla.**

"When a patient gets a serious rash, the clinician has to make an executive decision about whether to hold the drug or continue the drug," says Dr. Weber, adding that PD-1 antibody is given every other week in most trials.

Skin eruptions that develop with the use of nivolumab and would be classified as grade one or two will likely improve with symptomatic treatment and topical steroid therapy, but patients can experience significant eruptions and rashes, according to Dr. Weber.

"The key issue is that you can sometimes see significant skin toxicities with nivolumab, with patients developing erythematous eruptions on sites like the chest, belt line, and groin," Dr. Weber says.

"Medical oncologists will be helped by their dermatologist colleagues in these situations," Dr. Weber says. "If medical oncologists are concerned with allergic eruptions or eruptions to the drug, they (dermatologists) can be helpful with the management of these (toxicities)."

Indeed, because many immunological agents produce skin manifestations, it's worthwhile for dermatologists to be aware of the latest immunological therapies, Dr. Weber says.

TOXIC EPIDERMAL NECROLYSIS

One of the rare but possible skin complications with immunotherapy occurs with the use of ipilimumab, another immune checkpoint inhibitor, and is the development of toxic epidermal necrolysis.

"It occurs in fewer than one in 1,000 patients," Dr. Weber says. "If you see that, it is a real problem. It is very rare, but you have to recognize when it is an issue."

Dr. Weber has received honoraria from Bristol-Myers Squibb, the manufacturer of nivolumab and ipilimumab. Dr. Weber has received honoraria from Bristol-Myers Squibb, the manufacturer of nivolumab and ipilimumab. **DT**

1 Weber JS, Kudchadkar RR, Yu B, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. J Clin Oncol. 2013;31(34):4311-8.

BCC TREATMENT:
Hedgehog pathway inhibitors effective against BCCs *from page 1*

in the Hedgehog pathway components patched (PTCH) or smoothened (SMO). The pivotal role of this signaling pathway was first recognized with the identification of the PTCH1 gene as the site of mutations underlying BCNS, or Gorlin syndrome. Subsequently, it became clear that the majority of sporadic BCCs have inactivating mutations of PTCH as well, and approximately 20% have activating mutations of SMO. These insights were critical for development of targeted therapies, such as vismodegib.

1-year overall survival reached

84

PERCENT

"We used to think that the defects within the Hedgehog signaling pathway were the primary or even the only driver in carcinogenesis," Dr. Macdonald says. "Over the last five years we have learned a lot, and have found that BCC is more than a molecular 'one trick pony,'" he says. "Now we know that in addition to this driver mutation, there are other mutational defects—such as in P53, which evolve over time and with UV exposure—that result in the various subtypes of BCC." Current studies may elucidate the impact of such molecular defects on clinical behavior of BCC subtypes.

> "Responses can be durable and patients can be treated with vismodegib for quite some time. You can go years without a recurrence."
>
> Karl D. Lewis, M.D.,
> Colorado, Denver

CURRENT, FUTURE INHIBITORS

"Abnormal Hedgehog signaling appears to be involved in most, if not all, of BCCs, and its ubiquitous expression offers the potential for targeted therapy," adds Karl D. Lewis, M.D., associate professor of medicine at the University of Colorado, Denver. "The approval of vismodegib and the potential for other agents to become available has changed our ability to treat this disease."

The phase 2 ERIVANCE trial of vismodegib 150 mg was recently updated. The 30-month analysis showed a median progression-free survival of 9.3 months in metastatic patients and 12.9 months in patients with locally advanced disease; median duration of response of 14.8 months and 26.2 months, respectively; and median overall survival of 22.4 months in metastatic patients and not reached in the locally advanced cohort.

"Responses can be durable and patients can be treated with vismodegib for quite some time. You can go years without a recurrence," Dr. Lewis has observes.

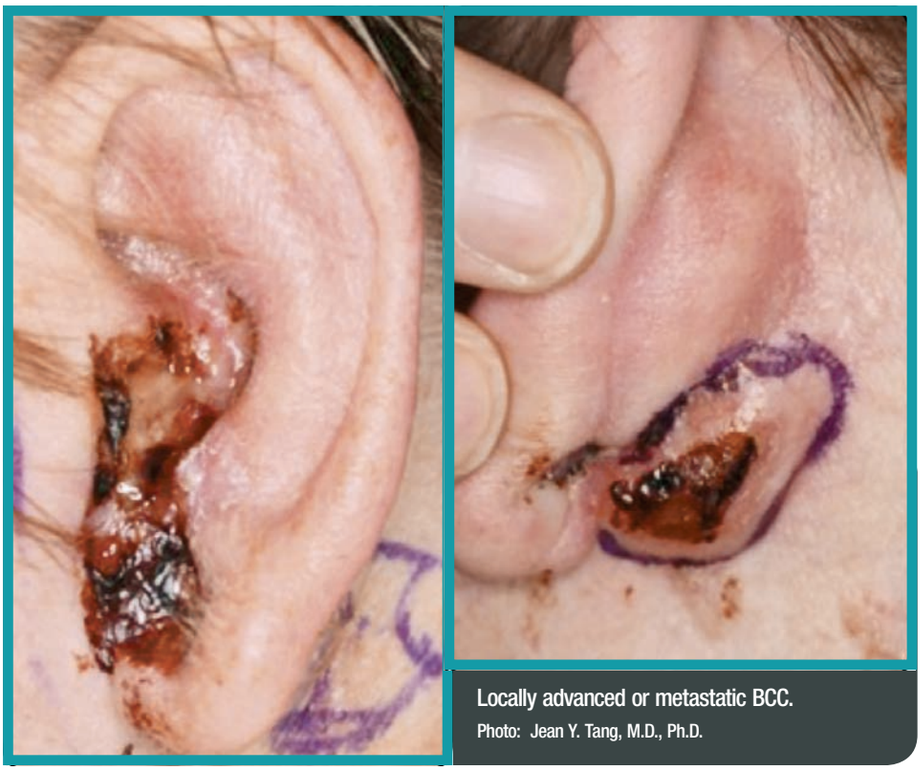
A second Hedgehog inhibitor, sonidegib, produced equally impressive results in the phase 2 BOLT trial. The study met its primary endpoint of ≥ 30% objective response rate after a median follow-up of 13.9 months. With 200 mg (the dose for future trials), responses were observed at 12 months in 58% of patients with locally advanced BCC and in 8% with metastatic disease; the disease control rate was 91% and 92%, respectively; and median progression-free survival was 22 months and 13.1 months.

These drugs' abilities to impact the natural history of advanced BCC is unclear, but Dr. Lewis believes that they will have an impact, at least in locally advanced cases. He notes that with vismodegib, 1-year overall survival reached 84%, compared with a historical rate of 58%.

MEETING A NEED

In BCNS, or Gorlin syndrome, hundreds of BCCs develop secondary to activation of target genes of the Hedgehog pathway in cells that have lost both normal copies of PTCH.

"Vismodegib has been life-changing for Gorlin patients," says Jean Y.



Locally advanced or metastatic BCC.
Photo: Jean Y. Tang, M.D., Ph.D.

BCC TREATMENT *see page* **77**

Desonate®
(desonide) Gel 0.05%

INDICATION & USAGE

Desonate® (desonide) Gel 0.05% is indicated for the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

Patients should be instructed to use Desonate® for the minimum amount of time as necessary to achieve the desired results because of the potential for Desonate® to suppress the hypothalamicpituitary-adrenal (HPA) axis. Treatment should not exceed 4 consecutive weeks.

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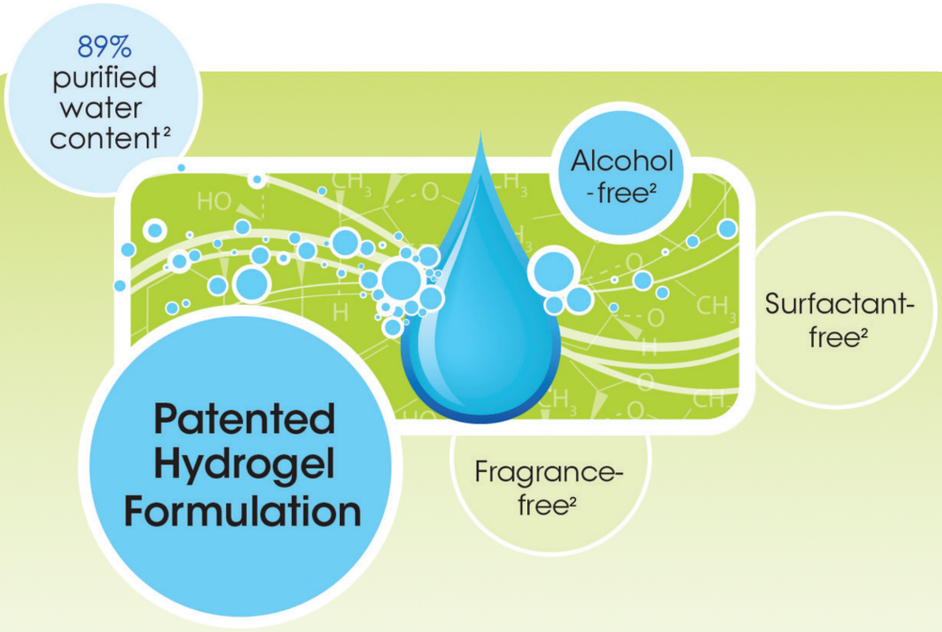

About Desonate®

- Approved for use in patients 3 months of age and older.
- Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body mass ratios. Unless directed by a physician, do not use on the underarm or groin area of children. Do not use to treat diaper dermatitis. Use in children less than 3 months of age is not recommended.
- No AB rated generic equivalent[1]

IMPORTANT SAFETY INFORMATION

Desonate® is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

Topical corticosteroids can produce reversible hypothalamic pituitary adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency, Cushing's syndrome, hyperglycemia and unmasking of latent diabetes. Systemic absorption may require periodic evaluation for HPA axis suppression. If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body mass ratios. Unless directed by a physician, do not use on the underarm or groin area of children. Do not use to treat diaper dermatitis. Use in children less than 3 months of age is not recommended.

Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include skin atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local adverse reactions may be irreversible.

If concomitant skin infections are present or develop during treatment, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Desonate® should be discontinued until the infection is adequately controlled.

If irritation develops, Desonate® should be discontinued and appropriate therapy instituted.

The most common adverse reactions (incidence ≥ 1%) are headache, application site burning and rash.

Desonate® is for topical use only. Not for ophthalmic, oral or intravaginal use. As with other corticosteroids, therapy should be discontinued when control is achieved.

See adjacent page for Brief Summary of full Prescribing Information.

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

References: **1**. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Active ingredient search results from "OB_Rx" table for query on "desonide." http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm. Accessed July 2014. **2**. Kircik L, Del Rosso J. A novel hydrogel vehicle formulated for the treatment of atopic dermatitis. J Drugs Dermatol. 2007;6(7):718-722. Drugs Dermatol. 2007;6(7):718-722.

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DESONATE® (desonide) Gel 0.05%

For Topical Use Only

Rx Only

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Desonate is indicated for the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

Patients should be instructed to use Desonate for the minimum amount of time as necessary to achieve the desired results because of the potential for Desonate to suppress the hypothalamic-pituitary-adrenal (HPA) axis *[see Warnings and Precautions (5.1)]*. Treatment should not exceed 4 consecutive weeks *[see Dosage and Administration (2)]*.

4 CONTRAINDICATIONS

Desonate is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Endocrine System

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

The effect of Desonate on HPA axis function was investigated in pediatric subjects, 6 months to 6 years old, with atopic dermatitis covering at least 35% of their body, who were treated with Desonate twice daily for 4 weeks. One of 37 subjects (3%) displayed adrenal suppression after 4 weeks of use, based on the cosyntropin stimulation test. As follow-up evaluation of the subject's adrenal axis was not performed, it is unknown whether the suppression was reversible *[see Use In Specific Populations (8.4) and Clinical Pharmacology (12.2)]*.

Pediatric patients may be more susceptible than adults to systemic toxicity from equivalent doses of Desonate due to their larger skin surface-to-body mass ratios *[see Use In Specific Populations (8.4)]*.

Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent steroids, use over large surface areas, use over prolonged periods, use under occlusion, use on an altered skin barrier, and use in patients with liver failure.

An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression. If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, to reduce the frequency of application, or to 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.

Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids.

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

5.2 Local Adverse Reactions with Topical Corticosteroids

Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include skin atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local adverse reactions may be irreversible.

5.3 Concomitant Skin Infections

If concomitant skin infections are present or develop during treatment, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Desonate should be discontinued until the infection is adequately controlled.

5.4 Skin Irritation

If irritation develops, Desonate should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

6 ADVERSE REACTIONS

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

In controlled clinical studies of 425 Desonate-treated subjects and 157 Vehicle-treated subjects, adverse events occurred at the application site in 3% of subjects treated with Desonate and the incidence rate was not higher compared with vehicle-treated subjects. The most common local adverse events in Desonate treated subjects were application site burning in 1% (4/425) and rash in 1% (3/425) followed by application site pruritus in <1% (2/425).

Adverse events that resulted in premature discontinuation of study drug in Desonate treated subjects were telangiectasia and worsening of atopic dermatitis in one subject each. Additional adverse events observed during clinical trials for patients treated with Desonate included headache in 2% (8/425) compared with 1% (2/157) in those treated with vehicle.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids. They may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, secondary infection, skin atrophy, striae, and miliaria.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C:

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

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

No reproductive studies in animals have been performed with Desonate. Dermal embryofetal development studies were conducted in rats and rabbits with a desonide cream, 0.05% formulation. Topical doses of 0.2, 0.6, and 2.0 g cream/kg/day of a desonide cream, 0.05% formulation or 2.0 g/kg of the cream base were administered topically to pregnant rats (gestational days 6-15) and pregnant rabbits (gestational days 6-18). Maternal body weight loss was noted at all dose levels of the desonide cream, 0.05% formulation in rats and rabbits. Teratogenic effects characteristic of corticosteroids were noted in both species. The desonide cream, 0.05% formulation was teratogenic in rats at topical doses of 0.6 and 2.0 g cream/kg/day and in rabbits at a topical dose of 2.0 g cream/kg/day. No teratogenic effects were noted for the desonide cream, 0.05% formulation at a topical dose of 0.2 g cream/kg/day in rats and 0.6 g cream/kg/day in rabbits. These doses (0.2 g cream/kg/day and 0.6 g cream/kg/day) are similar to the maximum recommended human dose based on body surface area comparisons.

8.3 Nursing Mothers

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. Because many drugs are excreted in human milk, caution should be exercised when Desonate is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of Desonate in pediatric patients less than 3 months of age have not been evaluated, and therefore its use in this age group is not recommended.

The effect of Desonate on HPA axis function was investigated in pediatric subjects, with atopic dermatitis covering at least 35% of their body, who were treated with Desonate twice daily for 4 weeks. One of 37 subjects (3%) displayed adrenal suppression after 4 weeks of use, based on the cosyntropin stimulation test *[see Warnings and Precautions (5.1)]*.

In controlled clinical studies in subjects 3 months to 18 years of age, 425 subjects were treated with Desonate and 157 subjects were treated with vehicle *[see Adverse Reactions (6) and Clinical Studies (14)]*.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment.

Adverse effects, including striae, have been reported with inappropriate use of topical corticosteroids in infants and children. 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 absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

8.5 Geriatric Use

Clinical studies of Desonate did not include patients aged 65 and older to determine if they respond differently than younger patients. Treatment of this patient population should reflect the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

17 PATIENT COUNSELING INFORMATION

Patients using topical corticosteroids should receive the following information and instructions:

- This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
- This medication should not be used for any disorder other than that for which it was prescribed.
- Unless directed by the physician, the treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive.
- Unless directed by a physician, this medication should not be used on the underarm or groin areas of pediatric patients.
- Parents of pediatric patients should be advised not to use Desonate in the treatment of diaper dermatitis. Desonate should not be applied in the diaper area, as diapers or plastic pants may constitute occlusive dressing *[see Dosage and Administration (2)]*.
- Patients should report to their physician any signs of local adverse reactions.
- Other corticosteroid-containing products should not be used with Desonate without first consulting with the physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, contact the physician.

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Whippany, NJ 07981
Manufactured in Canada

6706906BS1
Rev. July 2014

voice of the dermatologist

"There's now evidence that staph may have the ability to obstruct sweat glands, and this may be a pivotal event in the development of AD."

Sheila Fallon Friedlander, M.D., discussing staph as a causal agent rather than a secondary phemomenon
See "MRSA, tropical infections rising", page 28

BCC TREATMENT:
Neoadjuvant vismodegib shrinks BCC size *from page* **74**

Tang, M.D., Ph.D., associate professor of dermatology at Stanford School of Medicine in California, who co-led the U.S. Randomized Gorlin Study that tracked a total of 2,000 existing BCCs and followed 694 new BCCs.

"Patients randomized to vismodegib had a remarkable reduction in new lesions," Dr. Tang notes. "We found that vismodegib reduced the per-patient rate of new BCCs from 29 with placebo to 2 ($P < 0.001$) and reduced the size of existing BCCs by 65% over baseline, compared with an 11% change with placebo ($P = 0.003$). In some patients, all BCCs clinically regressed, and none progressed during treatment."

Abnormal Hedgehog signaling appears to be involved in most, if not all, BCCs.

Karl D. Lewis, M.D.
Colorado

REAL-WORLD EXPERIENCE

The RegiSONIC Disease Registry Study is the first cohort study of the real-world treatment of patients with advanced BCC or BCNS. The aim is to follow 750 patients from 75 sites in the United States to determine how patients are being managed in actual clinical practice. As of June 2014, the study had enrolled 312 patients.

"We are asking how patients are being managed, can we treat them indefinitely [with Hedgehog inhibitors], and can we interrupt treatment to manage side effects?" she says.

The first 131 patients have lesions mostly on the nose (19.8%), whose median lesion size is 20.5 mm and histopathology is primarily nodular (58.8%) and morpheaform/infiltrative (29.8%).

NEOADJUVANT TREATMENT

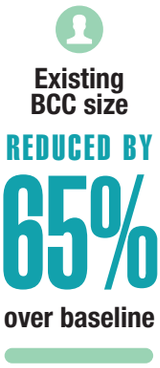
Neoadjuvant treatment might be the next clinical application of Hedgehog inhibitors. An open-label study of 15 patients with large BCCs led by Dr. Tang found that neoadjuvant vismodegib, given for three to six months, reduced the anticipated surgical defect size by 27% ($P = 0.006$). Vismodegib was not effective in patients who received less than 3 months' treatment.

"We saw dramatic shrinkage after 4 months of treatment, allowing Mohs surgery in difficult places, such as the eyelid," Dr. Tang reports. A randomized, double-blind study is now evaluating this strategy.

DEALING WITH TOXICITIES

Drug-related toxicities are on-target effects of tissues that rely on the Hedgehog signaling pathway. Common toxicities include muscle spasm, hair loss, taste abnormalities, and weight change. Sonidegib has also been shown to increase creatine kinase (CK) enzymes; whether this also occurs with vismodegib is not yet clear.

"The toxicity profile makes it difficult to maintain patients on long-term treatment," Dr. Lewis says. "Most (toxicities) are low-grade, but over the long term it wears on them. I give dose holidays."



Side effect management includes hydration and calcium, magnesium and potassium supplementation, muscle relaxants, calcium channel blockers, and drug holidays (intermittent dosing).

In the U.S. Randomized Gorlin Study, 54% of patients receiving vismodegib discontinued drug treatment because of adverse events; however, most patients elect to go back on treatment when tumors return, Dr. Tang says, noting, "The best management seems to be a short period of treatment interruption." Genentech is sponsoring a trial of intermittent vismodegib: three months on, three months off, three months on.

Dr. Tang suggests that clinicians prepare patients for these toxicities.

"When patients stop treatment, they continue to lose hair for two months, but the hair grows back," she says. "You can't avoid these side effects, so it's best to prepare patients." **DT**

Dermatology Times

Teledermatology enables efficient triage

LOUISE GAGNON | STAFF CORRESPONDENT

QUICK READ

While reimbursement questions linger, teledermatology can help dermatologists triage effectively in deciding whether a patient needs to go to the hospital. It is also a way to reduce the disparity in access to dermatological care, experts say.

TIMOTHY ABRAHAMSON, M.D., a dermatologist based in Des Moines, Iowa, has used standard telemedicine for patients who would otherwise not be seen by a dermatologist in the inpatient setting.

"Teledermatology is not going to replace seeing the patient, but it can help [inpatient dermatologists] triage," says Timothy Abrahamson, M.D., a dermatologist with Greater Des Moines Dermatology PC.

"As a solo dermatologist, it is impossible for me to go to five separate hospital locations on a randomly requested basis," Dr. Abrahamson says.

In particular, Dr. Abrahamson wishes he could use the store-and-forward format in the comfort of his home to view images when he has availability and to make a recommendation for care to the referring physician, a non-dermatologist who may be an emergency physician or internist.

"Store-and-forward [teledermatology] is a way to serve patients and a way for dermatologists to decide if a patient needs to be in hospital," explains Dr. Abrahamson. "Standard telemedicine requires too many logistics to provide efficient care for the consultant or the consulted dermatologist. Store-and-forward will be necessary to make this truly useful as this allows the consulting physician to immediately create the consult and the dermatologist to review the information at a different time.

"Also, the stored information can be saved for a period of time for future reference," he says. "The American Academy of Dermatology (AAD) is testing a prototype of this system currently. Unfortunately, funding is lacking for coverage even in a rural state like Iowa. Only Hawaii and Alaska are granted this privilege by Medicare at this time. These two states have been funded for a decade."

The use of teledermatology for inhospital patient dermatologic service does not compromise the quality of diagnoses, according to research published last spring.

STORE-AND-FORWARD ENABLES BETTER TRIAGE

A study found that store-and-forward teledermatology can be employed to assist in the triaging of inpatient dermatology consultations: The investigators were able to triage 60% of consultations to be seen the next day or later. In addition, teledermatologists were able to triage, on average, 10% of patients to be seen as outpatients. There was also good concordance in the decision to biopsy between in-person and teledermatology. Investigators concluded teledermatology to

TRIAGE *see page* **80**

Quotable

"When patients use telemedicine to meet with their doctors, the experience should feel as if the doctor is right there in the room with them."

Gene D'Amore
vice president, Hospital Operation and CIO, Shriners

On deploying a telemedicine program

See story page 82

DTExtra

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3. American Society for Dermatologic Surgery 2014 Consumer Survey on Cosmetic Dermatologic Procedures (N=8,315); Exact survey language was, "How bothered are you by excess fat under the chin/neck?"

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TRIAGE:
Teledermatology makes consults more efficient *from page* **78**

be reliable in the triage of inpatient dermatology consultations and that its use could improve efficiency.[1]

"There is a dearth of dermatologists able or willing to see patients who are hospitalized," says Misha Rosenbach, M.D., assistant professor of dermatology and internal medicine, director of the Dermatology Inpatient Consult Service at the University of Pennsylvania, Philadelphia, and an author of the study.

Dermatologists are expected to drive to a hospital for a consult that may take less than 15 minutes, and which sometimes could have been safely seen in the outpatient setting after discharge, which is an inefficient use of their time, Dr. Rosenbach says.

"Using teledermatology to triage consults by acuity may make it more efficient for dermatologists to decide if a case is urgent, as teledermatologists were able to accurately diagnose and triage inpatient consults in our pilot study," Dr. Rosenbach says. "If dermatologists could evaluate teledermatology images and assess consults for acuity, they could 'lump' consults together on a single, convenient, efficient trip to the hospital and see all the non-acute consults in one bundle."

The AAD has taken the lead with this concept, through the development of the secure teledermatology platform "AccessDerm," which provides timely diagnosis using the store-and-forward approach. Staffed by volunteer board-certified dermatologists, AccessDerm can be accessed via mobile devices, Dr. Rosenbach notes.

"There is an urgency that comes up with hospitalized patients," explains Lindy Fox M.D., associate professor and director of Hospital Consultations at the University of California at San Francisco. "A patient could have a bump on the leg that is benign and without significance or it could be something that requires further evaluation in a hospital setting."

ENABLING ACCESS TO CARE

Other dermatologists, such as Anne E. Burdick M.D., M.P.H., associate dean for TeleHealth and Clinical Outreach, professor of dermatology at the University of Miami Miller School of Medicine in Miami, Fla., and a leading advocate for the expansion of teledermatology, supplies her clinical judgment to physicians working out of a mobile van. A corporate grant reimburses for this teledermatology service.

"Forty percent of my practice is done with teledermatology, and I have been doing it for about 20 years," Dr. Burdick says. "In many places, there is a shortage of dermatologists, and this is the way to reduce the disparity in access to dermatological care. It shortens the time [to see a dermatologist] because there can be a wait of many months."

Dr. Burdick also uses the asynchronous store-and-forward method to provide consultations to personnel aboard cruise ships, but points out the merit of the live interaction with direct communication with the patient or referring provider that allows her to ask questions during the consultation. Dr. Burdick offers that teledermatology can provide accurate diagnosis, provide a recommendation for a targeted work-up, and, if need be, offer appropriate therapy.

There is no doubt that a clinical field like dermatology lends itself to telemedicine, says Jonathan Linkous, Chief Executive Officer of the American Telemedicine Association, noting that Veterans Affairs hospitals have been using teledermatology for some time.

REIMBURSEMENT LIMITATIONS

"It is largely a visual specialty," Mr. Linkous says. "We are working with the AAD to overcome barriers to implement teledermatology, issues like reimbursement and liability using store-and-forward. The issue of payment should not be in doubt for physicians who participate in telemedicine."

The AAD released a position statement on telemedicine which outlined reimbursement for live, interactive dermatology. The statement noted that, in some states, Medicaid reimburses for telemedicine services, but many states have restrictions. Private insurers vary in their reimbursement policies, but most will reimburse services provided to patients in rural areas.

The statement also noted that there are more limitations to reimbursement with the store-and-forward format with the exception of demonstration projects or in states like Hawaii and Alaska. There is reimbursement of store-and-forward teledermatology for Medicaid patients in a handful of states, including California and Illinois.

TELEDERMATOLOGY SERVICES

Some have seen the void in dermatological care in the United States and have taken the opportunity to develop private services to match up patients with board-certified dermatologists licensed in a patient's geographic area to provide dermatological care. *Dermatologist-On-Call* was launched in response to consumer preparedness for teledermatology and technology advances that ensure privacy and supply high-resolution images.

Patients send images to *Dermatologist-On-Call*, which then finds a dermatologist in the local area of that patient to review the images and render a clinical diagnosis. If dermatologists receiving the images judge that the image quality is not appropriate, they can request other images, Dr. Seraly explains.

"With severely limited access [to dermatologists], it makes sense to use a tool like store-and-forward to provide the same type of service," says Mark Seraly, M.D., F.A.A.D., Chief Medical Officer and Founder of *Dermatologist-On-Call*. "Our goal is to give patients access to the highest quality care, and that means consulting with a dermatologist who specializes in hair and skin conditions."

Access to a dermatologist appears to be increasingly critical given that non-dermatologists express a lack of confidence dealing with dermatological presentations. One investigation found 40% of primary care residents in California who were surveyed reported that they did not feel prepared through their medical school education to respond to dermatologic issues.[2]

A retrospective chart review in a midwestern U.S. university hospital revealed that the primary care team had a correct diagnosis in less than one out of every four cases (23.9%) involving dermatological problems. Consultation with a dermatologist led to a change in or addition to treatment in the balance of cases.[3]

Cameron Rokhsar, M.D., F.A.A.D., a board-certified dermatologist and assistant clinical professor of dermatology at Mount Sinai Hospital in New York, said

TRIAGE *see page* **84**

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Childhood burn care: a telemedicine success story

BILL WOHNOUTKA | Vice President of Solutions Architects at Level 3 Communications

WHEN IT comes to burn patients, particularly children, recovery is a long road because skin can't grow and change as quickly as the body develops. Skin is a vital organ and is the first line of sensation and defense against external factors. It's the body's heating and cooling system. But when skin is severely burned, it loses much of that function and requires reconstructive surgeries, rehabilitation, tissue expansion, pressure garments and ongoing check-ups. It's because of this extensive and time consuming treatment that Shriners has been one of the first hospital networks in the country to employ telemedicine practices.

Caregivers at Shriners collaborated with the Shriners IT department to determine ways they could leverage technology to reduce stress on the lives of families and patients needing routine check-ups. The team suggested employing telemedicine technologies so families could minimize travel time, yet meet with world class physicians at Shriners hospital locations in the U.S. , Mexico and Canada.

Telemedicine is the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. It includes a growing variety of applications and services using two-way video, email, smart phones, wireless tools and other forms of telecommunications technology. These days, healthcare providers are taking telemedicine to new heights, with the market seeing growth of a whopping 237% within a five-year period, according to a new Kalorama report. In fact, the American Telemedicine Association says there are currently about 200 telemedicine networks, with 3,500 service sites in the U.S. alone.

Shriners is on the leading edge of that growth, having implemented cutting-edge telemedicine technologies more than 10 years ago and now working with global network partner Level 3 Communications.

"Telemedicine is a must-have in today's healthcare environment," Richard Kagan, M.D., chief of staff at Shriners' Cincinnati hospital says. "If you're not doing telemedicine, you're traveling on a gravel road while everyone else is taking the highway."

Dr. Kagan has worked with Shriners for more than 25 years and knows firsthand the importance of having a robust telemedicine program.

"Telemedicine is all about enhancing the patient experience. Our patients are children who have been through a traumatic set of circumstances. By using telemedicine, we are able to significantly reduce the amount of medical disruptions in children's lives, giving them more time to do the normal things that kids do – go to school, play with friends, and spend quality time with their families."

QUICK READ

Burn recovery requires an ongoing care plan, particularly in children because skin can't grow and change as quickly as the body develops. Telemedicine leverages technology to reduce stress on the lives of families and patients needing routine check-ups.

> **"Telemedicine is a must-have in today's healthcare environment...If you're not doing telemedicine, you're traveling on a gravel road while everyone else is taking the highway."**
>
> Richard Kagan, M.D.
> chief of staff at Shriners' Cincinnati hospital

EASING ONGOING PATIENT BURN CARE

When you hear the word "Shriners," you may think of television commercials or fundraising drives. But talk to any burn survivor and they'll tell you that Shriners is about giving children with severe burns the ability to heal, grow and prosper in their lives. Shriners Hospitals for Children is a network of 22 hospitals across the country, each dedicated to giving children the world-class, life-changing care they need — not only burn care, but also medical treatment in the areas of orthopedic conditions, cleft lip and palate, congenital nevus and other congenital skin/soft tissue deformities, and spinal cord injury.

Nicole Gannon came to Shriners after spending nearly six months at a Kansas hospital following a house fire that burned nearly 90 percent of her body. At the time of the fire, she was just six months old.

The type of treatment Nicole requires is extensive, and she often has to fly out-of-state to meet with doctors who specialize in working with patients like her — burn survivors who have undergone tremendous trauma, both physically and mentally. But thanks to Shriners Hospitals for Children, Nicole can utilize the telemedicine program to meet with a world class pediatric burn specialist without making the long journey to Shriners' Cincinnati hospital.

ACCOMODATING CIRCUMSTANCES

Melissa Raines of Asheville, N.C. has three children under Shriners' care after they were involved in a kerosene can explosion that left each of them with severe third-degree burns. Ethan, 16 years old and the oldest of the three, sustained the worst injuries, with more than 50 percent of his body affected. His younger sisters, Hannah, 11, and Abby, 5, also sustained severe burns. All three have undergone several procedures and continue to receive care from Shriners as they grow up.

With three children, Melissa says that travel to Shriners' Cincinnati hospital was cumbersome, but thanks to the hospital's telemedicine network, she has been able to cut her travel significantly.

BURN CARE *see page* **84**

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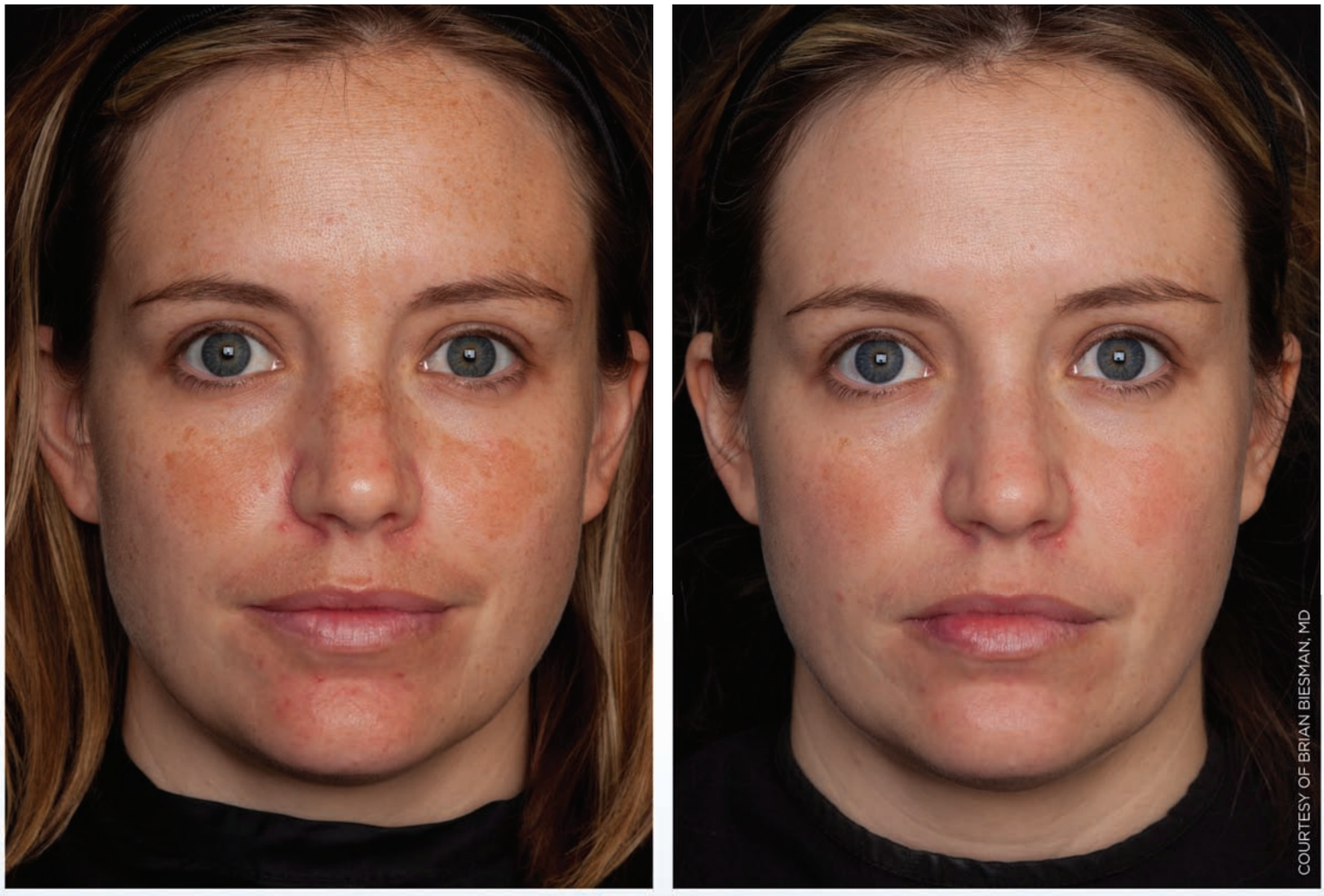

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BURN CARE:
Telemedicine helps ease the recovery road for burn patients *from page* **82**

"Instead of driving seven hours each way, we can visit the nearby Shriners hospital in Greenville and be there and back in a fraction of the time it takes to see our doctor in person. Plus, we get the same level of care we would get if we went to Cincinnati — it's really like our doctor is in the room with us."

Asked what the experience is like, Melissa says it's really no different than a normal visit to the doctor.

"It's set up like a normal hospital room, except for the huge TV monitor and the camera, which allows our doctor and nurses to talk to us face-to-face and take a look at the kids' progress. There's of course a nurse on our side who helps with everything, and so far, it has all gone really smoothly."

DEPLOYING THE PROGRAM

Deploying a telemedicine program is no easy task because the experience provided to the patients must be as authentic and engaging as the in-office experience.

"When patients use telemedicine to meet with their doctors, the experience should feel as if the doctor is right there in the room with them," says Gene D'Amore, vice president of Hospital Operations and CIO at Shriners. "It has to happen in real-time, in front of a high-resolution screen and over a reliable, secure network. With these types of patients and the critical nature of their injuries, there's no room for compromise or error."

According to Mr. D'Amore, the key to an effective telemedicine program boils down to three things:

- staff team members who are not only receptive to the telemedicine concept, but also willing to learn and operate the equipment needed to successfully run the program
- an advanced teleconferencing system connected to key locations in the markets served
- a strong network partner that provides fast and reliable connectivity.

"Telemedicine can be daunting at first, both from a budget and implementation standpoint," Mr. D'Amore adds. "But in the case of Shriners, there are clear benefits to integrating telemedicine solutions into the care continuum. With a wide movement of payment reform that now covers telemedicine visits in 44 states, adoption of these technologies will likely accelerate. The technology is here, the infrastructure is here, the next step is for technology leaders to collaborate with physicians and care staff to make it happen."

To take full advantage of the possibilities of telemedicine and create the right network environment to realize the advantages on behalf of physicians and patients, healthcare providers also need to conduct a thorough review of the core competencies of their internal IT team, clearly defining any potential gaps and needs from outside vendors.

Nicole Gannon can attest to the benefits. And thanks to Shriners, Nicole has been able to grow up and do the things kids her age do. She loves playing sports like volleyball, hangs out with her girlfriends, plays the cello and, much to her mother's chagrin, is learning to drive.

"I white-knuckle it every time we drive together, but then I think to myself, if it weren't for Shriners, I wouldn't have the opportunity to even experience this milestone with my daughter," says Nicole's mother, Brandy.

"It feels good to know that Shriners always has our backs," adds Melissa. "They're always innovating to make sure their patients not only have the best care, but also the most convenient care, which means so much to my family." **DT**

TRIAGE:
Teledermatology makes consults more efficient *from page* **80**

the conventional thinking is that live interaction trumps a video conferencing consultation, but store-and-forward technology is a much more convenient teledermatology format for busy teledermatologists.

"Most dermatologists probably feel that there is nothing that can truly substitute a face-to-face consultation," says Dr. Rokhsar. "You can show someone a picture, but that picture is truly not the same thing as seeing the patient live."

EXPANDING TELEDERMATOLOGY

To expand teledermatology, Dr. Rokhsar comments that features such as multistate licensing and an interstate compact would enable dermatologists who are participating in teledermatology to easily prescribe treatment and be involved in follow-up care.

The Federation of State Medical Boards is contemplating a new framework for expediting licenses to allow physicians to practice in multiple states, a move that would open the doors more widely to telemedicine and teledermatology. Licensed physicians could apply for rapid multistate licensure to treat patients who reside outside the principal licensing state.

Teledermatology is responding to a "real issue of access," and the expansion of cosmetic dermatology has not been a significant factor in reducing that access, says Darrell Rigel M.D., a clinical professor of dermatology at New York University Medical Center and an AAD past-president.

"There is a greater burden of dermatologic illness," Dr. Rigel says. "There is more and more dermatologic disease such as skin cancer, eczema, and acne. It is still in an embryonic phase, and a lot of insurers don't have official reimbursement policies." **DT**

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[1]Bhatnagar A. Electronic Brachytherapy for the Treatment of Nonmelanoma Skin Cancer: Results at 3 Years. Int J Radiat Oncol Biol Phys 2013;87:S65

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Digital Marketing

Use visuals to tell your story

We have all heard that a picture is worth a thousand words. This adage especially applies to your digital presence. When it comes to using the power of digital images for marketing yourself as a physician, you can use pictures to represent the story of your practice. Eighty percent of patients start their search for aesthetic services on the web, including those who received a word-of-mouth referral. A great reputation should be a given, but how you portray yourself makes all the difference.

Question: Which elements of a typical practice website will most likely create a first and lasting impression on socially connected patients?

Answer: The visual images, including photos and video. Other factors, such as color schemes, layout, navigation and content, are also important, but the first impression will almost always be the result of the images.

PUT YOUR SITE TO THE TEST

Try performing your own illustrative research:

- Choose a few topics of interest unrelated to your practice
- Enter the associated keywords into Google search
- Pick a few sites from the search return
- Pay attention to what you see first on each site, and consider the way it makes you feel

Now try this with your practice's website: If you can be unbiased about it, what type of story is being told by the visual imagery on the home page of your site? Collectively, how do the images make you think, feel, and (most importantly) what do they tell you to do?

From a digital marketer's perspective, that's what *really* matters: What do you want prospective and existing patients to think, feel, and do when they visit you online? How can you turn their red lights to green lights, and encourage them to go further in the process of choosing your practice?

The purpose of using images at your website is to tell a vivid tale of good things to come. If you are not 100% satisfied with the tale your website tells, there are a few simple steps you can take to create alignment between your site and the internet-savvy social patient.

> There are simple steps you can take to create alignment between your site and the internet-savvy social patient.

Step 1: If you're maintaining your practice's website internally, get more than one opinion. While it makes sense to get feedback from your spouse, staff, and friends, keep in mind that their opinions can be affected by your relationship, and nobody wants to hurt your feelings. Getting unbiased, outside feedback can be more helpful—different age groups, genders, and professional backgrounds may give you a more accurate assessment.

Step 2: Most contemporary sites have a slider on the home page. A slider allows you to incorporate a series of rotating images that highlight different aspects of the practice. Having more than one image will increase the site's appeal.

Step 3: When you do make changes to the site, limit the number of variables you change at one time, so that you see the true results of each change.

Step 4: Embrace the idea of change. Your digital presence should be considered a means to an end, as opposed to an end in and of itself. Online trends change rapidly and the way you respond to those changes can mean the difference between a successful, dynamic web presence and a website that gathers dust instead of patients.

TELL YOUR STORY

Keep in mind that strong visuals will grab the attention of socially connected patients, but that's just chapter one. Other important chapters in your story include unique and relevant content, professional video production, contact forms that are easily found and completed, physician and staff member biographies, and on-site positive reviews.

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PART 4 OF 4 ARTICLES ON GETTING PAID IN THE NEW HIGH DEDUCTIBLE LANDSCAPE

Win patients over while asking for money

The final article in this four-part series tackling the high-deductible landscape of healthcare today is all about how to equip staff to ask patients for payment. It sounds simple, but it really can be difficult for some and even awkward for others. By understanding the psychological needs of both staff and patients, we can bolster staff's ability not only to ask for money, but also win patients over in the process.

It's essential that staff understand that many patients are frustrated by the changes in healthcare. They might have paid just $15 for an office visit in years past and are not mentally or financially prepared to pay their deductibles. For years, HMO plans caused patients to grow accustomed to paying only nominal fees at point of service, yet many of these patients are now on high deductible plans that they hardly understand.

When we approach our patients with the intent to educate and remind them of their financial responsibility, we must also keep in mind that a direct but kind answer will get the best results. In other words, letting patients know that you're on their side, ready to offer options as they adjust to the new plan and possibly your new financial policy, is the best strategy.

INFORMED PATIENTS ARE PREPARED PATIENTS

For starters, it's crucial that staff not be put in the uncomfortable position of catching patients off guard, thus creating more hostile and negative reactions and interactions. Whenever possible, patients need to be informed of your financial policy *before* the day of their appointment.

At the time of scheduling, patients should be reminded of the policy even if they've previously seen and signed it. They also need to be told specifically that if their deductible hasn't been met, they will be responsible to pay for the visit and services in full.

Some patients will scratch their heads and not understand terms we consider common, like "high deductible." When your scheduling staff is prepared to answer basic questions and take the extra minute or two to explain the payment structure, your front desk and/or checkout staff will encounter more prepared patients, boosting their odds at successfully collecting balance dues.

Be sure your financial policy is introduced to each new patient and signed. It also needs to be on your website and accessible via your patient portal. Knowing that patients have been prepped will give your staff more confidence in asking for payment.

GET YOUR STAFF ON BOARD

Staff buy-in for these actions is increased when all staff members have a greater understanding of what patient collections mean to the practice. You can really make the idea of collecting payments click by showing them a visual dollar amount of what is being left on the table when the practice fails to collect patient portions. Bring it full circle by measuring, setting reasonable goals, instituting incentives, and explaining how the increase in revenue will be applied to the practice — now you have a team that's on board and gets it!

A great way to ease the pain for staff in asking patients for money is by creating scripts and practicing how they can tackle patient complaints and excuses regarding paying at time of service.

For example, when patients say they didn't bring their checkbook, staff can remind the patient in a soft way like, "I apologize, we try to always inform patients at the time of scheduling that they will need to be prepared to pay balances at the time of their visit. However, for your convenience, we do accept credit card payment."

If the patient continues to balk, one strategy is to offer to accept partial payment saying something like, "I understand, Mr. Smith. I can take 50% now and give you a self-addressed envelope to send us the other half within 10 days, will that work for you?"

For this strategy to work, your staff needs to understand what their options are and how to communicate them to patients in a way that expresses a willingness to work with them.

KEEP EVERYONE ON THE SAME PAGE

Coming to an agreement with patients of how payment will be made is very important. Documenting it means that billing staff can follow up and remind patients of that agreement. Patients are more likely to pay their balances after having made a verbal as well as written agreement with your practice.

If your practice has a clear financial policy in place and is using technology tools that support efforts to collect, you've got two of the three key elements. Now, make sure staff are equipped to inform and remind patients of payment expectations and ask for payment confidently while expressing that the practice is on their side and willing to work with them. After all, building strong clinic-patient relationships is good for the health of your patients as well as your practice! **DT**

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Melanie D. Palm, M.D.,
is director of Art of Skin MD
in Solana Beach, California

Ten tips for a smart website

In this two-part series, I'll explore emerging trends in social media and search engine optimization (SEO). Alexa Mokalis is an adjunct lecturer at the San Diego State University School of Journalism and Media Studies. In her class titled "Advertising Strategies and Social Media," she educates students on the trends in successful online marketing strategies. Here are her top ten tips for physicians' web presences.

1. **Do use the 80/20 rule.** Approximately 80 to 90 percent of the content put forth by your practice on social media should be high-interest, with 10 to 20 percent reserved for promotional content. "Promotional content is okay as long as it is balanced and often incorporates a call to action. Ask fans about their favorite skincare trend or how their New Year's resolution is faring."
2. **Don't delete (or ignore) negative comments.** "In today's age of unlimited access to information, transparency is crucial." Ms. Mokalis recommends that if someone uses your platform as a soapbox, first respond politely in public (minding your HIPAA compliance), and then ask to speak privately. This will garner respect from others and will address negative comments directly in a respectful manner.
3. **Do use visuals.** "According to one study, sites with visuals receive 94 percent more page visits than those without." Ms. Mokalis recommends a mix of different visual content including before and after photos, behind the scenes videos from your practice, testimonial videos, and infographics on diseases or trends in dermatology. "This helps to keep them curious as to what to expect week to week."
4. **Don't feel pressured to be on every platform.** Does the idea of being on Facebook, Twitter, Instagram, YouTube, Pinterest, and a blog seem daunting? It would to most of us. "Not all platforms are necessarily beneficial to your business," Ms. Mokalis says. Instead, focus on a few. Facebook, she says, is an absolute must, with 1 billion users. Next, try videos on YouTube or photos on Pinterest, which has a largely female adult demographic and is the fastest growing platform on the web.
5. **Do establish community guidelines.** "In order to avoid any miscommunication, be sure to establish your purpose for being on each particular platform. I recommend outlining this in the "About" section of the business." Such guidelines state the purpose of behavior as well as etiquette for guests. For example, you may state that patients' clinical questions need to be directed to the clinic phone number and that comments with explicit language are prohibited and will be removed.

> **"Do get started on good social media practices, but don't be intimated by the process."**

6. **Don't forget to proofread.** More viewers disengage from social media outlets because of grammar and spelling errors than any other reason. Mind your Ps and Qs, dot your Is, and cross your Ts!
7. **Do be consistent.** "As much as possible, post new content weekly. Establish a schedule so that your clients know when to expect new content from you. I recommend posting 1 to 3 times per week." She emphasizes the importance of responding before posting new content. "Engage in a two-way conversation with your audience."
8. **Don't use auto-responses.** "Today we live in what advertising professionals call, 'The Relationship Era', meaning that your clients expect you to engage with them as you would with a friend. Having a human touch on each of your posts, responses, and replies is no longer an option, but a necessity," she says. Instead of creating pre-formed responses to inquiries, tailor responses to the individual.
9. **Don't be afraid to apologize.** To err is human, and your audience forgives mistakes as long as you own up to them. "The way your business handles those mistakes will set you apart from your competitors," Ms. Mokalis says. "Follow this simple road to resolution: 1) address the problem, 2) express concern, 3) offer remedial options, and 4) follow up." Apologizing for a mistake doesn't admit fault, but it goes a long way toward regaining trust.
10. **Do be aware of your audience.** Knowing your audience is the key to creating a connection that brings them back to your social media platform again and again. "If your clients are 45 to 60 years old, and are generally spectators on social media, you don't want to ask them to enter into a drawing by uploading a video to your page." Ms. Mokalis also suggests using a Social Technographics Profile (STP) to determine what type of social media your clients best embody. Never heard of STP? Check it out here: *http://empowered.forrester.com/tool_consumer.html*

Next month, we will explore effective tools for SEO on your practice websites and social media platforms. We will also explore why "Top 10" lists are powerful tools for your next blog entry. Do get started on good social media practices, but don't be intimated by the process. **DT**

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ALTERNATIVES:

Rationale behind alternative theories and approaches to AD treatment *from page* **21**

patient instead of a needle inserted by an acupuncturist—in 15 adults with moderate-severe AD.[18]

This investigator blinded randomized controlled trial found a significant decrease in itch at 4 weeks compared to control (p=0.04). Interestingly, some of my patients who were participants in the study tell me that they continue to massage the area when they feel itchy to this day! Further work is required to substantiate this, but perhaps there is something to it.

> The study that got me excited about acupuncture was actually not in atopic dermatitis at all, but rather for the intractable itch of uremic pruritus.

EVENING PRIMROSE OIL & BORAGE OIL

Finally, we have discussed many promising ideas, and perhaps it's also important to close the door on some not-so-promising ones. Evening primrose oil and borage oil both have a somewhat mixed set of evidence from trials. The rationale being that these natural oils are rich in gamma-linolenic acid, which may benefit the skin barrier and may have anti-inflammatory and anti-itch properties.[19]

However, The Cochrane Library published a fairly definitive report in 2013[20] that summarized the evidence for both agents thus far and concluded:

"Oral borage oil and evening primrose oil lack effect on eczema; improvement was similar to respective placebos used in trials… [We] concluded that further studies on EPO or BO for eczema would be hard to justify."

This is a powerful statement, to be sure, but in some ways a welcome one. With so many possibilities and relatively limited resources to test them all, crossing something off the list is actually good news and allows us to focus on things that may yet hold promise but require more research. **DT**

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An alternative approach

Q&A

ELAINE SIEGFRIED, M.D.

In part 2 of our discussion on the use of alternative therapies in dermatology *Dermatology Times* editorial advisor, Elaine Siegfried, M.D., talks with Peter Lio, M.D., assistant professor of clinical dermatology and pediatrics at Northwestern University's Feinberg School of Medicine, and private practice, Dermatology andAeshtetics of Wicker Park, Wicker Park, Chicago, about the pros and cons of specific techniques and treatments.

DR. SIEGFRIED: I had a 4-month-old with infantile eczema/seborrheic dermatitis who was seeing me for a second visit during which I find they had not followed any of my instructions. The parent was opposed to bleach baths and didn't want to use any topical corticosteroids. Do you recommend sodium hypochlorite baths?

A Dr. Lio: I do. I think that's one of the most powerful things that has come into our armamentarium in the past nine years that I've been in practice. I feel like that's changed everything.

DR. SIEGFRIED: People would rather try apple cider vinegar, dead sea salts, or Epsom salts, etc. What do you think of those? Second, how do you handle the patients like mine who just don't want to follow that regimen?

A Dr. Lio: First of all, I feel like each of those can be helpful for some patients, but in my opinion it's underwhelming compared to the power of the bleach. I've been talking with a friend of mine at the National Institutes for Health about doing a study to compare bleach versus vinegar, because I think it would be interesting to see what it does to the microflora on the skin.

I think a lot of parents do react negatively, perhaps because it sounds like a toxic thing to put on your child's skin. My general approach is to compare it with swimming: If they've ever been in a swimming pool, I explain that all I'm asking is for them to go swimming a little more often. Sometimes I can't convince them.

I've had good luck with a lot of patients that really have closed the doors to other doctors, and I think that's because I am open to talking about these other therapies. With many patients I will start talking about sunflower seed oil[1] or coconut oil[2] (my two favorites). Even if they want to engage in the diet

Listen to the discussion.
bit.ly/alternativetherapyinderm

realm, which is one of the tougher parts for me, we can do that at first. I'll engage it honestly, and a lot of times, by the end of the visit, they're using fluticasone and the bleach baths. I'm able to convince them to try conventional treatments, but I think it's because we connected on the alternatives and I regained their trust. Oftentimes, it is a fully conventional regimen, but with alternatives added; an integrative approach.

DR. SIEGFRIED: What is your standard approach to refractory warts, and what are the alternatives?

A Dr. Lio: I want to make a disclaimer first that most of the patients that I see for warts have already tried conventional treatments. Many of them have had a few rounds of cryotherapy; they have used some form of salicylic acid at home. They are still being bothered so much that they are seeking other opinions. So, once a physician has tried the basics, you really do become stuck, because then the conventional evidence starts to fail us.

One of the things that I've been interested in is supplementing some of these patients with zinc. There's an interesting suggestion in the literature that a subgroup of patients with refractory warts may be slightly zinc deficient.[3] The caveat is that a fair number of people get sick to their stomachs on zinc, but I've had some patients really respond.

The other one is propolis, which is a natural glue that bees make to seal their hives. There was an interesting double blinded, randomized, controlled study that showed that people taking oral propolis actually cleared their refractory warts better than the control group.[4] I'll try that when the warts are really refractory; the only issue there would be caution in patients who are allergic to bees. There may be bee fragments or bee proteins in it, and you don't want to cause a serious allergy. This is something that can be found in a health food store, relatively safe and inexpensive.

Another therapy I've been interested in is topical garlic. There was a small case-controlled study and then a larger study that looked at the efficacy of gently rubbing a fresh piece from the clove on the warts at bed time and then applying a bandage over them.[5,6] The disclaimer is that you should not tape the piece of garlic to the wart or to the skin, because that can actually cause a chemical burn. There probably are some anti-viral properties to the garlic, and it seems to be a pretty good natural irritant. If all those things fail, however, we go right back to more conventional things. Although certainly not for everyone, I also use intralesional candida albicans antigen and even intralesional bleomycin — off label of course — in those situations.

DR. SIEGFRIED: Do you have any alternatives for vitiligo?

A Dr. Lio: Nothing that I've tried or read about seems convincing enough to me. Pseudocatalase has been around for a while, and there were some provocative studies with it a few years back.[7] A paper came out a year or two ago kind of re-igniting interest in it, but I just have not had much luck at all with it.[8]

Supplements in general have not been that helpful; however, the one I do use is ginkgo. There have been

TAKEAWAY *see page* 106

An **ETA** for acne results: 12 weeks[1]

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Balanced acne treatment

Aczone® (dapsone) gel, 5%

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INDICATION

ACZONE® (dapsone) Gel 5% is indicated for the topical treatment of acne vulgaris.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hematological effects: Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. There was no evidence of clinically relevant hemolysis or anemia in patients treated with ACZONE® Gel 5%, including patients who were G6PD deficient. Some subjects with G6PD deficiency using ACZONE® Gel 5% developed laboratory changes suggestive of mild hemolysis.

If signs and symptoms suggestive of hemolytic anemia occur, ACZONE® Gel 5% should be discontinued. ACZONE® Gel 5% should not be used in patients who are taking oral dapsone or antimalarial medications because of the potential for hemolytic reactions. Combination of ACZONE® Gel 5% with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

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Peripheral neuropathy: Peripheral neuropathy (motor loss and muscle weakness) has been reported with oral dapsone treatment. No events of peripheral neuropathy were observed in clinical trials with topical ACZONE® Gel 5% treatment.

Skin: Skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria) have been reported with oral dapsone treatment. These types of skin reactions were not observed in clinical trials with topical ACZONE® Gel 5% treatment.

ADVERSE REACTIONS

The most common adverse reactions of ACZONE® Gel 5% (incidence ≥ 10%) are oiliness/peeling, dryness, and erythema at the application site.

DRUG INTERACTIONS

Topical application of ACZONE® Gel followed by benzoyl peroxide in subjects with acne vulgaris resulted in a temporary local yellow or orange discoloration of the skin and facial hair (reported by 7 out of 95 subjects in a clinical study) with resolution in 4 to 57 days.

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

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ACZONE® (dapsone) Gel 5%

BRIEF SUMMARY—PLEASE SEE THE ACZONE® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

ACZONE® Gel, 5%, is indicated for the topical treatment of acne vulgaris.

DOSAGE AND ADMINISTRATION

For topical use only. Not for oral, ophthalmic, or intravaginal use. After the skin is gently washed and patted dry, apply approximately a pea-sized amount of **ACZONE®** Gel, 5%, in a thin layer to the acne affected areas twice daily. Rub in **ACZONE®** Gel, 5%, gently and completely. **ACZONE®** Gel, 5%, is gritty with visible drug substance particles. Wash hands after application of **ACZONE®** Gel, 5%.

If there is no improvement after 12 weeks, treatment with ACZONE® Gel, 5%, should be reassessed.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hematological Effects

Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs. G6PD deficiency is most prevalent in populations of African, South Asian, Middle Eastern, and Mediterranean ancestry.

There was no evidence of clinically relevant hemolysis or anemia in patients treated with **ACZONE®** Gel, 5%, including patients who were G6PD deficient. Some subjects with G6PD deficiency using **ACZONE®** Gel developed laboratory changes suggestive of mild hemolysis.

If signs and symptoms suggestive of hemolytic anemia occur, **ACZONE®** Gel, 5% should be discontinued. **ACZONE®** Gel, 5% should not be used in patients who are taking oral dapsone or antimalarial medications because of the potential for hemolytic reactions. Combination of **ACZONE®** Gel, 5%, with trimethoprim/sulfamethoxazole (TMP/SMX) may increase the likelihood of hemolysis in patients with G6PD deficiency.

Peripheral Neuropathy

Peripheral neuropathy (motor loss and muscle weakness) has been reported with oral dapsone treatment. No events of peripheral neuropathy were observed in clinical trials with topical **ACZONE®** Gel, 5% treatment.

Skin

Skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria) have been reported with oral dapsone treatment. These types of skin reactions were not observed in clinical trials with topical **ACZONE®** Gel, 5% treatment.

ADVERSE REACTIONS

Clinical Studies Experience

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

Serious adverse reactions reported in patients treated with **ACZONE®** Gel, 5%, during clinical trials included but were not limited to the following:

- Nervous system/Psychiatric – Suicide attempt, tonic clonic movements.
- Gastrointestinal – Abdominal pain, severe vomiting, pancreatitis.
- Other – Severe pharyngitis.

In the clinical trials, a total of 12 out of 4032 patients were reported to have depression (3 of 1660 treated with vehicle and 9 of 2372 treated with **ACZONE®** Gel, 5%). Psychosis was reported in 2 of 2372 patients treated with **ACZONE®** Gel, 5%, and in 0 of 1660 patients treated with vehicle.

Combined contact sensitization/irritation studies with **ACZONE®** Gel, 5%, in 253 healthy subjects resulted in at least 3 subjects with moderate erythema. **ACZONE®** Gel, 5%, did not induce phototoxicity or photoallergy in human dermal safety studies.

ACZONE® Gel, 5%, was evaluated for 12 weeks in four controlled studies for local cutaneous events in 1819 patients. The most common events reported from these studies include oiliness/peeling, dryness, and erythema. One patient treated with **ACZONE®** Gel in the clinical trials had facial swelling which led to discontinuation of medication.

In addition, 486 patients were evaluated in a 12 month safety study. The adverse event profile in this study was consistent with that observed in the vehicle-controlled studies.

Experience with Oral Use of Dapsone

Although not observed in the clinical trials with **ACZONE®** Gel (topical dapsone) serious adverse reactions have been reported with oral use of dapsone, including agranulocytosis, hemolytic anemia, peripheral neuropathy (motor loss and muscle weakness), and skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria).

DRUG INTERACTIONS

Trimethoprim-Sulfamethoxazole

A drug-drug interaction study evaluated the effect of the use of **ACZONE®** Gel, 5%, in combination with double strength (160 mg/800 mg) trimethoprim-sulfamethoxazole (TMP/SMX). During co-administration, systemic levels of TMP and SMX were essentially unchanged. However, levels of dapsone and its metabolites increased in the presence of TMP/SMX. Systemic exposure (AUC_{0-12}) of dapsone and N-acetyl-dapsone (NAD) were increased by about 40% and 20% respectively in the presence of TMP/SMX. Notably, systemic exposure (AUC_{0-12}) of dapsone hydroxylamine (DHA) was more than doubled in the presence of TMP/SMX. Exposure from the proposed topical dose is about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.

Topical Benzoyl Peroxide

Topical application of **ACZONE®** Gel followed by benzoyl peroxide in subjects with acne vulgaris resulted in a temporary local yellow or orange discoloration of the skin and facial hair (reported by 7 out of 95 subjects in a clinical study) with resolution in 4 to 57 days.

Drug Interactions with Oral Dapsone

Certain concomitant medications (such as rifampin, anticonvulsants, St. John's wort) may increase the formation of dapsone hydroxylamine, a metabolite of dapsone associated with hemolysis. With oral dapsone treatment, folic acid antagonists such as pyrimethamine have been noted to possibly increase the likelihood of hematologic reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. Dapsone has been shown to have an embryocidal effect in rats and rabbits when administered orally in doses of 75 mg/kg/day and 150 mg/kg/day (approximately 800 and 500 times the systemic exposure observed in human females as a result of use of the maximum recommended topical dose, based on AUC comparisons), respectively. These effects were probably secondary to maternal toxicity. **ACZONE®** Gel, 5%, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Although systemic absorption of dapsone following topical application of **ACZONE®** Gel, 5%, is minimal relative to oral dapsone administration, it is known that dapsone is excreted in human milk. Because of the potential for oral dapsone to cause adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue **ACZONE®** Gel, 5%, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy was evaluated in 1169 children aged 12-17 years old treated with **ACZONE®** Gel, 5%, in the clinical studies. The adverse event rate for **ACZONE®** Gel, 5%, was similar to the vehicle control group. Safety and efficacy was not studied in pediatric patients less than 12 years of age, therefore **ACZONE®** Gel, 5%, is not recommended for use in this age group.

Geriatric Use

Clinical studies of **ACZONE®** Gel, 5%, did not include sufficient number of patients aged 65 and over to determine whether they respond differently from younger patients.

G6PD Deficiency

ACZONE® Gel, 5% and vehicle were evaluated in a randomized, double-blind, cross-over design clinical study of 64 patients with G6PD deficiency and acne vulgaris. Subjects were Black (88%), Asian (6%), Hispanic (2%) or of other racial origin (5%). Blood samples were taken at Baseline, Week 2, and Week 12 during both vehicle and **ACZONE®** Gel, 5% treatment periods. There were 56 out of 64 subjects who had a Week 2 blood draw and applied at least 50% of treatment applications. **ACZONE®** Gel was associated with a 0.32 g/dL drop in hemoglobin after two weeks of treatment, but hemoglobin levels generally returned to baseline levels at Week 12.

There were no changes from baseline in haptoglobin or lactate dehydrogenase during **ACZONE®** or vehicle treatment at either the 2-week or 12-week time point.

The proportion of subjects who experienced decreases in hemoglobin ≥1 g/dL was similar between **ACZONE®** Gel, 5% and vehicle treatment (8 of 58 subjects had such decreases during **ACZONE®** treatment compared to 7 of 56 subjects during vehicle treatment among subjects with at least one on-treatment hemoglobin assessment). Subgroups based on gender, race, or G6PD enzyme activity did not display any differences in laboratory results from the overall study group. There was no evidence of clinically significant hemolytic anemia in this study. Some of these subjects developed laboratory changes suggestive of mild hemolysis.

OVERDOSAGE

ACZONE® Gel, 5%, is not for oral use. If oral ingestion occurs, medical advice should be sought.

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UPCOMING CME ACTIVITIES

Closure Course and Dermatologic Surgery: Focus on Skin Cancer

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May 20-21, 2015 – Closure Course
This intense learning experience provides didactic instruction and practical experience in multiple closure techniques, and includes numerous anatomic site-specific discussions. A hands-on laboratory session allows for closely-monitored practice of new and complex reconstruction techniques on realistic visco-elastic models. Information presented in the course strongly complements the activities featured in Dermatologic Surgery: Focus on Skin Cancer (below), without direct overlap or duplication of material.

May 22-24, 2015 – Dermatologic Surgery: Focus on Skin Cancer
Top experts in cutaneous oncology and dermatopathology will present a multi-faceted program for dermatologists and dermatologic surgeons. Presenters in interactive panel discussions will share their unique perspectives on special tumor management, melanoma diagnosis and treatment, and reconstruction challenges. Advanced Mohs techs will receive updates on quality assurance measures, trouble-shooting, safety, and regulatory compliance in the Mohs lab. Meeting provides an excellent follow-up to our Fundamentals of Mohs surgery technician training.

Basal and Squamous Cell Cancer Pathology for Mohs Surgeons and Fundamentals of Mohs Surgery

DoubleTree Hotel San Diego, Mission Valley – San Diego, California

November 4, 2015 – Basal and Squamous Cell Cancer Pathology for Mohs Surgeons
Taught by Board-certified dermatopathologists, this intense one-day course will provide a "pure pathology" experience for physicians interested in understanding the subtler characteristics of basal and squamous cell carcinoma, the tumors most commonly treated with Mohs surgery. Participants will learn to accurately interpret BCC and SCC in all its variations, as well as to differentiate tumor characteristics from background findings, reactive changes present in recently biopsied tissue, etc.

November 5-8, 2015 – Fundamentals of Mohs Surgery
Dermatologists and other specialists will be introduced to the basic surgical and histopathologic aspects of Mohs surgery, preparing a solid foundation for long-term proficiency in the procedure. Microscope laboratory case review and pathologist-led small group discussions will promote greater understanding and enhanced accuracy in this most critical facet of Mohs surgery. Intensive cryostat lab instruction will benefit Mohs technicians at all levels of training and experience, deepening their understanding of Mohs tissue processing and the importance of the physician-technician "team" in successful Mohs surgery.

For additional information, please contact:
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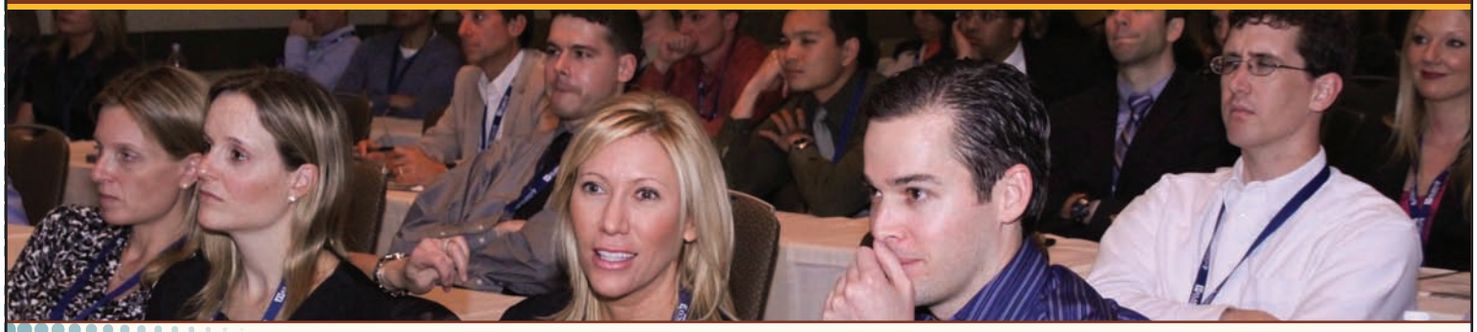

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TAKEAWAY

Selecting alternative therapies for specific conditions *from page* **94**

a couple of studies from around the world showing that oral supplementation with gingko can decrease the formation of new areas of vitiligo. [9,10]

I don't know if it works. If it does, it's pretty subtle, but if patients really want to do something more natural I think ginkgo is a reasonable thing to consider. It can increase risk for bleeding, so we have to keep an eye on that, but in a healthy patient it's probably okay at the doses we're talking about.

"If all of those things fail, we go right back to more conventional."

Peter Lio, M.D.
Chicago

DR. SIEGFRIED: Are there any other alternative approaches that you use the most often?

A Dr. Lio: Something I'll put out there because there is no evidence on this and I want someone to study this: There was a paper that came out a few years ago looking at spearmint tea. It showed that drinking spearmint tea had measurable effects on free and total testosterone levels and on FSH and LH in women with polycystic ovarian syndrome.[11] Researchers noticed, too, that hirsutism decreased when the patients drank spearmint tea. So it seems to be affecting androgen levels in patients with PCOS, in particular, but potentially in anybody, and the question is: Could this help with hormonal acne? We see it in so many young adult women, and often benzoyl peroxide and retinoids can be irritating to them. So I've had a number of patients with this hormonal micronodulocystic mandibular acne that have tried drinking a few cups per day of spearmint tea and they do well on it. So, I feel like this is an area that has a scientific rationale but no clinical data. I do use it all the time, because a lot of my patients for whom I recommend spironolactone will blanch — they've read about the risks of certain types of cancers and they get nervous. I feel like this is a more natural approach that potentially can help.

DR. SIEGFRIED: How do you approach itch?

A Dr. Lio: One of the toughest problems we face, and of course being pediatric focused, we see a lot of itch in multiple contexts. And of course, we have the other end of the population: elderly patients with terrible itch, sometimes without any rash, but just a generalized pruritus. One of my favorite things — we did a study about because it really made such an impression on me — there was a study a few years ago looking at patients with uremic pruritus, the terrible itch associated with kidney failure.[12]

We don't really get why this happens of course, but it's intractable and they had tried everything all the way through the list up to naltrexone and failed. This acupuncture group stimulated one point called the large intestinal eleven (LI 11), which is at the lateral aspect of the antecubital fossa. They compared that to a sham placebo point. The experimental group did amazingly well compared to the sham group in terms of itch reduction.

I thought, what if we could harness this for eczema? So we did a study a couple of years ago for the itch of eczema and instead of using needles, we tried acupressure. We had the patients massage that same point three times a week for three minutes. We compared that to a control group, and it really did significantly reduce itch.[13]

Their visual analog scales for their itch report were significantly improved by just rubbing one little point on the arm. So that's one of my favorite things for itch. If the patient isn't able to see an acupuncturist (which can be expensive and time consuming), then they can just literally do this at home whenever they're feeling itchy.

This could be a distraction and placebo effect, but there may actually be a neurologic effect — this gate control theory of pain and itch may somehow be deeply related to the underlying pathophysiology in the way that acupuncture and acupressure works. **DT**

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IMPORTANT INFORMATION ABOUT

SOOLANTRA®

(ivermectin) Cream, 1%

BRIEF SUMMARY

This summary contains important information about SOOLANTRA (soo lan' trah) Cream. Read this information carefully before you prescribe SOOLANTRA Cream. For full Prescribing Information and Patient Information please see the package insert.

WHAT IS SOOLANTRA CREAM?

SOOLANTRA Cream is a topical prescription medicine indicated for the treatment of the inflammatory lesions of rosacea.

WHO IS SOOLANTRA CREAM FOR?

SOOLANTRA Cream is indicated for people with inflammatory lesions of rosacea. It is not known if SOOLANTRA Cream is safe and effective for children. Advise your patients to not use SOOLANTRA Cream for a condition for which it was not prescribed and remind them to not give SOOLANTRA Cream to other people, even if they have the same symptoms as it may harm them.

WHAT SHOULD I ASK MY PATIENTS BEFORE PRESCRIBING SOOLANTRA CREAM?

Before you prescribe SOOLANTRA Cream, ask your patients if they:

- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if SOOLANTRA Cream can harm an unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SOOLANTRA Cream passes into breast milk and if it can harm a baby.

WHAT ARE THE MOST COMMON SIDE EFFECTS OF SOOLANTRA CREAM?

The most commonly reported side effects when using SOOLANTRA Cream include skin burning sensation and skin irritation. Remind your patients to tell you if they have any side effect that bothers them or that does not go away. These are not all of the possible side effects of SOOLANTRA Cream. For more information, see the full Prescribing Information.

You are encouraged to report negative side effects of prescription drugs to the FDA at *www.fda.gov/medwatch* or call 1-800-FDA-1088. You may also contact GALDERMA LABORATORIES, L.P. AT 1-866-735-4137.

HOW SHOULD PATIENTS USE SOOLANTRA CREAM?

- SOOLANTRA Cream is for use on the face only and should not be used in the eyes, mouth, or vagina.
- SOOLANTRA Cream should be applied to the affected areas of the face once a day.

APPLYING SOOLANTRA CREAM:

- A pea-sized amount of SOOLANTRA Cream should be applied to each area of the face (forehead, chin, nose, each cheek) that is affected. Avoid contact with the lips and eyes.

SOOLANTRA Cream is supplied in a child-resistant capped tube.

- To open, gently press down on the child resistant cap and twist counterclockwise. To avoid spilling, do not squeeze the tube while opening or closing.
- To close, gently press down on the child resistant cap and twist clockwise.

WHAT ARE THE INGREDIENTS IN SOOLANTRA CREAM?

Active ingredient: ivermectin. **Inactive ingredients:** carbomer copolymer type B, cetyl alcohol, citric acid monohydrate, dimethicone, edetate disodium, glycerin, isopropyl palmitate, methylparaben, oleyl alcohol, phenoxyethanol, polyoxyl 20 cetostearyl ether, propylene glycol, propylparaben, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT SOOLANTRA CREAM?

- This Brief Summary summarizes the most important information about SOOLANTRA Cream. For full Prescribing Information and Patient Information please see the package insert.
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ONCE-DAILY soolantra® (IVERMECTIN) CREAM, 1%

References: 1. Stein Gold L, Kircik L, Fowler J, et al; Ivermectin Phase III Study Group. Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drugs Dermatol*. 2014;13(3):316-323. **2.** Data on file. Galderma Laboratories, L.P. **3.** Taieb A, Ortonne JP, Ruzicka T, et al; Ivermectin Phase III Study Group. Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. *Br J Dermatol*. In press.

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*The efficacy and safety of SOOLANTRA® Cream, 1% once daily was evaluated in subjects aged ≥18 years in 2 identically designed phase 3 clinical trials (N=1371). Final results were comparable between the 2 studies, with the least favorable results presented here.

† A phase 3, multicenter, randomized, double-blind, 12-week, vehicle-controlled, parallel-group study assessing the efficacy and safety of SOOLANTRA® Cream, 1% once daily in 683 subjects with moderate to severe papulopustular rosacea (Investigator Global Assessment [IGA] score of 3 or 4).

‡ An investigator-blinded, multicenter, randomized, parallel-group study comparing the efficacy and safety of SOOLANTRA® Cream, 1% once daily with metronidazole 0.75% cream twice daily in 962 subjects with moderate to severe papulopustular rosacea (IGA score of 3 or 4) over a 16-week treatment period.

CME MONOGRAPH

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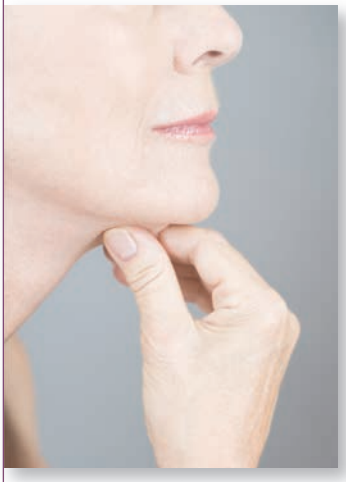
Achieving Total Facial Rejuvenation with Submental Contouring

Current and Emerging Strategies



Highlights from a Hot Topic CME Educational Session held during the American Society for Dermatologic Surgery 2014 Annual Meeting

Original Release: March 1, 2015 | **Last Review:** February 10, 2015 | **Expiration:** March 1, 2016

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This activity intends to educate aesthetic dermatologists and facial plastic surgeons.

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The appearance of the neck has a major influence on facial harmony and overall aesthetics. Neck rejuvenation, however, remains an unmet need for many patients seeking cosmetic intervention. New treatment is being investigated, and this activity will provide participants with an update on the latest evidence for current approaches, as well as an introduction to emerging treatment.

Educational Objectives

After completing this activity, the participant should be better able to:

- Articulate the details of chin and neck anatomy and soft tissue and skeletal changes as they pertain to patient analysis and treatment for excess submental fat
- Evaluate the comparative efficacy, safety, and patient selection criteria for current treatment options for submental contouring
- Describe the chemistry and mechanism of action of emerging adipolytic therapy for submental fat reduction
- Review the efficacy and safety data on emerging adipocytolytic treatment for submental fat reduction
- Identify appropriate patients for emerging adipocytolytic submental fat reduction treatment according to criteria of clinical trials

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Introduction

Excess submental fat leading to the appearance of a "double chin" affects the aesthetic appearance of the neck and face and is a common concern among cosmetic surgery patients, regardless of sex or age. Focal accumulation of fat leading to submental convexity is particularly associated with obesity and age-related tissue changes. Genetics also plays a role in such development, however, which explains why younger adults and normal-weight individuals may develop a double chin.

Available data indicate that people with excess submental fat are dissatisfied with their appearance and may feel that it makes them look older and heavier than they are.[1] In addition, they may experience feelings of embarrassment and self-consciousness.[1] Considering its psychological burdens and because submental fullness is difficult to conceal with clothing, it is not surprising that there is high patient interest in techniques for reducing submental fat. In a study that surveyed 385 patients who had seen a dermatologist or plastic surgeon for nonsurgical facial rejuvenation procedures, 77% responded that they noticed extra fat underneath the chin, and 61% agreed that they would like to be able to safely reduce the submental fat.[2]

Liposuction is considered the gold standard for surgical removal of fat,[2] and up to 25% of liposuction procedures target the submental region.[3] Not all patients are willing or able to undergo liposuction, however. Patient survey data along with the proliferation of energy-based techniques for lipolysis highlight that there is high patient interest and demand for effective and well-tolerated noninvasive alternatives.

In a series of articles, this monograph provides an overview of current and emerging strategies for submental fat reduction. It begins with a review of relevant anatomy, which is the basis for the planning and success of any cosmetic procedure intended to address excess submental fat.

Understanding Neck Anatomy

Lisa Donofrio, MD

The morphology of the jawline and submental area are important determinants of neck attractiveness and a common focus of aesthetic concerns. Characteristics of a youthful, attractive neck include a well-defined cervicomental angle and a sharp yet full mandibular contour. Accumulation of fat in the submental area, with a resulting increase in submental convexity, will blunt these features. Although a variety of procedures can be used to remove excess submental fat and rejuvenate the submental contour, excess submental fat is just one of many issues affecting appearance of the neck and submental region. Understanding of neck anatomy, including age-related tissue changes, is the key to an appropriate patient analysis and the physical examination that will inform the treatment plan and guide its safe execution.

Fat

Fat in the submental region is found in 3 planes (superficial, intermediate, and deep) that are defined based on their relation to the platysma muscles **(Figure 1)**.[4]

Preplatysmal fat, which is subcutaneous fat lying in the superficial planes between the dermis and platysma, is the target of minimally invasive and noninvasive procedures for rejuvenating the neck by reducing submental fat.

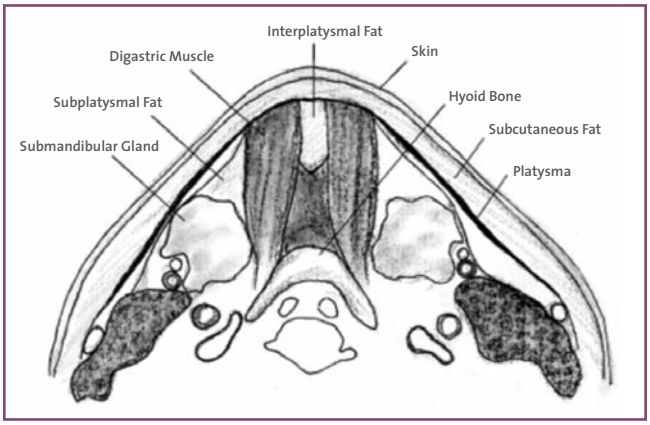


Figure 1. Fat in the submental region lies in 3 planes: 1) above the platysma; 2) between the platysma muscles; and 3) deep to the platysma muscles, superficial to the digastric muscles and the submandibular glands.[4]

Mejia JD et al. Semin Plast Surg. *2009;23(4):264-273.*

Research using cadaver specimens shows that the subcutaneous fat in the submental region resides in its own compartment, which is segregated from subcutaneous adipose tissue in the chin and jowls and bounded by the submental crease anteriorly, the cervicomandibular angle posteriorly, and a caudal continuation of the labiomandibular fold laterally **(Figure 2)**.[5,6]

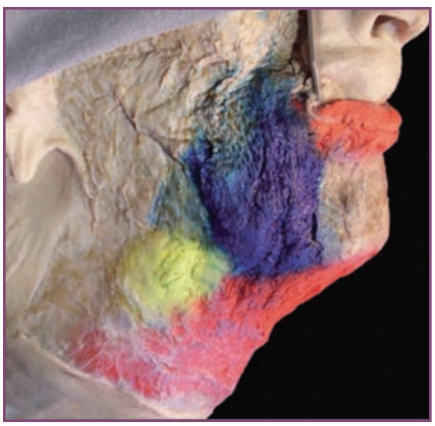


Figure 2. Injection of colored gelatin into the subcutaneous tissues of cadaver heads shows compartmentalization of fat in the neck and lower face. The submental region and lower lip appear in red.[5]

Pilsl U, Anderhuber F. Dermatol Surg. *2010;36(2):214-218.*

Submental fat in the intermediate plane is actually fat from the deep plane extending between the medial edges of the platysma muscles in individuals with limited or no platysmal decussation beneath the chin.[4] Subplatysmal fat in the submental region overlies the digastric muscles and the submandibular glands. Although it also may be contributing to submental fullness and can be reached through invasive surgical procedures, removal of subplatysmal fat as a strategy for submental contouring should be approached cautiously, because it can result in an unnaturally severe jawline. Interestingly, lift procedures can sharpen and improve the cervicomental angle, but they do not fully restore the youthful sweep of the mandibular contour that also depends on fullness in the upper part of the submental area.

A pinch test is used to distinguish between preplatysmal and subplatysmal fat. With the patient at rest, the surgeon grasps the submental tissue between thumb and forefinger and then asks

the patient to contract the platysma muscles by grimacing. The tissue remaining in the pinch represents the preplatysmal fat.

Platysma

The platysma comprises a pair of large muscles extending from the level of the clavicle, across the neck, and over the jawline. Age-related changes in platysmal tone affect the appearance of the neck, the cervicofacial contour, and the dynamics and morphology of the buccal region and mouth.

As mentioned above, the development of intraplatysmal fat is determined by the relationship between the 2 platysma muscles in the submental area. Three variations have been described for that relationship, of which limited decussation (extending 1 to 2 cm below the mandibular symphysis) is most common.[4]

Platysmal banding may develop with aging, secondary to weakening of the ligaments that keep the muscle medial edges approximated to the deep cervical fascia, and is an issue to consider when performing procedures for neck rejuvenation. Platysmal banding may be visible at rest in some patients, appear only on animation, or become unmasked after submental fat removal. Injection with botulinum toxin (eg, onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA) can produce temporary improvement in platysmal banding, as well as restore sharpness to the jawline and improve contour in the buccal region.[7,8]

Corset platysmaplasty represents a reliably effective technique for tightening the platysma to improve cervicomental contour and minimize the appearance of platysmal bands. This procedure is performed through a submental incision after removing a small ellipse of skin (~4 x 1.5 cm), and with its location under the chin, the resulting scar is reasonably well hidden.

Subplatysmal Structures

The submandibular glands are another important structure to consider in patients with complaints about submental fullness. These major salivary glands, which lie below the platysma in the submental region, may become ptotic or hypertrophied with age, creating a bulge that is visible **(Figure 3)** or that becomes apparent after subcutaneous fat removal. Surgical resection of the submandibular salivary glands can be performed as part of a traditional surgical lifting procedure.

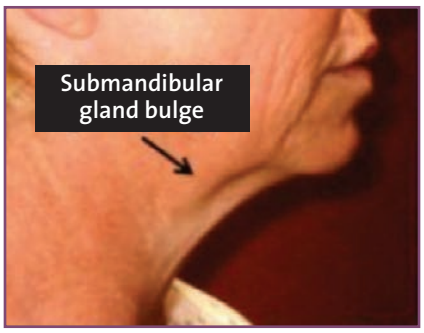


Figure 3. Submandibular gland bulge can contribute to submental fullness.

Photo: Angelo Cuzalina, MD, in Plasticsurgery practice.com, November 4, 2012.

Other deep structures in the submental region include the facial artery and the marginal mandibular nerve. The facial artery branches off from the external carotid artery in the neck, and, if inadvertently nicked, will result in significant bleeding. The marginal mandibular nerve runs below the inferior border of the mandible and over the facial artery **(Figure 4)**. This nerve is susceptible to injury with a variety of modalities used in cosmetic procedures of the neck and submental region, including ultrasound- and radiofrequency-based treatments, as well as incisional surgeries and liposuction.

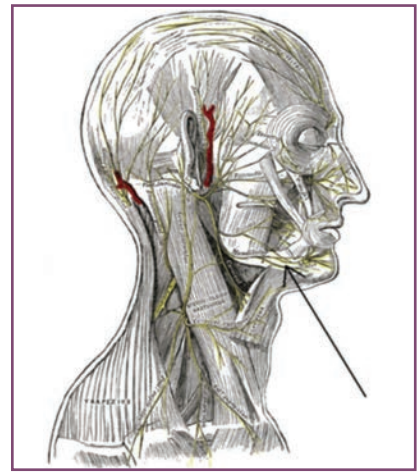


Figure 4. Nerves in the head and neck. The marginal mandibular nerve lies at the tip of the arrow.

Source: Gray's Anatomy. http://www.fpnotebook.com/_media/entNervesGrayBB805.gif.

The examination of a patient seeking neck rejuvenation surgery also should include assessment for cervical adenopathy and enlargement of the thyroid gland, both of which can contribute to an appearance of neck fullness. In addition, consideration should be given to hyoid bone position, chin projection, and the presence of photodamage- and age-related changes in skin elasticity, tone, and texture, because they all affect neck aesthetics and may influence management decisions.

Current Treatments for Submental Fat

Lisa Donofrio, MD, and Derek Jones, MD

Liposuction

Liposuction represents a safe and effective technique for treating submental fullness due to excess subcutaneous fat. In addition, liposuction can be combined with other procedures as needed for more complete rejuvenation of the lower face and neck. Although it may be possible to get good skin retraction with liposuction alone, the outcome will depend on the quality of the skin.

Performed with local tumescent anesthesia, liposuction is a minimally invasive procedure that results in approximately 3 to 5 days of social downtime for the patient.

The tumescent solution used for anesthesia contains a low concentration of lidocaine (0.05% or 0.1%) in lactated Ringer solution or normal saline along with sodium bicarbonate for buffering and epinephrine. Infiltration of the tumescent solution expands the subcutaneous space and thereby creates pressure that compresses deeper nerves and vessels away from the treatment site to protect them from trauma during the procedure. By inducing vascular constriction, the epinephrine in the solution provides hemostasis and limits absorption of the solution into the circulation, allowing for prolongation of the anesthetic effect.

After liposuction is completed, the area is wrapped with tape or a compression garment to encourage smooth redraping of the skin. The compression also will minimize the risk of developing a hematoma or a seroma as a complication.

Weakness of the muscles controlling the lower lip secondary to nerve injury is another possible complication of submental liposuction. The nerve injury is generally the result of blunt trauma and can occur if the liposuction cannula is advanced over the bone. The potential for injury to the marginal mandibular nerve can be reduced by pulling outward on the skin during the suctioning. The sequelae of blunt injury to the marginal mandibular nerve are usually temporary. The resulting temporary asymmetry of the lower lip can be very upsetting to patients, however, and they may require a lot of hand-holding and reassurance from the surgeon.

Other potential complications of liposuction include contour irregularities of the skin and/or fat. These problems are a particular risk with aggressive techniques, including oversuctioning of fat from the underside of the dermis or treating the underside of the dermis with a carbon dioxide laser.

Laser Lipolysis

A variety of laser platforms on the market have indications for lipolysis. These systems represent different types of lasers (neodymium-doped yttrium aluminium garnet [Nd:YAG] or diode) featuring single or multiple wavelengths selected to target adipose tissue and the skin. Laser lipolysis is often performed in combination with liposuction as a means of reducing liposuction morbidity and improving skin tightening.[9] It also has been used by itself to treat small areas of localized fat, including fat in the submental region.[10]

Despite the number of laser lipolysis platforms available, there is a lack of good evidence to demonstrate the efficacy of these procedures as stand-alone techniques or the superiority of liposuction with laser lipolysis vs liposuction alone. In addition, laser lipolysis carries risks of thermal damage, including injury to the skin and even the marginal mandibular nerve.[9]

Noninvasive Lipolysis

Several energy-based methods have been developed to address patient interest in noninvasive treatments for localized fat reduction. As discussed below, these devices are based on selective delivery of cold, ultrasound, or radiofrequency to produce targeted adipocyte destruction.

Cryolipolysis

Cryolipolysis is available as a noninvasive approach for addressing focal adiposity. Its mechanism of action involves selective destruction of adipocytes by exposure to controlled cooling.

The commercially available cryolipolysis platform is approved for treatment of the abdomen and flanks. Currently there is no commercially available handpiece for submental treatment, but a pilot study of cryolipolysis for reduction of submental fat has been completed.[11]

There is objective evidence from ultrasound imaging to show that cryolipolysis reduces subcutaneous fat. The effect is somewhat modest, with an approximately 20% decrease in fat thickness reported after a single treatment.[12] A second treatment may improve the recontouring benefit of cryolipolysis.[13]

The procedure is generally well tolerated, safe in all skin phototypes, and associated with limited to no downtime. Patients develop localized edema and erythema that is usually transient, but can last for several hours and even longer. Ecchymosis and soreness also can occur because the device uses vacuum suction to pull sections of skin and adipose tissue up into the cup-shaped treatment applicator. In addition, there may be some sensory changes.[12] The latter consist mainly of localized numbness that can persist for days to weeks but is generally not very bothersome given its location. Rarely, patients experience severe pain.[14] Recently, there have been reports of paradoxical adipocyte hyperplasia as a delayed side effect of cryolipolysis.[14] Although rare, treatment has required liposuction or abdominoplasty.

Cryolipolysis has some practical limitations. The device itself is very large, and the treatment is time-consuming, typically requiring 1 hour for each region.

Focused ultrasound

Focused ultrasound is another energy-based modality that can target the adipose layer. Available platforms work via 2 different mechanisms.[15] Devices operating at a lower frequency disrupt adipocytes using mechanical energy via a nonthermal, cavitation-based effect. In contrast, devices delivering high-intensity ultrasound produce cellular necrosis secondary to thermal coagulation.

These ultrasound techniques can be used safely in patients of all skin phototypes, and, depending on the platform, can be administered at multiple depths to target the dermis, with the potential to induce skin tightening. Increasing the level of treatment also increases procedural time, however.

Treatment using higher-frequency ultrasound can be very painful and almost intolerable for some patients.[15] The nonthermal technique has been reported to cause mild pain as well as blister formation.[15]

Radiofrequency

Radiofrequency energy also can cause lipolysis through heating. Available platforms include monopolar, bipolar, and unipolar devices, and some systems combine radiofrequency with other modalities (eg, light, mechanical manipulation, vacuum, and aspiration). Penetration depth varies depending on the radiofrequency mode. Selective heating of subcutaneous fat is achieved noninvasively with manipulations for skin cooling or with insertion of the treatment tip into the adipose tissue, and radiofrequency also can be used to induce skin tightening.

Regardless of radiofrequency mode, the treatment results in limited to no downtime. Local side effects include erythema and edema, which are mostly transient.[16,17] Burns also have been reported.[16,17]

Injection Lipolysis

Injection lipolysis involves the delivery of agents into adipose tissue to reduce fat volume nonablatively by activating adipocyte lipolytic pathways or by inducing permanent adipocyte destruction.[18] There are no injectable products for lipolysis approved by the US Food and Drug Administration

(FDA). Several injectable products are being developed for treating localized deposits of subcutaneous fat in different anatomic areas. For reduction of submental fat, only 1 agent, ATX-101, has completed phase 3 trials. ATX-101 is a purified synthetic version of deoxycholic acid that causes adipocyte cell lysis. The New Drug Application for its approval is under FDA review.[19] The beta-agonist salmeterol xinafoate, which acts via a nonablative mechanism, is headed into phase 3 trials during which it will be evaluated for the reduction of subcutaneous abdominal fat in nonobese individuals.[20]

Both ATX-101 and salmeterol xinafoate are administered as a subcutaneous injection. A topical formulation of XAF5, a novel small molecule that modulates fat cells via a nonablative mechanism, is in a phase 2a study for reduction of submental fat.[21]

Historically, injection lipolysis has been performed using compounded solutions prepared without any regulatory oversight and often administered by nonphysicians in spas or other nonmedical facilities.

This practice, which has been referred to as mesotherapy or "lipodissolve", has raised important safety issues relating to the potential for adulteration and contamination of the injectables and their administration by unskilled hands. Supporting those concerns are the many reports of serious adverse events associated with mesotherapy, including the development of mycobacterial infections, scarring, and skin deformation.[22]

In reaction to these problems, in April 2010 the FDA issued warning letters to 6 US-based medical spas and a company in Brazil that were making false or misleading statements on their Web sites about drugs that they claimed would eliminate fat in a procedure that was marketed as "lipodissolve" or for otherwise misbranding lipodissolve products.[23]

There is some evidence in the peer-reviewed literature of injection lipolysis using deoxycholate alone or combined with phosphatidylcholine. A randomized, double-blind trial by Rotunda et al. enrolling 42 patients compared the mixture of the 2 agents vs deoxycholate alone for reduction of submental fat.[24] Evaluations performed after patients received up to 5 monthly injections showed that the 2 treatment groups had similar, albeit minimal, improvement in submental contour, supporting previous laboratory research by Rotunda et al. identifying deoxycholate as the major active component in deoxycholate-phosphatidylcholine mixtures.[25]

As mentioned earlier, a purified synthetic version of deoxycholic acid, ATX-101, is being developed for reduction of submental fat.

Summary

Liposuction remains the gold standard treatment modality for patients with aesthetic concerns focusing on submental fat. Although there may be laboratory evidence to show that various noninvasive lipolysis techniques can target the subcutaneous adipose layer, there is limited to no scientific evidence supporting their clinical efficacy. Most published reports describe small case series or uncontrolled studies, use subjective outcome measures, and lack long-term follow-up. Results indicate that responses vary among individuals; however, improvement is generally modest, and the treatment may be time-intensive and expensive. Furthermore, with all of these techniques there is the potential for adverse events, some of which can be significant.

Injection lipolysis is a simple, minimally invasive procedure for targeting submental fat. Historically it has been performed using unregulated solutions. A proprietary formulation of synthetic deoxycholic acid has demonstrated promising efficacy and safety in phase 3 studies investigating its use as a submental contouring drug for reducing submental fat.

REFINE-1 and REFINE-2 Pivotal North American Phase 3 Studies With ATX-101

Jean Carruthers, MD, FRCS(C), FRC (OPHTH)

ATX-101 is an adipocytolytic agent that acts by solubilizing adipocyte membrane lipids, resulting in fat cell breakdown with subsequent induction of a mild, local inflammatory response that clears the cellular debris and also may stimulate neocollagenesis.[26]

The North American pivotal trials investigating injections with ATX-101 for the reduction of submental fat consisted of 2 identically designed multicenter, randomized, parallel-group, double-blind, placebo-controlled studies known as REFINE-1 and REFINE-2. The 2 trials included 1022 randomized patients, both men and women, at 70 centers. The primary inclusion criteria for determining eligibility were based on 3 validated instruments: the 5-point photonumeric Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) **(Figure 5)**, the 5-point Patient-Reported Submental Fat Rating Scale (PR-SMFRS), and the 7-point Subject Self-Rating Scale (SSRS). Patients needed to have a score of 2 or 3 on both the CR-SMFRS and the PR-SMFRS,

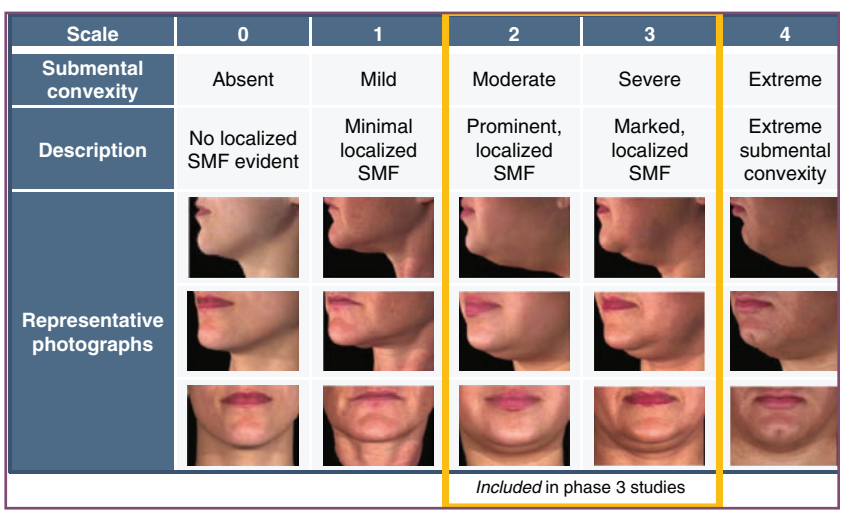


Figure 5. Clinician-Reported Submental Fat Rating Scale. Patients with ratings of 2 or 3 were included in REFINE-1 and REFINE-2, the ATX-101 phase 3 trials.

SMF, submental fat.

Photos reproduced from McDiarmid J et al. Aesthetic Plast Surg. *2014;38(5):849-860.*

indicating presence of moderate to severe submental fat, and a score of 0 to 2 on the SSRS, indicating dissatisfaction with the appearance of their submental area.[27]

Eligible patients were randomized to receive up to 6 injections of ATX-101 2 mg/cm² or placebo at approximately monthly intervals. Phase 3 studies conducted in Europe included a third arm that evaluated ATX-101 1 mg/cm², which also demonstrated significant efficacy compared with placebo; however, that arm showed a trend of being less effective than the 2-mg/cm² dose.[1,28]

Efficacy

The primary efficacy assessment in the North American pivotal trials was conducted at 12 weeks after the last injection and was based on a coprimary end point defined as the proportion of patients achieving a ≥1-grade improvement from baseline in both the CR-SMFRS and PR-SMFRS scores ("treatment responders").

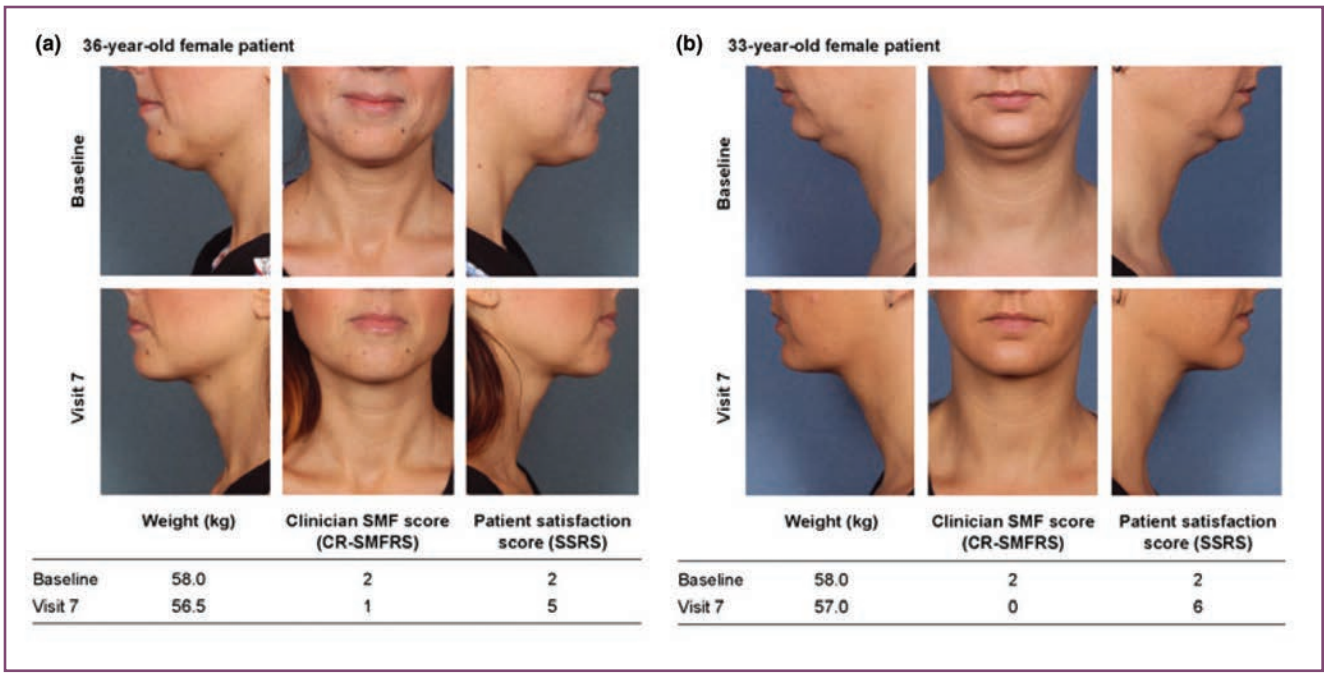
The prespecified efficacy end point was met in both studies. In REFINE-1, 70.3% of ATX-101 patients and 18.7% of controls achieved a ≥1-grade improvement in the CR-SMFRS/PR-SMFRS composite end point; treatment-responder rates for the ATX-101 and control groups in REFINE-2 were 66.9% and 22.4%, respectively (*P*<.001, ATX-101 vs placebo in both studies).[29] A pooled analysis of the REFINE-1 and REFINE-2 data showed 68.2% of ATX-101 patients and 20.5% of placebo patients achieved a ≥1-grade change in the CR-SMFRS/PR-SMFRS composite (*P*<.001).[30]

Although a 1-grade improvement on the CR-SMFRS and PR-SMFRS is clinically meaningful, a secondary efficacy end point analysis of the pivotal trial data considered the proportion of patients achieving a ≥2-grade improvement from baseline in both the CR-SMFRS and PR-SMFRS. This outcome represented an FDA-preferred end point that was intended to minimize the placebo responder rate, and the results showed statistically significant superiority of ATX-101 over placebo in both REFINE-1 (13.4% vs 0%, respectively),[29] REFINE-2 (18.7% vs 3.2%, respectively),[29] and the pooled analysis (16.0% vs 1.5%, respectively)[30] (*P*<.001 for all comparisons).

Magnetic resonance imaging in a subset of 449 patients showed that a significantly higher percentage of ATX-101 patients than controls were categorized as responders based on achieving a prespecified reduction in submental volume (43.3% vs 5.3%; *P*<.001).[30] Skin laxity was also assessed using a subjective scale and shown to be improved or unchanged in the vast majority of patients.[27] Patients judged to have very lax skin were excluded from enrollment.

Patients participating in the pivotal trials also completed a validated, 6-item submental fat impact scale that assessed whether they perceived themselves as being happier, less bothered, less self-conscious, less embarrassed, younger, or less overweight after their treatment. The results showed statistically significant greater improvement with ATX-101 vs placebo for all 6 components of the scale as well as in the composite score (*P*<.001).[31] In the ATX-101 treatment groups, 88.9% of REFINE-1 patients and 84.2% of REFINE-2 patients reported satisfaction with the treatment they received; the patient satisfaction rates were significantly lower in the placebo groups in both REFINE-1 and REFINE-2, 37.7% and 43.6%, respectively (*P*<.001 for both comparisons).

Figure 6 shows pretreatment and posttreatment photographs and data from 2 patients treated with ATX-101 2 mg/cm² in a European phase 3 study investigating its use for reduction of unwanted submental fat.[28]



	Weight (kg)	Clinician SMF score (CR-SMFRS)	Patient satisfaction score (SSRS)
Baseline	58.0	2	2
Visit 7	56.5	1	5

	Weight (kg)	Clinician SMF score (CR-SMFRS)	Patient satisfaction score (SSRS)
Baseline	58.0	2	2
Visit 7	57.0	0	6

Figure 6. Baseline and final visit photographs from 2 patients who received ATX-101 2 mg/cm² in a randomized, controlled, phase 3 study investigating ATX-101 for reduction of unwanted submental fat.[28] The protocol allowed a maximum of 4 treatment sessions (visits 2–5) approximately 28 days apart; visit 7 was a posttreatment visit 12 weeks after visit 5. A maximum of 6 treatment sessions was allowed in REFINE-1 and REFINE-2.

Photos reproduced from Ascher B et al. J Eur Acad Dermatol Venereol. *2014;28(12):1707-1715.*

Safety

The safety analyses showed ATX-101 had an acceptable safety profile and was well tolerated. The most common adverse events included swelling, pain, bruising, numbness, and erythema.[30,31] These adverse events were expected as a result of the pharmacological action of ATX-101 and the injection. As reported in a pooled analysis of European phase 3 ATX-101 studies, with the exception of bruising, the localized adverse events were much more frequent in patients treated with ATX-101 than in the controls.[32] They were generally mild to moderate in severity, however, and, anecdotally, were most severe after the first treatment and less intense with subsequent treatments. There were no treatment-related serious adverse events, and only 1.4% of the patients discontinued the study because of an adverse event.[30]

The effect of treatment with ATX-101 on lipid levels was investigated in a pharmacokinetic study of healthy participants who had ATX-101 injected into subcutaneous abdominal fat, and the results showed no significant changes in the serum levels of total cholesterol, total triglycerides, or free fatty acids.[33]

Summary

In summary, the pivotal trial results showed that ATX-101 significantly reduced submental fat compared with placebo, based on clinician-reported and patient-reported outcome measures. In addition, treatment with ATX-101 resulted in significant improvements in visual and psychological impact of submental fat. Those findings may be the most compelling evidence of the benefit of ATX-101, considering that patients are motivated to seek treatment for submental fat based on their perceived self-image and how that perception makes them feel.

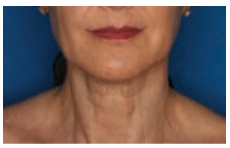
If ATX-101 is approved, information on its side effects will need to be included in informed consent discussions with patients. It seems likely, however, that once the product becomes available, clinicians will find ways to minimize the treatment sequelae.

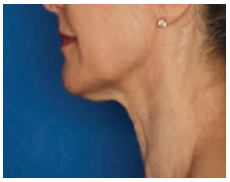
Tailoring Decisions on Treatment for Submental Fat

Removal of excess subcutaneous submental fat will improve cervicomental contour, jawline definition, and overall facial appearance. The choice of technique and the need for additional surgeries to optimize harmony, however, depend on careful assessment to characterize the severity of submental fat along with changes in other soft tissues, the skin, and bone.

The following case-based discussions illustrate these concepts.

Case 1. A 57-year-old white woman





Courtesy of Derek Jones, MD

Dr Jones: Skin laxity appears to be a more prominent feature than localized fat in this patient, so she may be a reasonable candidate for a procedure that is indicated for skin tightening. The options might include thermal radiofrequency, focused ultrasound, or laser-assisted lipolysis.

I use both thermal-focused ultrasound and monopolar radiofrequency platforms for contouring and skin tightening in the neck. While they are both effective, the improvement is generally modest and may need multiple sessions. In addition, the treatments are time intensive and expensive, and the focused ultrasound can be very painful. I thoroughly counsel patients about all of these issues, am careful to never overpromise the results, and show before-and-after photographs of patients whom I personally treated with these devices so that patients can understand the type of results that may be achieved.

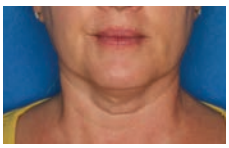
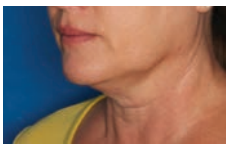
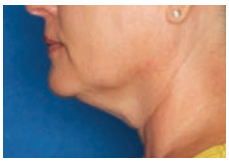
Dr Donofrio: For patients with submental skin laxity, I favor excising a small ellipse of skin rather than treating with one of the energy-based devices. Dermatologic surgeons have the training and expertise to do the excisional procedure. It is a great option that takes just 45 minutes, and patients are consistently satisfied with the results.

Dr Carruthers: I also have monopolar radiofrequency and thermal-focused ultrasound systems, but tend to use the radiofrequency device more often, because it is less painful. I estimate this patient would need 3 or 4 treatments with the ultrasound platform to achieve satisfactory skin tightening and possibly the same number or more with monopolar radiofrequency.

In the past when I used liposuction for reducing submental fat, I would treat the underside of the skin with a carbon dioxide laser to promote tightening. My experience showed that the submental skin is hard to shrink but easy to scar, so I abandoned that technique. As another consideration for avoiding contour irregularities after liposuction, surgeons should always leave a small layer of superficial subcutaneous fat.

Dr Jones: In the future we may have ATX-101 as another option. While it is under FDA review for an indication to reduce submental fat, a skin tightening effect was observed in some patients who were treated with it in the premarketing studies. That benefit was not originally anticipated, but it has biological plausibility, considering that the treatment may stimulate collagen production by its induction of an inflammatory response.

Case 2. A 54-year-old white woman

Courtesy of Derek Jones, MD

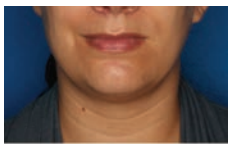
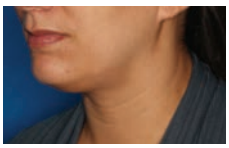
Dr Donofrio: This patient has a moderate amount of submental fullness due to fat and moderate mid-neck skin laxity. She would do well with submental liposuction but may need an adjunctive submental ellipse and platysmal plication as well as filler in her jawline and pre-jowl sulcus.

If she was in the ATX-101 trial, I would have expected her to take 2 to 4 sessions, but she would need to be counseled in regard to possible resultant skin laxity.

Dr Carruthers: I expect she might respond well to at least 2 treatments with ATX-101, and she may get sufficient tightening of her skin laxity. Monopolar radiofrequency or high-intensity focused ultrasound are options if skin laxity remains a concern.

Dr Jones: I agree that this patient is a candidate for liposuction or ATX-101. Energy-based devices may be tried, but the patient needs to be informed that the result will not be predictable.

Case 3. A 42-year-old Hispanic woman


Courtesy of Derek Jones, MD

Dr Carruthers: This woman has a very discreet pocket of submental fat. She has good skin turgor, no skin laxity, and excellent mandibular bone contour. Dissolution of submental fat with ATX-101 would be an optimal treatment.

Dr Jones: She also could be treated with liposuction or be offered one of the energy-based treatments with the caveat that the results are not predictable.

Dr Donofrio: In addition to her submental convexity, this patient has a weak chin that I would address with a contouring procedure targeting the fat compartments in the chin. They can be inflated with autologous fat or one of the more robust hyaluronic acid or calcium hydroxylapatite fillers. I would inflate the deep fat compartment that lies above the periosteum. That would deepen the mental sulcus, and to ameliorate that, I would go into the superficial fat compartment that is on top of the mentalis muscle. She also could benefit from submental fat removal and is an excellent candidate for ATX-101.

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CME Questions

To obtain credit for this activity, complete the following CME test by writing the best answer to each question in the Post Test Answer Box found on the bottom of page 12 in the Activity Evaluation Form and Application for Continuing Medical Education Credit. Alternatively, you can complete the CME test online at **http://tinyurl.com/submentalcontouring**.

1. Anatomic factors that can cause blunting of the cervicomandibular angle (increase submental convexity) include all of the following, except:
   - A. Excess subplatysmal fat
   - B. Hypertrophied parotid salivary glands
   - C. Hyoid bone position
   - D. Platysmal laxity

2. What branch of the facial nerve is subject to injury during minimally and noninvasive cosmetic procedures focusing on reduction of submental fat?
   - A. Buccal
   - B. Cervical
   - C. Mandibular
   - D. Zygomatic

3. Which of the following techniques will help minimize the risk for skin contour irregularities post-liposuction?
   - A. Avoiding aggressive oversuctioning of fat from the underside of the dermis
   - B. Laser-assisted lipolysis
   - C. Local tumescent anesthesia
   - D. Treating the underside of the dermis with a carbon dioxide laser to tighten the skin

4. High-intensity focused ultrasound:
   - A. Can be used safely in patients with skin of color
   - B. Can be used to reduce subplatysmal fat
   - C. Disrupts adipocytes via a cavitation-based mechanism
   - D. Is generally associated with no more than mild pain

5. Which of the following treatments has the potential to both reduce submental fat and cause skin tightening?
   - A. Laser-assisted liposuction
   - B. Focused ultrasound
   - C. Monopolar radiofrequency
   - D. All of the above

6. In April 2010, the FDA issued warning letters to several US-based medical spas that were making false or misleading statements about eliminating fat through what procedure?
   - A. Bipolar radiofrequency
   - B. Cryolipolysis
   - C. Mesotherapy (“lipodissolve”)
   - D. Nd:YAG laser lipolysis

7. Results of a randomized, double-blind trial by Rotunda et al. comparing injection with deoxycholate (DC) alone or combined with phosphatidylcholine (PC) to reduce submental fat showed submental contour improvement was:
   - A. Significantly greater in the DC group
   - B. Significantly greater in the DC-PC group
   - C. Minimal with both treatments
   - D. More durable in the DC-PC group

8. A 63-year-old woman presents seeking cosmetic surgery to reduce the appearance of her double chin. Which of the following features would be least important to consider when conducting a clinical evaluation to determine the appropriate procedure?
   - A. Location of the fat (subcutaneous vs subplatysmal)
   - B. Body mass index
   - C. Neck skin laxity
   - D. Jowling

9. What criterion/criteria was/were used for the primary efficacy analysis in the North American pivotal trials investigating ATX-101 for submental fat reduction?
   - A. ≥1-grade improvement on both the CR-SMFRS and the PR-SMFRS
   - B. ≥2-grade improvement on the CR-SMFRS
   - C. ≥20% reduction in submental volume measured by magnetic resonance imaging
   - D. ≥4 on the SSRS (indicating satisfaction with face/chin appearance)

10. In the North American ATX-101 pivotal trials, which of the following adverse events occurred at a similar rate in the ATX-101 and placebo treatment groups?
    - A. Bruising
    - B. Edema
    - C. Erythema
    - D. Pain

Activity Evaluation Form and Application for Continuing Medical Education Credit

Achieving Total Facial Rejuvenation with Submental Contouring: Current and Emerging Strategies

We greatly value your opinion. Please complete this evaluation and submit it via e-mail to PostActivityData@globaleducationgroup.com or fax it to 303-648-5311. You will receive your certificate via e-mail within 4-6 weeks. Your responses will be used in future planning of activities and materials.

I am a: ❑ MD ❑ DO ❑ PharmD ❑ RN ❑ NP ❑ PA ❑ Other _____

Upon completion of this activity, participants will be able to:	**Strongly Agree**	**Agree**	**Disagree**	**Strongly Disagree**
• Articulate the details of chin and neck anatomy and soft tissue and skeletal changes as they pertain to patient analysis and treatment for excess submental fat	④	③	②	①
• Evaluate the comparative efficacy, safety, and patient selection criteria for current treatment options for submental contouring	④	③	②	①
• Describe the chemistry and mechanism of action of emerging adipolytic therapy for submental fat reduction	④	③	②	①
• Review the efficacy and safety data on emerging adipocytolytic treatment for submental fat reduction	④	③	②	①
• Identify appropriate patients for emerging adipocytolytic submental fat reduction treatment according to criteria of clinical trials	④	③	②	①

Please indicate the extent of your agreement with the following statement:	**Strongly Agree**	**Agree**	**Disagree**	**Strongly Disagree**
• The faculty for this activity were effective	④	③	②	①

- Overall, was this activity free from bias? ❑ Yes ❑ No
- Of the patients you will see in the next week, about how many will benefit from the information you learned today?
  ❑ More than 50 ❑ 26 to 50 ❑ 11 to 25 ❑ 1 to 10 ❑ Not applicable
- Based on what I learned today, I will improve my practice by incorporating the following (check all that apply):
  ❑ Improved diagnosis/patient assessment ❑ Useful therapies and appropriate uses
  ❑ Cutting-edge science in this therapeutic area ❑ Best practices of my colleagues and leaders
  ❑ I do not plan to make any changes to my practice at this time
  ❑ Other (explain) _____
- Which ***ONE*** delivery method do you find the most effective for CME/CE learning?
  ❑ Live symposia at national/regional conferences ❑ Live local meetings ❑ Live grand rounds
  ❑ Internet webcasts ❑ Internet/print monographs ❑ Other (explain) _____
- Based on your experience, which of the following are the primary barriers to implementing changes in practice (check all that apply):
  ❑ Lack of knowledge regarding evidence-based strategies ❑ Lack of convincing evidence to warrant change
  ❑ Lack of time/resources to consider change ❑ Insurance, reimbursement or legal issues
  ❑ Other (explain)_____
- What motivated you to participate in this activity? ❑ CME credits ❑ Faculty ❑ Topic or therapeutic area ❑ Format type

Other Comments: _____

Activity Evaluation Form and Application for Continuing Medical Education Credit

Achieving Total Facial Rejuvenation with Submental Contouring: Current and Emerging Strategies

Application for Continuing Medical Education Credit

For purposes of certification, please complete the following information. Please note that we will not forward or sell your contact information. **Please PRINT clearly in the boxes provided.**

Degree: ❑ MD ❑ DO ❑ PharmD ❑ RN ❑ NP ❑ PA ❑ Other _____

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❑ NO, I do NOT want to be contacted in the future.

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❑ I participated in the entire activity and claim 1.5 *AMA PRA Category 1 Credits*™.

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I certify that I have participated in the continuing education activity titled *Achieving Total Facial Rejuvenation with Submental Contouring: Current and Emerging Strategies.*

Signature:_____ Date:_____

Post Test Answer Box

1	2	3	4	5	6	7	8	9	10