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EDITOR’S NOTE: The lingering recession can derail even the best-laid retirement plans. In this issue, we examine the effects of the economic downturn, and some of the reasons for staying — or not staying — in practice. Experts also offer advice on when and how to start gearing down.

By Lisette Hilton
Staff Correspondent

National report — Steve Shama, M.D., M.P.H., was between patients at his Brookline, Mass., dermatology practice when he started to scribble a note on a sticky pad.

It read, “I don’t want to die on the job.”

At 63, Dr. Shama says he realized that if he continued to practice, “they” would one day find him, more likely than not in his office, slumped over in his chair.

“Was that the way I had written the scenario of my life? The answer was resoundingly ‘No,’” Dr. Shama says.

But he found that closing his doors wasn’t so easy — an experience shared by other dermatologists looking to shift out of busy careers. The impact of a struggling economy is changing the equation for doctors who may have planned to retire due to age, changes in the practice of medicine, or for other reasons.

Still, experts and those who have made the transition say foresight and wise planning can ease many of the difficulties surrounding stepping away.

Mounting toll
For older physicians, accumulating stresses and burnout can take a steep toll. Despite having a sound practice, Harvard-trained Dr. Shama

Advancing on BCC

‘Exciting’ Erivedge melts away tumors; FDA also OKs LEO’s Picato for AKs

By Bob Roehr
Staff Correspondent

National report — Dermatologists have new noninvasive tools to treat advanced basal cell carcinoma and actinic keratoses, thanks to federal approval of two drugs in early 2012.

The Food and Drug Administration has approved Erivedge (vismodegib, Genentech/Roche) for treatment of metastatic basal cell carcinoma and Picato (ingenol mebutate, LEO Pharma) for treatment of actinic keratosis.

Vismodegib is a first-in-class drug that inhibits the Hedgehog signaling pathway.

The new therapy is “one of the most exciting drug developments in my career. It is so impressive how the tumors melt away,” says Ellen S. Marmur, M.D., an investigator in the pivotal study and vice chairwoman of cosmetic and surgical dermatology at Mount Sinai Medical Center, New York.

The Hedgehog pathway is crucial to early embryonic development but then largely shuts down. However, it is reactivated in many metastatic and solid tumor cancers. Clinical trials are under way with the new drug and similar compounds as anticancer agents.

Erivedge has an initial label indication for treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following
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New Zealand white rabbits were treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.2, 0.5, and 1.0 mg/kg/day, administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. There appeared to be increased incidences of certain alterations, including domed head and hypochromic, typical of retinoid-induced fetal malformations in this species, at 0.3 and 1.0 mg/kg/day. Similar malformations were not observed at 0.2 mg/kg/day (2 times the maximum human systemic dose of tretinoin after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area). In a repeat study of the highest topical dose (1.0 mg/kg) in pregnant rabbits, these effects were not seen, but a few alterations that may be associated with tretinoin embryotoxicity were observed. Other pregnant rabbits exposed topically for six hours at 0.2 or 0.1 mg/kg/day tretinoin while restrained in stocks to prevent ingestion, did not show any teratogenic effects at doses up to 17 times (1.0 mg/kg/day) the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, adjusted for total body surface area, respectively, (assuming a 50 kg adult applied a daily dose of 1.0 g of 0.1% gel topically). In these topical doses, however, delayed ossification of the tail was noted in rats, and a dose-dependent increase of supernumerary ribs was observed.

Topical tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day. A 1 mg/kg/day dose of tretinoin was found to be teratogenic in rabbits (17 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area). Congenital abnormalities reported in pigtail macaques have been confirmed in the rat. Oral tretinoin was found to be embryotoxic at 0.5 mg/kg/day (8 times the maximum human systemic dose applied topically and normalized for total body surface area). Similarly, in female mice there was a reduction in ovarian weights, but with no underlying pathological changes, at 5.0 mg/kg/day (21 times the maximum human systemic dose normalized for total body surface area). Although specific dose-effect relationships have been established from these cases, the frequency and importance of these spontaneous reports in terms of risk to the fetus are not clear.

Topical tretinoin has been shown to be teratogenic in rats, mice, rabbits, the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area) for 90 days, a reduction in testicular weight, but with no underlying pathological changes. At these concentrations, the only effect noted was a reduction in intrauterine death in rats administered 2.5 mg/kg/day (21 times the maximum human systemic dose applied topically and normalized for total body surface area).

Topical tretinoin is probably related to ingestion. Male and female dogs treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, showed no evidence of mutagenic potential in the Ames assay, the chromosomal aberration assay in mammalian cells in vitro, or in the comet assay. There was no evidence of genotoxic potential in the micronucleus assay, with or without metabolic activation. The skin of certain individuals may become excessively dry, red, swollen, or blistered. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount of medication or discontinue use temporarily or, discontinue use altogether and contact their health care provider for advice. However, efficacy has not been established for lower dosing frequencies.

In dermal Segment I fertility studies of another tretinoin formulation in rats, slight (not statistically significant) increases in the number and percent of nonviable embryos were observed at doses of 0.2 mg/kg/day (4 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, respectively, (assuming a 50 kg adult applied a daily dose of 1.0 g of 0.1% gel topically). Segment II and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (17 times the human topical dose normalized for total body surface area). Deferiprone and deferiprone development studies with Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, have not been performed in any species. Pregnancy: Teratogenic Effects: Pregnancy Category C. In the embryo-fetal development studies with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.5 to 1 mg/kg/day on gestation days 6–15 (4.5 to 8 times the maximum human systemic dose of tretinoin normalized for total body surface area, respectively, (assuming a 50 kg adult applied a daily dose of 1.0 g of 0.1% gel topically), some alterations were seen in vertebral and ribs of offspring. In another study, pregnant female mice were treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.02 mg tretinoin/kg body weight. There was a dose-dependent increase of supernumerary ribs in rats and rabbits, as well as a dose-dependent increase of supernumerary ribs in mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day (8 times the maximum human systemic dose applied topically and normalized for total body surface area), although increased skeletal variations were seen at the two highest doses. Similarly, in female mice these concentrations are near the tretinoin concentration of these clinical products that have a strong drying effect, products with high concentrations of alcohol, astringents, or compounds that may exacerbate the drying effects of such preparations to subside before use of Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, have not been performed in any species.
Remembering the good old days

Did simplicity of healthcare in years past allow better medicine than what we have today?

When I was a kid and had to go to the pediatrician (who could ever forget Dr. Storts?), it always seemed to be a pretty uncomplicated, albeit sometimes painful (what with vaccinations or shots of some other kind), process.

My mom would take me into the doctor’s office, we’d wait patiently (no pun intended) — not very long, I’m sure, but for a lifetime of a 4- or 5-year-old — and await the arrival of “The Doctor.”

After all my medical issues had been addressed, my mom and I would end the visit with a stop at the front desk to settle our account. I can’t really recall if the bill was paid right then or if we even had insurance through my dad’s employer, but that was how medicine was practiced back then — uncomplicated and straightforward.

Of course, as a child, I also had no understanding that there were many who could not afford medical care, especially the elderly, and that they suffered greatly for their inability to get it.

As a child, I also had no understanding that there were many who could not afford medical care.

Big change

It wasn’t too long before the availability of affordable healthcare for the elderly changed, when in July 1965, President Lyndon Johnson signed into law some amendments to existing Social Security legislation that became known as the Social Security Act of 1965. This act established the new social insurance program, Medicare, which provided health insurance coverage to people ages 65 and over, changing the practice of medicine forever.

I was old enough to know about this, although I wasn’t really all that interested, and I certainly did not fully comprehend the ramifications of this new program. However, I do vividly recall reading in the paper or hearing on the television various politicians saying how Medicare “wasn’t going to work” (Bob Dole), that it was nothing more than “socialized medicine” (George H.W. Bush), that it took away our freedom (Ronald Reagan), and that it was going to end the crucial doctor-patient relationship, making the practice of medicine more complicated and worse.

As a physician who never had the experience of practicing medicine without patients relying on Medicare for their healthcare insurance, I don’t think I can fairly comment on how good or bad it is. As I vividly recall trying to explain — unsuccessfullly — to my elderly mother-in-law some years ago about Medicare Part D, however, I do think it can be more complicated to practice under the Medicare rules than some third-party insurance providers.
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from our board from page 4

At the same time, I also believe that during the nearly 50 years since Medicare was introduced, it hasn’t turned out to be the intrusive program it was projected to be, and that the doctor-patient relationship has not suffered irreparable harm from it.

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The Dermatology Times Editorial Advisory Board and Editorial Council qualify the editorial content of the magazine. Members review meeting programs; suggest story topics, special reports and sources; evaluate manuscripts; conduct interviews and roundtables; and counsel editors as questions arise.

Facing ‘fairness’
The number of people enrolled in the Medicare program, which is a measure of its acceptance and success, is now causing financial challenges to the system, and now the system is threatening its own collapse. Some of our elected officials are even calling Medicare an “unearned entitlement” and have proposed huge budgetary cuts to the program.

Not being a healthcare economist, I rely on those experts who point out that entitlement to Medicare is based most commonly on a record of contributions made to the Medicare fund when they are no longer able to work.

The “fairness” of this system is difficult to evaluate, since some individuals will pay more into the fund than they receive and others will receive far more than they paid in.

I do think it can be more complicated to practice under the Medicare rules than some third-party insurance providers.

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when individuals are young and able to work. Thus, it is a form of social insur-

Ronald G. Wheeland, M.D.

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A Passion for Dermatology
Lessons in liability

How far does the learned intermediary doctrine hold physicians accountable?

Cosmetic surgery has enormous liabilities. He sees both medical and cosmetic patients, and he injects thousands of patients with botulinum toxin injections. One of these patients, after seeing multiple television and magazine ads, came to Dr. Cosmetic and asked for the toxin by name.

After treatment, the patient suffered an anaphylactic reaction to one of the toxin-associated proteins contained in the chosen botulinum toxin. She went into anaphylactic shock and suffered permanent renal damage. Such a terrible reaction has not been reported. Experts agree that such a reaction is certainly possible, but warning a patient of this reaction is not reasonable. The patient sued the drug manufacturer but not the physician.

The manufacturer said responsibility lies with the physician because of the learned intermediary doctrine. What is the learned intermediary doctrine? Is Dr. Cosmetic liable?

Learned intermediary doctrine

Under traditional theories of products liability, a manufacturer is liable for injury caused because of inadequate instructions or warnings when the foreseeable risks of harm posed by the product could have been reduced or avoided by the provision of such information.

Since drugs are sold to consumers only at the recommendation of a physician, a different regime of products liability law is needed to govern tort actions when patients are injured by a medication.

Consumers have long accepted, however, that prescription pharmaceuticals come with inherent risks. But since the drugs are sold to consumers only at the recommendation of a physician, a different regime of products liability law is needed to govern tort actions when patients are injured by a medication.

The learned intermediary doctrine arose to address the inadequacy of the standard products liability doctrine due to the special relationship between doctors and patients. As an expert in the medical field, a doctor assists patients in weighing the risks and benefits of a particular drug purchase, since the consumer on his or her own. Cosmetic surgery has enormous liabilities. He sees both medical and cosmetic patients, and he injects thousands of patients with botulinum toxin injections. One of these patients, after seeing multiple television and magazine ads, came to Dr. Cosmetic and asked for the toxin by name.

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legal eagle from page 8

her own does not possess the requisite scientific knowledge to make an informed decision.

Learned intermediary doctrine does not absolve a drug manufacturer of its duty to warn; rather, it replaces the consumer with the doctor in terms of who the manufacturer must warn. The drug company has a duty to warn the prescribing doctor, but not a duty to warn the end-consumer. Drug companies would find it impossible, or at the very least, difficult to properly provide a complex medical warning directly to the consumer in language that is easy to understand. Instead, the manufacturer must provide an adequate warning of risks to the prescribing doctor to fulfill its duty to warn.

Case in point
A New York state court opinion in Marcus v. Specific Pharmaceuticals, Inc. developed the basic reasoning that became modern learned intermediary doctrine. The Marcus court granted summary judgment for the defendant pharmaceutical manufacturer because it had made no direct representations to the patient, only to the treating doctor.

The doctor had elected to rely on his own scientific knowledge and prescribe a dosage higher than what the manufacturer suggested. Even when the higher dose resulted in the plaintiff’s death, the court absolved the manufacturer of any liability, as a matter of law, due to the doctor’s influence over the ultimate purchase and use of the drug. The pharmaceutical manufacturer never made representations directly to consumers and thus could not be held liable to the plaintiff.

The basic assumption at the heart of doctrine is that the doctor is the “primary decision maker” when it comes to determining whether a patient should use a drug. Whether true or not, courts have attempted not to interfere with the doctor-patient relationship.

Contraceptives exception
Some states have limited the scope of learned intermediary doctrine depending on the type of pharmaceutical. Massachusetts created an exception for contraception in 1985.

In a duty-to-warn case, the Supreme Judicial Court of Massachusetts recognized a difference between birth control and other prescription drugs. The court noted that the decision to use oral contraceptives typically lay solely with the patient, and the doctor serves only to decide on dosage. The court held that the manufacturer of oral contraceptives is not justified in relying on warnings to the medical profession to satisfy its common law duty to warn, and that the manufacturer’s obligation encompasses a duty to warn the ultimate user (the patient). Of note, courts have not extended similar exceptions for cosmetic treatments with collagen fillers, breast implants and penile implants.

Consumer advertising
To be sure, there has been a recent emphasis on manufacturers targeting the patient directly. With this, drug manufacturers have (at least in part) bypassed the intermediary by providing information to the consumer through print, radio and television advertisements. Under such a model, consumers are likely making more decisions on their own and targeting certain drugs in their discussions with treating physicians. Patients know more about the drug options available to them based on substantial marketing campaigns by the pharmaceutical companies.

The New Jersey Supreme Court addressed the issue of direct-to-consumer advertising in a 1999 decision that carved out a new exception to traditional learned intermediary doctrine. Perez v. Wyeth involved alleged injuries arising from the plaintiff’s use of the Norplant contraceptive device, which Wyeth began advertising in what the court described as a massive ad campaign.

The advertisements did not mention the negative side effects related to the Norplant device, including hair loss, high blood pressure and permanent scarring, among many others. The court found that the plaintiff would not have had a claim for failure to warn had Wyeth not advertised directly to consumers.

Dr. Cosmetic’s patient sought botulinum toxin injections because of the manufacturer’s advertising campaign. The courts will need to decide if Dr. Cosmetic has liability under the learned intermediary doctrine. DT
Supreme challenge
High court prepares to hear arguments against Obama’s health reform law

During the last week of March, the U.S. Supreme Court will hear oral arguments on challenges made by 26 states and a small business organization that provisions of the new healthcare reform law are unconstitutional, a major step toward an eventual ruling by the high court later this year.

While much of the media attention has been focused on those states’ challenges of the law’s mandate that everyone must purchase insurance or face a financial penalty, another provision that directly affects many physicians also would be wiped out if the court rules against the entire law.

Full disclosure
As required by the new healthcare statute, the Obama administration is preparing to require drug companies to disclose payments they make to doctors for research, consulting, speaking, travel and entertainment — even bagels bought by a salesman for the doctor’s office. Under those standards, if a company has even one product covered by Medicare or Medicaid, it must disclose all payments to nonemployee physicians. That information will be posted on a publicly accessible website.

According to the Obama administration, more than 1,100 drug, device and medical supply companies will be required to file reports, which will be inspected and audited by the federal government. Failure to comply could bring penalties up to $10,000 for each unreported payment, and companies found to have deliberately failed to report such payments could face fines up to $100,000 per violation, with a maximum of $1 million per year.

The deadline for public comments on the requirements was Feb. 17, and after Medicare officials consider the comments, final rules will be issued.

The new standards, which were called for by the Medicare Payment Advisory Commission in a 2009 report, will implement legislation pushed by Senators Charles E. Grassley (R-Iowa) and Herb Kohl (D-Wis.).

“The goal is to let the sun shine in and make information available to foster accountability,” said Sen. Grassley.

Of course, all of this depends on the decision by the Supreme Court; if the law is struck down, those requirements also will be gone. However, in late January, the Obama administration filed a brief arguing that if the mandate provision is found to be unconstitutional, the rest of the law should be allowed to stand.

The overall issue of Medicare reform is expected to play a major role in this year’s presidential campaign.

“Other provisions can operate independently and would still advance Congress’s core goals of expanding coverage, improving public health and controlling costs, even if the minimum coverage provision were held unconstitutional,” Justice Department lawyers wrote.

Countering that argument was Karen Harned, executive director of the National Federation of Independent Business (NFIB) Small Business Legal Center. Ms. Harned issued a statement contending that if the requirement to purchase health insurance is found to be unconstitutional, the entire law must go. “To argue otherwise would be like arguing a house can stand after its foundation has crumbled,” she said. NFIB is the plaintiff in the Supreme Court case, along with the states.

Medicare mindset
Of course, the new Medicare physician fee schedule was to take effect March 1, following a two-month reprieve from the 27 percent reduction that was slated for implementation on Jan. 1. At press time, lawmakers were negotiating a solution, and reports from the leaders of both parties were optimistic that one would be found.

The overall issue of Medicare reform, however, is expected to play a major role in this year’s presidential campaign, and Republican members of the House Budget Committee planned to finalize and bring to the floor a proposed federal budget that is expected to include broad changes in Medicare.

The budget passed by the GOP last year called for $5.8 trillion in spending cuts by 2021, repealing the federal healthcare law and reforming Medicare. It passed the GOP-led House, but it died in the Democrat-controlled Senate.

That measure proposed a voucher system that would give seniors money to buy private health insurance. While House Budget Committee Chairman Rep. Paul Ryan (R-Wis.) said those 55 or older would not be affected, he warned that major changes must be made or Medicare will go broke.

“The Congressional Budget Office also says Medicare is going bankrupt in 2021,” Rep. Ryan said. “The trustees at Medicare say there’s $37 trillion unfunded liability.”

Rep. Ryan said his plan would provide people age 54 and younger “a list of guaranteed coverage options,” similar to those provided to federal employees. “We’re not going to subsidize the wealthy as much as everybody else,” he said. “And we’re going to subsidize the poor even more. That saves Medicare. That fixes Medicare.”

Rep. Ryan also blasted the new healthcare law for creating the Independent Payment Advisory Board, which is strongly opposed by the American Academy of Dermatology Association. He said the IPAB’s purpose is to impose price controls and ration care.

If the Supreme Court tosses out the entire healthcare law, then the IPAB will be gone as well. Stay tuned. DT
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Getting guidance
Dermats discuss utility, practicality of AAD, other best practice resources

For more than a decade, the American Academy of Dermatology has been issuing best practices guidelines. Despite initial concerns that these guidelines would be detrimental to the practice of medicine, they seem to have become an integral part of many dermatologists’ practices.

On Call wondered if some dermatologists still view these guidelines with skepticism. We asked dermatologists around the country whether they refer to guidelines when determining which treatment protocols to use, or if they rely more on their own knowledge and experience.

While each dermatologist interviewed sees benefits in some of the guidelines, the guidelines have not become the first resource they turn to when making treatment decisions.

“Initially, I rely on my experience. Probably like most people, I’m more comfortable with my experience because I’ve seen first-hand the results of the choices I’ve made for treatments. I know what to expect,” says Robert Gunnoe, M.D., Stanley, Kan. “If I get to a point where I see that I need to look for some other source of ideas, then I feel the practice guidelines do offer quite a bit there. They may offer some ideas outside my box of ideas.” Dr. Gunnoe has been in practice for more than 30 years.

Science and evidence

Susan Goodlerner, M.D., in Torrance, Calif., had been practicing for a number of years before practice guidelines came along. She says the guidelines fulfill a need, but not always a primary one.

“Guidelines in many conditions are helpful because they are based on science and evidence,” she says. “One example of a guideline I do follow is for a patient with a melanoma 1 mm or less. It has been shown that it’s not necessary to do laboratory tests or imaging studies to properly monitor that patient; they just need to be seen for a complete skin exam, and generally twice a year. Some physicians do these tests, which have been shown to be unnecessary. That’s an example of a practice guideline that is helpful and provides more cost-effective care for the patients.

“On the other hand, there have been some acne guidelines I did not find to be particularly helpful,” says Dr. Goodlerner, associate professor at Harbor UCLA Medical Center.

Guidelines also provide support for categorizing care, she says. “They provide a guideline for quality, so when there is an issue with the outcome — if a patient has a negative outcome — and you have taken all the appropriate measures in taking care of that patient, “Guidelines in many conditions are helpful because they are based on science and evidence.”

Susan Goodlerner, M.D.
Torrance, Calif.

if you followed some guidelines for care, then I think you’re exonerated in terms of blame. It also helps to look at some of those guidelines with the difficult patient, so it provides a framework upon which to make your decisions.”

Getting better

In St. Augustine, Fla., David J. Gross, M.D., says he agrees that dermatologists know how to approach most of the conditions they see.

“I think in dermatology, every year, you just get better. You see things; you go to these talks and you hear things; you learn from the dermatologists around you, and you get better as time goes on,” he says. “If you’re a conscientious, hard-working dermatologist, you get better every year. With the volume we see, we know what works and what doesn’t.”

Dr. Gross says some guidelines can lead to more cost-effective care for patients.

“I’m particularly impressed at how well the Mohs surgery guidelines work to prevent overutilization of this technique by my peers,” he says.

Best of both worlds

Christopher C. Gasbarre, D.O., in Spearfish, S.D., says he doesn’t feel a need to rely solely on guidelines four years out of residency.

“I tend to rely a little bit on both — guidelines and experience,” he says. “It really depends on the situation. If it is a problem with which I’ve had a lot of experience, I’ll do what the guidelines say. If it’s a new presentation, I’ll use the guidelines, but I won’t rely on them.”
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on call from page 18

experience and am familiar with, I tend to fall back on my experience. If it’s something unfamiliar or I haven’t seen a lot of cases, then I think I tend to follow guidelines more.

“The American Academy of Dermatology’s guidelines are usually based on literature and a consensus of experts in the field, most of whom have significant experience with that problem, so I usually feel pretty comfortable with those,” Dr. Gasbarre adds. “They tend to be fairly conservative and not controversial, at least from a derm’s perspective.”

Dr. Gasbarre says the guidelines can also help when dealing with the public.

“Guidelines can be helpful in terms of dealing with controversial topics or things that hit the news media,” he says. “It’s helpful to have the strength of a national organization as backup for recommendations you would make anyway. To have organizational guidelines behind what you’re recommending or what you tell patients is sometimes a nice thing.”

Future focus

Dermatologists do have suggestions for some additional guidelines.

“One evolving area where not much is known is complications from cosmetic fillers,” Dr. Goodlmer says. “Some patients get severe redness or inflammation and it’s not well understood whether it’s an inflammatory reaction or whether there is an infectious basis. I recently had two patients with that condition; one was referred in. I did a literature search and could not find anything recent about the best way to manage those patients. So I called several people who were experts in the area and ultimately got some help. The ideas for managing these two patients were not anything I found anywhere else in the literature.

“That’s an area where it would be helpful if the academy would gather a group of experts and come up with guidelines, in particular because there are non-physicians doing cosmetic injections and don’t know what to do with complications,” Dr. Goodlmer says.

Dr. Gasbarre, on the other hand, says he doesn’t see a need for specific new guidelines, and he thinks too many could be too intrusive in a practice.

“Guidelines are a double-edged sword,” Dr. Gasbarre says. “They’re helpful, but you don’t want to pigeonhole all of your treatments. Medicine is still not a cookbook; you can’t just fall back on guidelines. Not every patient fits into standard scenarios and situations. You have to be careful because if you create guidelines for every condition, you may have a tendency to treat everyone the same; that’s a mistake, too.”

Another potential problem could be when proposed guidelines get ahead of accepted practice, Dr. Gross says.

“Listening to a speaker explain that the PPD (purified protein derivative) is no longer the latest thing for TB (tuberculosis) and that we should switch to the gold test sounded great, so I called the labs around here, but no one orders them. That’s the point. These guidelines are sometimes released and they’re just not used yet in the real world,” he says.

“Guidelines can be helpful in terms of dealing with controversial topics or things that hit the news media. It’s helpful to have the strength of a national organization as backup for recommendations you would make anyway.”

Christopher C. Gasbarre, D.O.
Spearfish, S.D.

Ongoing evolution

Dr. Gunnoc says guidelines have evolved over the years, as have his views of them.

“Initially, I was very optimistic and thought it was a good way to get a lot of input from a variety of specialists — a variety of pundits in each field, of each disease or diagnoses, to see what they would do and arrive at a consensus of possible therapies for diagnostic procedures,” Dr. Gunnoc says.

“But then I also realized we’re not the only ones looking at these guidelines. I think the biggest concern early on, as well as now, was how the legal profession would use them, that they would be a means of artillery for court cases,” he says.

“As it turns out, the guidelines are worded in such a way that they’re not made to be what’s expected of everyone. Instead, they’re more of a possible course of action, so it’s a little bit harder for the legal profession to use as expert witnesses per se,” Dr. Gunnoc says.

“They have become less restrictive. I think early on they were little more restrictive, but become less so as they were revised. I see them more as a reference source.”

DT
Indications and Usage
Picato® gel is indicated for the topical treatment of actinic keratosis.

Important Safety Information
For topical use only; not for oral, ophthalmic, or intravaginal use. Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, periorbital edema can occur after exposure. Patients should wash hands well after applying Picato® gel, and avoid transfer of the drug to the periocular area during and after application. Severe skin reactions in the treated area, including erythema, crusting, swelling, vesiculation/pustulation, and erosion/ulceration, can occur after application. Administration of Picato® gel is not recommended until the skin is healed from any previous drug or surgical treatment. The most common adverse reactions (≥2%) observed in clinical trials are local skin reactions, application site pain, application site pruritus, application site irritation, application site infection, periorbital edema, nasopharyngitis and headache. There are no adequate and well-controlled studies of Picato® gel in pregnant women. Picato® gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The safety and effectiveness of Picato® gel for actinic keratosis in patients less than 18 years of age have not been established.

Please see reverse for brief summary of full Prescribing Information for Picato®.
Picato® (ingenol mebutate) gel, 0.015%, 0.05%

For topical use only. Not for oral, ophthalmic, or intranasal use.

BRIEF SUMMARY

INDICATIONS AND USAGE: Picato® gel is indicated for the topical treatment of actinic keratosis.

WARNINGS AND PRECAUTIONS: Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, periorbital edema can occur after exposure. Patients should wash hands well after applying Picato® gel, and avoid transfer of the drug to the periorcular area during and after application. If accidental exposure occurs, the area should be flushed with water and the patient should seek medical care as soon as possible. Severe skin reactions in the treated area, including erythema, crusting, swelling, vesiculation/ulceration, and erosion/ulceration, can occur after topical application of Picato® gel. Administration of Picato® gel is not recommended until the skin is healed from any previous drug or surgical treatment.

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 clinical practice. The data described below reflect exposure to Picato® gel in 499 subjects with actinic keratosis, including 274 subjects exposed to Picato® gel field treatment (skin area of 25 cm² in the face or scalp regions) at a concentration of 0.015% once daily for 3 consecutive days, and 225 subjects exposed to Picato® gel field treatment (skin area of 25 cm² in the trunk or extremities regions) at a concentration of 0.05% once daily for 2 consecutive days.

Table 1: Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (face/scalp trials)

<table>
<thead>
<tr>
<th>Skin reactions</th>
<th>Any Grade &gt; Baseline</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>258 (94%)</td>
<td>69 (25%)</td>
</tr>
<tr>
<td>Flaking/Scaling</td>
<td>233 (85%)</td>
<td>67 (25%)</td>
</tr>
<tr>
<td>Crusting</td>
<td>220 (60%)</td>
<td>46 (17%)</td>
</tr>
<tr>
<td>Swelling</td>
<td>217 (79%)</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Vesiculation/Postulation</td>
<td>154 (50%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Erosion/Ulceration</td>
<td>87 (32%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

* Mild (grade 1), Moderate (grade 2-3) or Severe (grade 4).

Table 2: Investigator Assessment of Maximal Local Skin Reactions in the Treatment Area during the 57 Days Post Treatment Period (trunk/extremities trials)

<table>
<thead>
<tr>
<th>Skin reactions</th>
<th>Any Grade &gt; Baseline</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>207 (92%)</td>
<td>43 (19%)</td>
</tr>
<tr>
<td>Flaking/Scaling</td>
<td>203 (90%)</td>
<td>44 (19%)</td>
</tr>
<tr>
<td>Crusting</td>
<td>167 (74%)</td>
<td>23 (10%)</td>
</tr>
<tr>
<td>Swelling</td>
<td>143 (64%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Vesiculation/Postulation</td>
<td>98 (44%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Erosion/Ulceration</td>
<td>58 (26%)</td>
<td>6 (3%)</td>
</tr>
</tbody>
</table>

* Mild (grade 1), Moderate (grade 2-3) or Severe (grade 4).

Table 3: Adverse reactions occurring in ≥2% of subjects treated with Picato® gel and at higher frequency than vehicle (trunk/extremities trials)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Picato® gel, 0.015% (N=224)</th>
<th>Vehicle (N=232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Site Pain</td>
<td>42 (15%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Application Site Pruritus</td>
<td>42 (15%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Application Site Irritation</td>
<td>7 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Periorbital Edema</td>
<td>7 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (2%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

Table 4: Adverse reactions occurring in ≥22% of subjects treated with Picato® gel and at higher frequency than vehicle (trunk/extremities trials)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Picato® gel, 0.05% (N=226)</th>
<th>Vehicle (N=232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Site Pruritus</td>
<td>18 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Application Site Irritation</td>
<td>8 (4%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Application Site Pain</td>
<td>5 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Less common adverse reactions in subjects treated with Picato® included: eyelid edema, eye pain, conjunctivitis. A total of 108 subjects treated with Picato® gel on the face/scalp and 38 subjects treated on the trunk/extremities were followed for 12 months. Results from these studies did not change the safety profile of Picato® gel.

USE IN SPECIFIC POPULATIONS:

Pregnancy: Pregnancy Category C

There are no adequate and well-controlled studies of Picato® gel in pregnant women. Picato® gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Systemic embryofetal development studies were conducted with ingenol mebutate in rats and rabbits. Intravenous doses of 1.5, 3, and 5 µg/kg/day (9, 18, and 30 µg/m²/day) ingenol mebutate were administered during the period of organogenesis (gestational days 6–18) to pregnant female rats. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at doses up to 5 µg/kg/day (30 µg/m²/day). Intravenous doses of 1, 2, and 4 µg/kg/day (12, 24, and 48 µg/m²/day) ingenol mebutate were administered during the period of organogenesis (gestational days 6–18) to pregnant female rabbits. An increase in embryo-fetal mortality was noted at 4 µg/kg/day (48 µg/m²/day). An increased incidence of fetal visceral and skeletal variations was noted in all three ingenol mebutate dose groups. The clinical relevance of these findings is unclear since systemic exposure of ingenol mebutate was not detected in subjects with actinic keratosis treated with Picato® gel, 0.05% applied to a 100 cm² treatment area.

Pediatric Use: Actinic keratosis is not a condition generally seen within the pediatric population. The safety and effectiveness of Picato® gel for actinic keratosis in patients less than 18 years of age have not been established.

OVERDOSSAGE: Topical overdosing of Picato® gel could result in an increased incidence of local skin reactions.

DOSSAGE AND ADMINISTRATION: Picato® gel is for external use only. Advise patients to avoid contact with the eyes. For the treatment of actinic keratosis on the face and scalp, Picato® gel, 0.015% should be applied to the affected area once daily for 3 consecutive days. For the treatment of actinic keratosis on the trunk and extremities, Picato® gel, 0.05% should be applied to the affected area once daily for 2 consecutive days. Picato® gel may be applied to the affected area, up to one contiguous skin area of approximately 25 cm² (e.g., 5 cm x 5 cm) using one unit dose tube.

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BRFS-PI-0112
Clinical Dermatology

- **LOCATION OF ITCH IMPACTS**

  PLEASURE OF SCRATCHING

  British Journal of Dermatology
  January 2012

  The area of the body that is perceived to itch impacts the intensity of the itch and the pleasure of itch relief from scratching or rubbing. A study was published online in January in the British Journal of Dermatology.

  Researchers with Wake Forest Baptist Medical Center sought to examine the role of scratching pleasure in providing itch relief by examining whether itch intensity is perceived differently at three body sites. They also investigated whether there was a positive correlation between the pleasure and itch attenuation induced by scratching.

  Using cowhage spicules, investigators induced itch on the forearms, ankles, and backs of 18 healthy participants. The sites were then scratched by an investigator with a cytology brush immediately after inducing the itch. Intensity with and without scratching was measured with VAS ratings at 30-second intervals.

  The average itch intensity and scratching pleasure ratings at the ankle and back were found to be “significantly higher” than on the forearm, according to the researchers. On the forearm and the ankle, then, the itch was “less higher,” increasing the higher the pleasure.

  “Pleasure paralleled the curve of itch reduction for the back and forearm, however scratching pleasure at the ankle remained elevated and only slightly decreased while itch was diminishing,” the authors wrote.


- **ADULTS, ELDERLY HAVE SIMILAR POSITIVE PATCH TEST REACTIONS**

  Journal of the American Academy of Dermatology
  February 2012

  The elderly are more likely than children to have at least one positive patch test reaction, but their reaction rates were similar to those for other adults, according to a study published in the February issue of the Journal of the American Academy of Dermatology.

  Investigators with the Veterans Affairs Medical Center, seeking to determine the frequency of positive patch test reactions in people ages 65 and older compared to younger individuals, conducted a retrospective cross-sectional analysis of North American Contact Dermatitis Group patients from 1994 to 2008. The frequency of at least one allergic reaction in older individuals was 67.3 percent, compared to 66.9 percent for adults ages 18-64, and 52.7 percent for children ages 18 and younger.

  In older individuals, reaction rates were statistically higher for Myroxylon Pereirae, fragrance 1, 2-quinal, en-15, formaldehyde, neomycin, bacitracin and diazolidinyl urea, among others, compared to reactions in children and adults, the researchers found.

  “The frequency of positive reactions to specific allergens differed by age group, most likely at result of exposures,” the study authors wrote.

  http://www.ebule.org/article/S0190-9622(10)02261-9/abstract

- **FEWER CHILDREN BORN TO WOMEN WITH RA, SLE**

  Arthritis Care & Research
  February 2012

  More than half of women with rheumatoid arthritis and systemic lupus erythematosus had fewer biological children than they wanted, according to a study published in the February issue of Arthritis Care & Research.

  Researchers with Duke Medicine, Durham, N.C., and other institutions across the country conducted a survey of 1,017 female patients in the National Data Bank for Rheumatic Diseases to assess the role of infertility, pregnancy loss, and current choice of ART in female patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The survey group was divided into three groups: those needed to have children at symptom onset who had fewer children than planned (group A), or the same number as planning (group B), and those who no longer interested in having children at diagnosis (group C).

  Of the 578 RA and 114 SLE women surveyed, more than 60 percent were included in group C. Of those interested in having children, 55 percent with RA and 64 percent with SLE had fewer children than initially planned. Compared to SLE group B, SLE group A had a similar number of pregnancies, but had a threefold higher rate of miscarriage and one less live birth. Concerns about child health and personal welfare were associated with lower pregnancy rates, according to the study.

  In this population, more than half of young women with RA or SLE had fewer biologic children than desired. While patient choice, lifestyle, infertility in RA patients and miscarriage in SLE patients are also important,” the study authors wrote.


- **TOPICAL CORTICOSTEROIDS IMPAIR SKIN BARRIER RESTORATION**

  Allergy
  March 2012

  Topical corticosteroids provide an effective treatment for atopic dermatitis, but may also hinder the restoration of the skin barrier, according to a study published in the March issue of Allergy. Researchers with the University of Berlin, Germany, examined lesional atopic dermatitis skin samples after topical treatment with either betamethasone valerate or pimecrolimus that were subjected to gene expression profile analysis.

  Samples treated with betamethasone valerate resulted in a significant reduction in mRNA levels of genes encoding markers of immune cells and inflammation, dendrite cells, T cells, cytokines, chemokines and serum proteases were not changed, according to the study abstract, whereas pimecrolimus had only minor effects. The researchers also determined that genes encoding molecules crucial for skin barrier function were differently affected.

  Betamethasone valerate significantly reduced the expression of rate-limiting enzymes for lipid synthesis and the


- **NO MITOTIC DIFFERENCE IN SINGLE, MULTIPLE PRIMARY MELANOMAS**

  Cancer
  January 2012

  There is no significant difference in the absence or presence of mitosis, a tumor proliferation marker, in patients with single or multiple primary melanomas, according to a study published online Jan. 13 in Cancer.

  Studying 788 patients with melanoma who were enrolled prospectively in the Interdisciplinary Melanoma Coopera-

  tive Group database from 2002 to 2008, researchers with New York University School of Medicine compared the clini-

  copathologic features of patients with multiple primary melanomas (MPM) and single primary melanomas (SPM) to better characterize the differences between the two groups. They also sought to determine whether there was an inherent difference in tumor aggression between the groups.

  The investigators found that 7.7 percent of patients had two or more primary melanomas, and the incidence of developing a second primary melanoma one year to five years after initial diag-

  nosis was 4.1 and 8.7 percent, respectively, with the risk of the accumulated within the first year. The incidence of MPM was greater in patients ages 60 and older than in those under age 60. The absence or presence of mitosis and other tumor char-

  acteristics didn’t differ significantly between patients with MPM and those with SPM, the researchers found (P = 0.61).

  “Because it has been demonstrated that the presence of mitosis is a powerful prognostic marker, the current findings suggested that the behaviors similar in patients with SPM and patients with MPM,” the authors concluded, adding that, “differences in tumor thic-

  kness and prognosis between SPM and MPM more likely are caused by factors other than tumor biology, such as increased surveillance.”


- **STAGING SYSTEM IDS RISK OF CSCC IN TRANSPLANT PATIENTS**

  Journal of the American Academy of Dermatology
  January 2012

  The American Joint Committee on Cancer (AJCC) updated its staging system for cutaneous squamous cell carci-

  noma (cSCC) to accurately predict the risk of recurrence of the disease in heart and lung transplant recipients, according to a study published online Jan. 30 in the Journal of the American Academy of Dermatology.

  Researchers with the University of California, San Francisco, conducted a 10-year retrospective cohort study of all primary cSCC diagnosed in heart and lung transplant recipients based on the seventh edition of the AJCC staging system. The cumulative incidence of local recurrence was 4 percent for cSCC in situ and 5 percent for stage I cSCC in five years and 54 percent for stage 2 cSCC at three years. Stage 2 tumors had a 10-fold greater risk of recurrence than stage 1, and a 45-fold greater risk of recurrence than in situ tumors.

  “Heart and lung transplant recipients are at high risk for local recurrence of cSCC. These data substantiate the prog-

  nostic accuracy of the newly updated seventh edition AJCC staging system for stages Ix and IIIC in the population, and demonstrate the aggressive behavior of this cancer in immunosuppressed patients,” the study authors wrote.

  http://www.ebule.org/article/S0190-9622(12)01903-X/abstract

Pediatric Dermatology

- **CHILDREN, ADOLESCENTS IGNORE SUN EXPOSURE RISKS**

  Pediatrics
  January 2012

  Most children and adolescents fail to regularly use sunscreen despite having suffered sunburns, according to a study published online Jan. 23 in Pediatrics.

  To assess sunburn and sun expo-

  sure behaviors in children, researchers from Memorial Sloan-Kettering Cancer Center, New York, analyzed data from 360 fifth-grade children who completed surveys in 2004 and 2007. The surveys were analyzed to assess prevalence of reported sunburns and sun behaviors and to determine changes in response over the follow-up period, according to the study abstract.

  In 2004, about 53 percent of the students reported having had at least one sunburn during the previous summer. That proportion remained similar by 2007 (55 percent, P = 0.79), the researchers found. Liking a tan and spending time in the sun to get a tan significantly increased (P = 0.001), according to the study. Half of the students reported in 2004 always or often using sunscreen when spending at least 15 minutes outside, but this figure dropped to 25 percent in 2007. The study authors noted that at least 50 percent of children experienced sunburns before age 11 and again three years later, which emphasized the impor-

  tance of targeting children in pediatric offices, and suggested that actions to reduce the hazards of unprotected UV exposure.

  “Because periodolaceness is a time of volatility with regard to sun behaviors, learning more about how children perceive sunburns versus those who avoid them is a critical research task,” the study authors wrote.

  http://pediatrics.aappublications.org/ content/early/2012/01/18/peds.2011-0104. abstract

research stat

abstracts from that pile of peer-reviewed journals on your desk
Less than 1 percent of the study participants experienced side effects, which included dandruff, eye irritation, conjunctivitis, dry skin and a burning sensation. Sklice is expected to become available in the United States within a few months, according to Sanofi.

**TAN SALON CLAIMS SCRUTINIZED**

Washington — Democratic members of the House Energy and Commerce Committee have accused the indoor tanning industry of giving false and misleading information about the risks of using tanning beds, the Los Angeles Times reports.

Democratic staff of the committee called indoor tanning salons representing themselves as teenage girls interested in getting tanning sessions for the first time. The committee claims that the vast majority of the 300 salons nationwide that were contacted provided “false information about the serious risks of indoor tanning and made specious claims about the health benefits” of indoor tanning, the Times reports.

The Indoor Tanning Association issued a statement saying that if those conducting the survey actually went to a salon and were under 18, “they and their parents would have had a more thorough conversation about the tanning process and the potential risks of overexposure.”

**FILLERS, PEELS DOWN SLIGHTLY**

Alexandria, Va. — Filler injections, botulinum toxin injections and chemical peels remain the most common nonsurgical cosmetic procedures, but the average number of those procedures declined slightly in 2011, according to survey results from the American Academy of Facial Plastic and Reconstructive Surgery.

Among women ages 35-60, botulinum toxin injections, facial fillers and chemical peels were the most common procedures, but the average number of those procedures dropped between 1 and 8 percent compared to 2010.

Botox (onabotulinumtoxinA, Allergan) was the most common procedure for women under age 35 (64 percent, down 1 percent from 2010), followed by hyaluronic acid injections (55 percent), chemical peels (24 percent) and microdermabrasion (15 percent).

**LYME DISEASE RISK FOCSI ID’D**

New Haven, Conn. — Researchers have identified two Lyme disease risk foci in the Northeast and upper Midwest, HealthDay News reports.

Investigators with Yale School of Public Health created an acrozoological risk map for Lyme disease. They used standardized field sampling in 304 sites to estimate the density of Borrelia burgdorferi-infected host-seeking nymphal B. burgdorferi in the Northeast and the upper Midwest.

“This map can assist in surveillance and control programs by identifying regions where human cases are expected and may assist treatment decisions,” the study authors wrote.

The study appeared in the February issue of The American Journal of Tropical Medicine and Hygiene.

**CTCL DRUG TREATS ALZHEIMER’S**

Cleveland — Bexarotene, indicated for treatment of cutaneous T-cell lymphoma, may help to reverse the symptoms of Alzheimer’s, The Plain Dealer (Cleveland) reports.

Researchers at Case Western Reserve University used bexarotene in mice and discovered the drug cleared out the amyloid beta protein plaques that scientists believe are key to the disease. Total plaque clearance and symptom improvement was found in only 72 hours, The Plain Dealer reports.

The patents for bexarotene (Targretin, Eisai) expire this year, and the manufacturer has not shown interest in funding studies for its application in Alzheimer’s, according to The Plain Dealer. The study was published in Science.

**DRUG BOOSTS HAIR GROWTH**

Durham, N.C. — Daily treatment with finasteride increases hair growth in all four areas of the scalp affected by male pattern baldness, HealthDay News reports.

Researchers with Duke University Medical Center analyzed results of a randomized, double-blind, multicenter study of men who were given finasteride or placebo for 24 months. Those taking finasteride had statistically significant hair growth and less hair loss in all four scalp regions compared to those taking placebo.

The study was published online Feb. 13 in the Journal of the American Academy of Dermatology.
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Retire: Older derms weigh the factors

Many doctors are finding their exit plans are on hold because the money they’ve saved has dwindled with the economic downturn.

According to the 2012 Edition of Physician Characteristics and Distribution in the United States, which is based on 2010 data, many dermatologists practicing today are nearing and past retirement age, at 55 and older. Age breakdowns of 11,316 active physicians who self-designated their specialty as dermatology were: 2,065 under age 35; 2,670, ages 35-44; 2,706, ages 45-54; 2,513, ages 55-64; and 1,362 over age 65.

A snapshot
Increasing numbers of dermatologists may well face the same scenario in the coming years.

story highlights
- Changes in medicine contribute to older doctors’ wishes to retire
- Selling a practice isn’t easy
- Successful transition may involve “phasing down” or experimenting

Many doctors are finding their exit plans are on hold because the money they’ve saved has dwindled with the economic downturn.

But the recession may mean the deck is stacked against older doctors hoping to retire in their early 60s.

“Looking at physicians as a whole, we know that there was some slowdown in retirements over the last few years, as the economic downturn and devaluation of savings meant that many doctors felt they needed to work longer than anticipated,” says Jack Resneck Jr., M.D., associate professor and vice chairman of dermatology, University of California, San Francisco School of Medicine. Dr. Resneck holds a joint appointment at the Philip R. Lee Institute for Health Policy Studies, where one of his research focuses is the future of the dermatology workforce.

The struggle for many physicians is that they’d like to retire.

“When we ask physicians what they plan to do, most say pretty much that they plan to retire at around the same age as everyone else (age 63 or 65),” says Atul Grover, M.D., Ph.D., chief public policy officer, Association of American Medical Colleges.

Among the forces contributing to that desire are the changes occurring in medicine, according to Dr. Grover. One example: the advent of electronic health records. It’s cumbersome for any practitioner to switch over to digitized records, he says. But while younger and middle-aged doctors might see the shift as worthwhile because they’ll be in practice for a decade or more, older practitioners are less likely to embrace the need to change.

Financial factors weigh on the other side of the scale.

Many doctors are finding their exit plans are on hold because the money they’ve saved has dwindled with the economic downturn.

That, plus the fact that it’s difficult to sell a practice nowadays, may keep needed dermatologists and other physicians in the workforce — but only temporarily, Dr. Grover says. Eventually, there could be a wave of physician retirements that could further stress fields such as dermatology and primary care that are already experiencing a numbers crunch.

Ultimately, that will impact patient care, experts say. “Overall, (retirements are) going to make it much harder to guarantee access to physicians,” Dr. Grover says. “Congress has been unwilling to invest in training the number of physicians that we need.”

Seller, be warned
Finding a buyer for a medical practice isn’t easy, despite the optimism of many sellers.

Dr. Shama says he thought, “Who wouldn’t want to walk into a practice that had a very good reputation … (with) charts, and all kinds of connections with insurance companies and referrals?”

Finally able to conclude a sale, Dr. Shama was one of the lucky ones.

... From page 1
For a single-agent retinoid with powerful efficacy and favorable tolerability

Prescribe Differin® (adapalene) Gel, 0.3% and offer your patients...

Proven results

![Patient before and after treatment]

Powerful efficacy

- Total lesion reduction with Differin® Gel, 0.3% is comparable to tazarotene gel 0.1% from baseline through week 12.

Favorable tolerability

- Differin® Gel, 0.3% is comparable to retinoic gel microsphere, 0.04% with a mean score below 1 (mild) across all 4 tolerability parameters.
- Adverse events that occurred in greater than 1% of the subjects included dry skin (14.0%), skin discomfort (5.8%), pruritus (1.9%), desquamation (1.6%), and sunburn (1.2%)

High patient satisfaction

- 86% of patients were satisfied or very satisfied with Differin® Gel, 0.3% treatment.

Rx

Differin® Gel, 0.3%
sig: QD

dispense as written

*4 phase 3, 12-week, multicenter, randomized, active- and vehicle-controlled, double-blind, parallel-group clinical study of patients 12 years or older with acne vulgaris (N=653).

*4 phase 3b, 12-week, noninferiority, multicenter, investigator-blinded, controlled clinical study of patients 12 to 35 years of age with acne vulgaris (N=172). At the end of 12 weeks, neither product was found to be inferior. 161 patients participated in the satisfaction survey.

*1 single-center, randomized, investigator-blinded, bilateral (split-face) comparison of healthy subjects ≥ 18 years of age (N=36). Subjects received Differin® Gel, 0.3% on one-half of the face and retinoic gel microsphere, 0.04% on the other half for 21 days. Tolerability parameters (erythema, dryness, burning/stinging, and scaling) were assessed in healthy subjects.

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.

Please see brief summary of Prescribing Information on adjacent page.

www.differin.com/hcp
DIFFERIN® (adapalene) Gel, 0.3%

BRIEF SUMMARY

For topical use only. Not for ophthalmic, oral or intranasal use.

INDICATIONS AND USAGE: DIFFERIN® Gel, 0.3% is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

CONTRAINDICATIONS: DIFFERIN® Gel, 0.3% should not be administered to individuals who are hypersensitive to adapalene or any of the components in the gel vehicle.

PRECAUTIONS:

General: Certain cutaneous signs and symptoms of treatment such as erythema, scaling, dryness, and stinging/burning may be exacerbated with use of DIFFERIN® Gel, 0.3%. These are mostly mild to moderate in intensity, and usually lessen with continued use of the medication. Depending upon the severity of these side effects, patients should be instructed to either use a milder strength medication, reduce the frequency of application of DIFFERIN® Gel, 0.3% or discontinue use. If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during use of adapalene. Patients who normally experience increased sensitivity to sunlight and those with inherent sensitivity to the sun, should be warned to avoid exposure. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene.

Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of "washing" as a depilatory method should be avoided on skin treated with adapalene.

Information for Patients: Patients using DIFFERIN® Gel, 0.3% should be informed of the following:

1. This medication is to be used only as directed by the physician.

2. It is for external use only.

3. Avoid contact with the eyes, lips, angles of the nose, and mucous membranes.

4. Do not use on cuts, abrasions, eczematous or sunburned skin.

5. Do not apply with alcohol, astringents or retinoids.

6. Do not use if pregnant or breastfeeding.

7. Do not use if you are taking any medications that may interact with adapalene.

8. Do not use if you have any other conditions that may be exacerbated by the use of adapalene.

9. Do not use if you are allergic to any of the components of the gel vehicle.

10. Do not use if you have any other conditions that may be exacerbated by the use of adapalene.

Drug Interactions: As with all retinoids, some drugs may interact with adapalene, resulting in increased or decreased effects of the drug. These interactions may be dose-dependent and may vary from individual to individual. Therefore, patients should be advised to avoid medications that are known to interfere with the metabolism or elimination of adapalene, and to consult their healthcare provider before starting any new medication.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenicity studies with adapalene have been conducted in mice at oral doses of 0.5, 5, and 50 mg/kg/day in rats at oral doses of 0.5, 5, and 50 mg/kg/day. These doses are up to 3 times (mice) and 2 times (rats) the recommended human dose (MDH) based on mg/m² comparisons. No effects of adaptalene were noted. These results are consistent with the preclinical pharmacology of adaptalene and are not indicative of a potential risk to humans.

PREGNANCY: Teratogenic Effects. Reproduction studies have shown that adaptalene may cause fetal abnormalities. However, there is no evidence that adaptalene is teratogenic in humans. Therefore, the use of adaptalene during pregnancy is not recommended. Patients should be advised to avoid the use of adapalene during pregnancy and to use alternative forms of contraception during treatment with adapalene.

ADVERSE REACTIONS: In a multi-center, controlled clinical trial, the signs and symptoms of local irritation were monitored in 258 acne patients who used DIFFERIN® Gel, 0.3% once daily for 12 weeks. Of the patients who experienced acne improvement (erythema, scaling, dryness, and stinging/burning), the majority of cases were mild to moderate in severity, occurring rarely in treatment and disappearing on treatment. The incidence of local irritation with DIFFERIN® Gel, 0.3% from the controlled clinical study is provided in the following table:

Table 2: Physician assessed local irritation with DIFFERIN® Gel

<table>
<thead>
<tr>
<th>Local Irritation</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>60 (24.5%)</td>
<td>33 (13.0%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Scaling</td>
<td>110 (43.5%)</td>
<td>47 (18.6%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Dryness</td>
<td>113 (44.7%)</td>
<td>43 (17.0%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Burning/Stinging</td>
<td>72 (28.3%)</td>
<td>35 (13.4%)</td>
<td>2 (0.8%)</td>
</tr>
</tbody>
</table>

*Total number of subjects with local irritation data for at least one post-Baseline evaluation.

Table 3: Patient reported local adverse events with DIFFERIN® Gel

<table>
<thead>
<tr>
<th>Local Event</th>
<th>N=258</th>
<th>N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td>57 (22.1%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>36 (14%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Skin Discomfort</td>
<td>10 (4.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Desquamation</td>
<td>4 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Selected adverse events defined by investigator as possibly, probably or definitely related to the drug, or severe or life-threatening.

ADVERSE EVENT: Retinal Adverse Events

DIFFERIN® Gel, 0.3% is intended for topical use only. If the medication is applied excessively, no more rapid or better results will be obtained and redness, scaling, or skin desquamation may occur. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of vitamin A.

Marketed by:

GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA
Manufactured by:

DPT Laboratories, Ltd.
San Antonio, Texas 78215 USA
GALDERMA is a registered trademark.
Revised: June 2007 052589-G007

References:

Fort Worth, TX 76177
DIFF 2658 12/11

www.diffi.com/fcpc

Committed to the future of dermatology.
Retire from page 26

according to W. Patrick Davey, M.D., M.B.A., a dermatologist and chairman of the AAD’s practice management task force. He says there’s so much work for dermatologists that they don’t need to buy an existing practice to be successful.

Retiring doctors, Dr. Davey says, may need to reset their expectations.

“Realize that what you’re going to get out of the practice is pretty much what you have invested — equipment,” he says. And, despite assumptions to the contrary, “There’s little value in having a name,” he says. “I’ve known people who have bought the established practices, with the idea that they’d get all those referrals. What they end up with is the person’s (problems and) records, and they become record-keepers.”

A doctor coming out of training today “could start his or her own practice and be just as busy,” Dr. Davey says.

Another issue facing doctors wishing to sell, according to Dr. Grover, is that young physicians today are much more likely to want to be part of a group practice or to be employed, rather than to go solo.

“They just don’t want to be involved in the hassles of the business of medicine,” he says.

Often a better option is to bring on a partner early in the business, or to transition out of a group practice, experts say.

“What I would say to somebody who is in their 40s and 50s and has an idea of

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Exit plans

Proper planning eases transition to retirement, experts say

By Lisette Hilton
Staff Correspondent

National report — Easing out of practice can go more smoothly with proper planning and attention to marketing, experts say. Here are some experts’ answers to often-asked questions:

■ What might buyers want?
Dermatologists should think about their practices as enterprises, and keep in mind what young people will be seeking, Ms. Grant says. “They’re going to be looking for lifestyle. So, if that practice has been set up in such a way that there’s ready profit, working four days a week, with entire systems in place, a staff who is happy, that can go a long way.”

Look at your practice like a business, Mr. Lion advises. “I think in the past … the money train was really rolling and docs were making more money,” he says. “That environment has really changed. You really have to run that medical practice as a business and have systems in place … to really make your business profitable.”

■ What steps should I take now?
Fund retirement plans with excess cash flow during working years, Mr. Lion says.

“There are a number of different types of retirement plans that can be set up for dermatology practices: 401(k), safe harbor 401(k), pension,” etc., he says.

The money put into those plans is a tax deduction and grows tax deferred. Another caveat: In most states, that money is credit-approved. Mr. Lion, who is past-president of the National CPA Health Care Advisors Association, recommends diversifying your investment portfolio to hedge against extreme market fluctuations. Hire a professional, but be involved and understand your finances, he says.

If you’re in private practice, he says, start about three years or more before retirement to look for a partner or employee to whom you plan to offer a partnership. DT
Filaggrin
Urea
Sodium Lactate
Amino Acids
PCA
Sodium Chloride
The term “natural moisturizing factor,” or NMF, was created by scientists studying skin hydration who discovered this naturally occurring collection of water-binding compounds found exclusively in the stratum corneum. These substances, decomposition products of the protein filaggrin, are highly effective humectants, whose hygroscopic properties bind water absorbed from the atmosphere, and retain water from the deeper layers of the skin.¹

When NMF is depleted, hydration in the stratum corneum is compromised, which may contribute to a range of skin problems from xerosis to psoriasis. By regulating water content, NMF helps skin elasticity and overall hydration of the stratum corneum, and plays a crucial role in maintaining overall barrier function.¹

NMF is composed of urea, lactate, pyrrolidone carboxylic acid, salts, and amino acids derived from the protein filaggrin.

Retire from page 29

when they want to start thinking about retiring from full-time practice is they probably ought to start looking earlier, rather than later, at strategies to bring somebody else in,” Dr. Grover says. “That’s rather than just flip a switch at the end of their career and say, ‘I’m going to sell the practice and get out now.’”

Off the charts

Another — and potentially easier — option for those who simply want out is to close up shop and turn over or maintain patient records.

That was the choice of Lenore S. Kakita, M.D., Los Angeles, who retired in March 2011 after more than four decades in practice.

“I loved dermatology immensely and have been diverse in my interests and activities,” she says. “It was time to put my family as my No. 1 priority, while I could actively enjoy my three sons, my two daughters-in-law and my three young grandchildren.”

Dr. Kakita says she was able to transition quickly: Within a month of deciding to retire, she closed her office, finding another dermatologist willing to buy her charts. “It was wonderful to have a fine dermatologist to take care of my patients,” she says.

The recession may mean the deck is stacked against older doctors hoping to retire in their early 60s.

Have that cushion

No matter how or when dermatologists decide to retire, it’s important that they have financial nest eggs, experts say. Building a retirement fund during the high-earning years is vital for maintaining an acceptable lifestyle. But in today’s economy, even that may not be enough.

William Lascheid, M.D., retired from his dermatology practice in Naples, Fla., about 13 years ago. By choice, he went right back to work, for no pay. He has spent his retirement years volunteering at the Neighborhood Health Clinic, which he and his wife founded to provide affordable care to the local working poor.

Like many of his patients who have seen hard financial times, Dr. Lascheid — now nearing his 86th birthday — has had to get a part-time, paying job, in his case at a medical practice.

“I have a part-time job because the economy was so bad and, fortunately, I was able to find (one),” he says.

Dr. Shama says one of the keys to a satisfying retirement, for him, was to determine what he needed to live on to be happy and to live a reasonably good life.

“That’s a very important number because, once you’ve established it, you can determine how much money you need to make,” he says.

How will it look?

The ideal retirement is in the eyes of the beholder, experts say. Some dermatologists are happy to stop working and live in a leisurely manner; others are not. Creating a fulfilling retirement may mean exploring new directions.

“One of the challenges many professionals face when they retire is that they fail to recognize the emotional benefits they receive from their work,” says Keith Weber, author of the book Rethinking Retirement: How to Create the Life You Want Without Waiting to Retire, and creator of the website www.Rethinking-Retirement.com.

Too often, retirees “look short term at the frustrations they’ll no longer have to deal with, or the time they’ll be able to spend doing the things they enjoy,” he says. “But after as little as six to 12 months, many professionals find they need something to apply their talent and energy toward. They miss being involved in making important decisions or … having their input valued.”

Dr. Shama found enjoyment and meaning by changing careers. He is now a full-time motivational speaker, an activity in which he dabbled while he was still in practice. Dr. Lascheid found purpose in caring for those who could not afford healthcare.

Not all retirees want to take on a full-time schedule, however. Some do well with what Mr. Weber calls a phased retirement, during which the time spent working is gradually reduced.

“This allows them to stay involved professionally, but also allows time to explore and find other activities that might be equally enjoyable or fulfilling,” he says.

The point, he says, is that it is human nature to feel a need to contribute and to make a difference to the world.

“Especially for medical professionals, retirement can leave a huge void in that part of their identity, and be a big hit to their self-esteem,” he says.

Dr. Shama says addressing that identity issue is a big step toward creating a happy retirement. Dermatology “might be what you do, but it’s not who you are,” he says.

“I think people should realize … that you don’t want to leave when you have a life-threatening illness that all-of-the-sudden hits you. You want to leave when you have something else that is still joyful in your life,” he says.

Dr. Kakita, whose retirement is still months away, found purpose in caring for those who have to deal with, or the time they’ll be able to spend doing the things they enjoy,” he says. “But after as little as six to 12 months, many professionals find they need something to apply their talent and energy toward. They miss being involved in making important decisions or … having their input valued.”

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For patients with mild to moderate rosacea,

Deliver a spectrum of benefits with FINACEA®

• The first and only gel approved to treat the inflammatory papules, pustules, and their associated erythema*
• Continuous lesion reductions consistent across 12-week pivotal studies¹
• Hydrogel formulation that’s nonsticky, alcohol- and fragrance-free²
• Maintains the skin barrier³

INDICATION & USAGE
FINACEA (azelaic acid) Gel, 15% is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea.

*Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

IMPORTANT SAFETY INFORMATION
FINACEA is for dermatologic use only, and not for ophthalmic, oral, or intravaginal use. FINACEA is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation. In clinical trials, sensations of burning/stinging/tingling occurred in 29% of patients, and itching in 11%, regardless of the relationship to therapy. Post-marketing safety—Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure to the eye. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

Please see following page for Brief Summary of full Prescribing Information.
INDICATIONS AND USAGE
FINACEA Gel, 15%, is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated. Patients should be instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

CONTRAINDICATIONS
FINACEA Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

WARNINGS
FINACEA Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral or intravaginal use. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS
General:Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA Gel, 15%, treatment should be discontinued and appropriate therapy instituted.

In a transgenic mouse study, chronic use of FINACEA Gel led to an increased number of animals with papillomas at the treatment site (see PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility). The clinical relevance of the findings in animal studies to humans is not clear.

Information for Patients: Patients using FINACEA Gel, 15%, should receive the following information and instructions:

• FINACEA Gel, 15%, is to be used only as directed by the physician.
• FINACEA Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
• Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA Gel, 15%. Avoid alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.
• Avoid contact of FINACEA Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
• The hands should be washed following application of FINACEA Gel, 15%.
• Cosmetics may be applied after FINACEA Gel, 15%, has dried.
• Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA Gel, 15%, should be discontinued, and patients should consult their physician (See ADVERSE REACTIONS).
• Avoid any foods and beverages that might provoke erythema, flushing, and itching (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
• Patients should report abnormal changes in skin color to their physician.
• Avoid the use of occlusive dressings or wrappings.

Drug Interactions: There have been no formal studies of the interaction of FINACEA Gel, 15%, with other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week dermal carcinogenicity study using transgenic (TG.AC) mice, FINACEA Gel, 15%, and the gel vehicle, when applied once or twice daily, did not increase the number of female TG.AC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male TG.AC animals after once daily application. After twice daily application, FINACEA Gel, 15%, and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males. This suggests that the positive effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear.

Azelaic acid was not mutagenic or clastogenic in a battery of in vitro Ames assay, HGPSRT in V79 cells (Chinese hamster lung cells), and chromosomal aberration assay in human lymphocytes and in vivo (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at doses levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) led to no consistent genotoxicity tests. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

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

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers: Equilibrium dialysis was used to assess human milk partitioning in vitro. At an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution coefficient was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when FINACEA Gel, 15%, is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of FINACEA Gel, 15%, in pediatric patients have not been established.

Geriatric: Clinical studies of FINACEA Gel, 15%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS
Overall, treatment-related adverse events, including burning, stinging/tinging, dryness/lighterness/ scaling, itching, and erythema/irritation/ redness, were 19.4% (24/124) for FINACEA Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks.

In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous Adverse Events Occurring in >1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity

<table>
<thead>
<tr>
<th></th>
<th>Mild n=59 (22%)</th>
<th>Moderate n=61 (15%)</th>
<th>Severe n=7 (1%)</th>
<th>Mild n=46 (14%)</th>
<th>Moderate n=30 (9%)</th>
<th>Severe n=5 (2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stinging/</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>tingling</td>
<td>71 (16%)</td>
<td>42 (9%)</td>
<td>17 (4%)</td>
<td>8 (2%)</td>
<td>6 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>29 (6%)</td>
<td>18 (4%)</td>
<td>5 (1%)</td>
<td>9 (3%)</td>
<td>6 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Scaling/dry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>skin/xerosis</td>
<td>21 (5%)</td>
<td>10 (2%)</td>
<td>5 (1%)</td>
<td>31 (9%)</td>
<td>14 (4%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Erythema/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>irritation</td>
<td>6 (1%)</td>
<td>7 (2%)</td>
<td>2 (&lt;1%)</td>
<td>8 (2%)</td>
<td>4 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Contact</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dermatitis</td>
<td>2 (&lt;1%)</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Edema</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Acne</td>
<td>3 (1%)</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event. FINACEA Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA Gel, 15%, caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies. In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

Post-marketing safety: Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure with FINACEA Gel, 15%, to the eye (see PRECAUTIONS).

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Indications is part of the Bayer Group
... From page 1

Advancing: FDA grants rapid approval for Erivedge

surgery, or who are not candidates for surgery and who are not candidates for radiation. It is an orally available 150 mg capsule taken once a day.

Parallel single-arm studies evaluated 33 patients with metastatic basal cell carcinoma, 97 percent of whom were previously treated (surgery, 97 percent; radiotherapy, 58 percent; systemic therapies, 30 percent); and 63 patients with locally advanced basal cell carcinoma, 94 percent of whom were previously treated (surgery, 89 percent; radiotherapy, 27 percent; and systemic/topical therapies, 11 percent).

Among metastatic patients, 30.3 percent (95 percent CI: 15.6, 48.2) had a partial response. Locally advanced patients achieved a 20.6 percent complete response rate as verified by no pathologic evidence of BCC, while 22.2 percent had a partial response.

The larger safety database of 138 patients exposed to vismodegib saw incidence of muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and aguesia that exceeded 10 percent.

Animal studies suggest a high risk for birth defects and death for a developing fetus. An FDA “black box” warning notes that Erivedge is contraindicated for use in women of childbearing years, including those who are nursing. The drug may be transmitted through semen, and men taking vismodegib should use condoms while on the drug and for two months afterward when having sex with women of childbearing potential.

Rapid approval
Vismodegib was approved more rapidly than anticipated and publication of the pivotal clinical trials lags, though at press time a paper was scheduled for publication in a leading journal.

While Dr. Marmur is impressed with the drug’s efficacy, she restricts her enthusiasm for its use to cases of advanced and difficult-to-treat patients in the label indication, chiefly because of the side effects. The effects are common for cancer chemotherapy treatment, but are far greater than what is seen with the most commonly used dermatologic treatments.

“I’ve had a couple of skin cancers myself, and I’m not sure that it is something I would be comfortable taking,” Dr. Marmur says. “At this point, I think I’d still rather have surgery for the occasional skin cancer.”

Brian Berman, M.D., Ph.D., co-director of the Center for Clinical and Cosmetic Research in Aventura, Fla., echoes those feelings. “(Erivedge) probably will be more easily accepted by medical oncologists and surgical oncologists, though a subset of dermatologists will be comfortable with medications that have significant side effects and ‘black boxed’ warnings,” he says.

He advises dermatologists “to adhere to the FDA-approved indication and not initially experiment with off-label uses. I would urge them to review the original phase 3 data and the patient photographs in that study so they get a realistic view of what types of patients were included,” he says.

Dr. Marmur believes physicians have underestimated the number of patients who might benefit from vismodegib. Her experience in the few weeks since FDA approval suggests, “We are going to see all of these new patients come out of the woodwork who are going to benefit from this medication.”

Ingenol mebutate
Ingenol mebutate is a topical gel, derived from the sap of the plant Euphorbia peplus, that was approved for treatment of actinic keratosis. The 0.15 percent concentration is for use over three consecutive days on the face and scalp; the 0.05 percent concentration is for use over two consecutive days on the trunk and extremities.

“(Erivedge) probably will be more easily accepted by medical oncologists and surgical oncologists.”
Brian Berman, M.D., Ph.D.
Aventura, Fla.

When compared with other topical field therapies for actinic keratosis, its efficacy and side effect profile are similar says Dr. Berman, who was involved with one of the trials. The principle benefits are in its significantly shorter course of treatment and short duration of local skin reactions.

“That’s important because patients are going to adhere to the regimen in the way it was carried out in the studies, and you are going to see real world efficacy rates that are close to those seen in clinical studies,” he says.

Dr. Marmur agrees with that evaluation from her experience with a study and adds, “No one topical treatment is 100 percent effective, and reactions will vary between patients, but for some patients, this is as good as it gets. It will have its niche.”

Disclosures: Dr. Marmur was an investigator on studies of both drugs; she has no declared financial conflicts of interest. Dr. Berman has been a consultant to both companies as well as to other companies marketing treatments for actinic keratosis.
Cellulitis uncertainty

Dermatologists best suited to diagnose condition that often resembles others

By John Jesitus
Senior Staff Correspondent

Boston — Dermatologists are best positioned to accurately diagnose cellulitis, a common misdiagnosis for look-alike conditions ranging from stasis dermatitis to cutaneous cancers, according to Daniela Kroshinsky, M.D.

Many conditions resemble cellulitis, says Dr. Kroshinsky, assistant professor of dermatology and director of pediatric dermatology and inpatient education and research at Massachusetts General Hospital, Boston. “Therefore,” she says, “utilizing a dermatologist is the best way to make sure that patients get appropriately diagnosed and treated.”

In hospital settings, Dr. Kroshinsky says dermatologists could play a greater role in diagnosing cellulitis by consulting with emergency or internal medicine departments, ideally before patients are admitted. This way, “We could save patients from unnecessary stays and exposures to inappropriate antibiotics,” she says.

In outpatient settings, Dr. Kroshinsky suggests that whenever possible, primary care physicians refer patients with suspected cellulitis for urgent dermatology visits. Several institutions and dermatology offices now offer urgent appointments for such purposes, she says.

Along with expanding the number of dermatologists and practices offering these appointments, “If community doctors had a list on hand of dermatologists who would participate in such a program — not only for cellulitis, but also for other urgent dermatologic conditions that come up in the primary care setting — it would be very beneficial for patients,” she says. “The best person to make these diagnoses or recognize when we’re dealing with a different diagnosis is a dermatologist.”

Outside of dermatology, many physicians currently rely solely on clinical symptoms or physical examination findings to diagnose cellulitis, Dr. Kroshinsky says. “Many medical students are taught to look for redness, warmth, swelling and tenderness. But these clinical findings were originally assigned to describe inflammation in general. Somehow they became the sine qua non of cellulitis,” she says. “If you don’t have a differential (diagnosis) for other conditions that can look like cellulitis in the skin, then everything becomes cellulitis.”

“The best person to make these diagnoses or recognize when we’re dealing with a different diagnosis is a dermatologist.”

Daniela Kroshinsky, M.D.
Boston

Different diagnoses
Dr. Kroshinsky says she commonly consults on cases that turn out to be Lyme disease. “We all know about the presentation of Lyme as a ring of erythema with central clearing,” she says. “That’s what most of our patients are taught to look for. Cellulitis see page 47

Quotable
“All of the potential serious side effects of corticosteroids … are either reversible or easy to avoid.”

Matthew J. Zirwas, M.D.
Columbus, Ohio

On treating steroid-responsive dermatoses
See story, page 37

DT Extra

Manuka honey tames biofilms

Manuka honey could help clear chronic wound infections or even keep them from developing, according to a study published in Microbiology. Researchers at Cardiff Metropolitan University, Wales, working with S. pyogenes bacteria reported that small concentrations of honey prevented the start of biofilm development. They also found that treating established biofilms grown in Petri dishes with honey for two hours killed up to 85 percent of resident bacteria. Investigators say the honey can prevent the bacteria from initially binding to wound tissue.

Source: medicalnewstoday.com
Promoting protection
Barrier repair creams target downside of topical corticosteroid treatment

By Cheryl Guttman Krader
Senior Staff Correspondent

Las Vegas — The combination of a topical corticosteroid with a physiologic lipid-containing product is an effective approach for the management of atopic dermatitis and other steroid-responsive dermatoses because it simultaneously addresses disease-related inflammation and the barrier impairment that can be worsened by a topical corticosteroid alone, according to Matthew J. Zirwas, M.D.

“Patients and parents of children with atopic dermatitis are often fearful about using topical corticosteroids because of safety concerns. However, all of the potentially serious side effects of corticosteroids, which include hypothalamic-pituitary axis suppression, skin atrophy, striae, cataract and glaucoma, are either reversible or easy to avoid.

“Rather, barrier impairment, which can occur within just three days of treatment initiation, is probably the most clinically important side effect of topical corticosteroid use,” says Dr. Zirwas, who discussed topical anti-inflammatory treatment at the 30th annual Fall Clinical Dermatology Conference.

Barrier compromise
Topical corticosteroid treatment disrupts the skin barrier by causing decreases in the production and release of the lipid-containing lamellar bodies, and it also substantially decreases the production of antimicrobial peptides.

Using the brick-and-mortar model as an analogy for the structure of the stratum corneum illustrates how initiation of topical corticosteroid therapy can lead to an immediate improvement of the skin barrier — the treatment rapidly reduces inflammation that is causing damage to the wall.

Despite maintenance of anti-inflammatory activity with ongoing corticosteroid treatment, however, the benefit for improving the skin barrier does not persist because of the effects of the corticosteroid on the lamellar bodies; i.e., the treatment causes damage to the mortar component of the brick wall, Dr. Zirwas says.

“A wall made of bricks held together with petrolatum might be a better model for the stratum corneum, considering the cells are held together by a lipid-rich substance. Treatment with a physiologic lipid-containing product can overcome the barrier impairment caused by topical corticosteroids because it enables repair of this petrolatum component,” says Dr. Zirwas, assistant professor of dermatology, Ohio State University, Columbus, Ohio.

Dr. Zirwas says he uses this analogy to explain the benefits of a barrier repair product to patients who may have been using conventional moisturizer products without success.

“Referring to the brick wall model, I tell patients that use of a barrier cream, which reduces irritant exposure and lipid removal, is like trying to repair a damaged brick wall by covering it with a coat of paint,” he says. “The intervention has an immediate effect, but the benefit is minimal because it

“Barrier impairment, which can occur within just three days of treatment initiation, is probably the most clinically important side effect of topical corticosteroid use.”

Matthew J. Zirwas, M.D.
Columbus, Ohio

hasn’t addressed the underlying damage. The same limitation applies to moisturizers containing ingredients that replace lost water or reduce further loss.

“In contrast, barrier repair creams are different because they contain the materials that can actually improve the damaged mortar,” Dr. Zirwas adds. “However, they also need to know that this repair takes time since it involves metabolic processes.”

Protection see page 40
Digging deeper

Livedo reticularis can be first manifestation of cholesterol embolism syndrome

By Ilya Petrou, M.D.
Senior Staff Correspondent

Granada, Spain — Livedo reticularis can have many different etiologies, one of which could be cholesterol embolism syndrome. Clinicians should consider cholesterol embolism as a potential cause of this skin condition, particularly when a patient presents with other specific associated signs and symptoms.

Typically occurring on the legs, arms and trunk, livedo reticularis is a vascular condition characterized by a purplish mottled net-like discoloration of the skin.

Livedo reticularis can be a normal condition that causes no symptoms and requires no treatment, but it also can be associated with serious underlying disorders such as lupus erythematosus, antiphospholipid syndrome and Sneddon’s syndrome. The condition can occur as a side effect to several medications, such as hydroxyurea, as well.

The cutaneous symptoms associated with cholesterol embolism syndrome in the lower extremities can include cyanotic toes and cutaneous nodules.

Patients who undergo angiography can develop cholesterol embolism syndrome, which may lead to the typical cutaneous manifestation of livedo reticularis.

Quick Read

Cholesterol embolism should be considered as a potential cause of livedo reticularis, especially when patients present with other signs and symptoms of this condition.

“The classic triad of cholesterol embolism syndrome includes livedo reticularis, acute renal failure and eosinophilia. The diagnosis of cholesterol embolism syndrome is sometimes challenging to make and often presents as a combination of signs and symptoms specific to end-organ damage and a systemic inflammatory response,” says Salvador Arias-Santiago, M.D., Ph.D., department of dermatology, San Cecilio Clinical Hospital, Granada, Spain.

Cholesterol crystal emboli are commonly an iatrogenic complication caused by mechanical damage to the arterial walls from vascular surgery or invasive percutaneous procedures. Material dislodged from atheromatous plaques in the arteries can occlude smaller vessels such as those in the lower extremities, leading to this syndrome.

“The time to the onset of smaller vessel infarction can often be delayed for days to weeks after diagnostic procedures such as angiography. Spontaneous plaque hemorrhage or disruption and anticoagulant or fibrinolytic therapy can also precipitate the embolization of the cholesterol crystals,” Dr. Arias-Santiago says.

Skin symptoms

The cutaneous symptoms associated with cholesterol embolism syndrome in the lower extremities can include cyanotic toes and cutaneous nodules, as well as livedo reticularis affecting the feet and legs, which can sometimes extend up to involve the trunk.

Many cases of cholesterol embolism syndrome are subclinical and dermatological findings can be subtle, Dr. Arias-Santiago says. Nevertheless, early recognition of clinical cutaneous findings such as livedo reticularis is essential in establishing an accurate diagnosis and appropriate treatment, particularly when associated with acute renal failure and eosinophilia.

“Cholesterol embolism syndrome can sometimes go unnoticed and livedo reticularis can oftentimes be one of the only clinical signs that may lead the clinician to the correct diagnosis.”

Salvador Arias-Santiago, M.D., Ph.D.
Granada, Spain

“Cholesterol embolism syndrome can sometimes go unnoticed and livedo reticularis can oftentimes be one of the only clinical signs that may lead the clinician to the correct diagnosis,” Dr. Arias-Santiago says.

Histological confirmation has been considered essential to diagnose cholesterol embolism, and as
Optimized for efficacy with minimal irritation

- 36% mean reduction in inflammatory lesions at 12 weeks
  \(^1\)
- 41% mean reduction in noninflammatory lesions at 12 weeks
  \(^1\)
- Low irritation profile
- Moisturizing and hydrating agents \(^2\)  \(^4\)

\(^*\) Combined results of two 12-week, prospective, multicenter, randomized, vehicle-controlled studies of patients with mild to moderate acne vulgaris of the face.

\(^1\) The contribution of individual components to efficacy has not been evaluated.

**Indication and Important Safety Information:** Atralin Gel is indicated for the treatment of acne vulgaris. The most common adverse reaction was mild to moderate irritation of the skin (ie., dry skin, skin burning, erythema, and exfoliative dermatitis), which occurred during the first few weeks of treatment with Atralin Gel. To prevent aggravating the skin, protect it from sun, tanning lights, extreme wind or cold, and harsh skincare products. Use of sunscreen products of at least SPF 15 and protective clothing over treated areas are recommended when exposure cannot be avoided. Atralin Gel should not be used on eczematous or sunburned skin due to potential for severe irritation.

Protection from page 37

Product selection

Currently, a number of topical products marketed as barrier repair creams are available that contain ceramides and/or hyaluronic acid. From a theoretical perspective, there is reason to believe that not all of these products are equally effective, and that concept is supported by results from clinical studies.

“Keep in mind that there are 11 classes of ceramides in the human stratum corneum and over 340 individual species in human skin,” Dr. Zirwas says. “The takeaway message is that ceramides are complex compounds and there are many different types. It is important that ceramide 1 and 3 are deficient in the skin of persons with atopic dermatitis, but assuming that any ceramide-containing product will be effective for barrier repair is like anticipating any antibiotic will be effective for treating an infection caused by a specific type of pathogen.”

Finding what works

While the available data suggest that not all barrier repair products are equally effective, there is currently no evidence base for deciding which one(s) work best. Dermatologists might take into account whatever study results are available, along with their personal experience and other pragmatic issues, according to Dr. Zirwas.

Dr. Zirwas says his own decision-making process includes considering whether there are efficacy data from an appropriately designed clinical trial, which should be at least four weeks in duration and include “regular” treatment without the barrier repair cream as a control. He also factors in product cost and whether the barrier cream is packaged in a large enough container to allow its use as a moisturizer.

As a practical approach to barrier repair in patients being treated with a topical corticosteroid, Dr. Zirwas says that he writes patients a prescription for 50 mL of 0.05 percent betamethasone solution with instructions to mix it with a 16-ounce jar of CeraVe cream (Cora) and apply twice daily to sites of active disease.

“I tell patients to ask the pharmacist if their insurance will cover compounding by the pharmacist, and if not, then the patient should fill the prescription for the betamethasone, buy a jar of CeraVe, and mix the entire bottle of clobetasol into the new jar of the barrier repair cream using a clean spoon,” he says. “I have found this strategy to be extremely simple and the least expensive way to combine corticosteroid therapy with a barrier repair cream, and anecdotally, it is also very effective.”

Dr. Zirwas says the final concentration of clobetasol after it is mixed into the barrier cream is 0.005 percent, which is approximately a class 3 corticosteroid. If a lower-potency corticosteroid is needed, such as when treating children under age 12, he prescribes 60 mL of betamethasone dipropionate 0.05 percent lotion instead of the clobetasol. The final betamethasone concentration is 0.006 percent, which Dr. Zirwas says he estimates to be a class 6 corticosteroid. DT

Disclosures: Dr. Zirwas is a consultant to Coria and Onset Therapeutics, which market barrier repair products, and to Taro, which markets a topical corticosteroid.
Digging from page 38

Skin is the most accessible site, skin biopsy is the best sample for histological diagnosis.

According to Dr. Arias-Santiago, biopsies should be made deep, as emboli tend to be patchily distributed and therefore difficult to find. Patients who undergo angiography can often develop cholesterol embolism syndrome and here, post-procedural embolism of a blood clot, vasculitis and infective endocarditis are the most important differential diagnosis.

Syndrome symptoms

A mosaic of signs and symptoms can be associated with cholesterol embolism syndrome, and several areas can be affected, such as the kidney (hypertension, acute renal failure), muscles (myalgias), gastrointestinal organs (bleeding abdominal pain, bowel infarction), pulmonary (acute respiratory distress syndrome), eye (Hollenhorst plaques in retinal arteries).

“There are many different clinical manifestations of cholesterol embolism syndrome, and therefore, an interdisciplinary approach ... is necessary.”

Salvador Arias-Santiago, M.D., Ph.D.
Granada, Spain

or central nervous system (stroke, confusion, delirium).

“There are many different clinical manifestations of cholesterol embolism syndrome, and therefore, an interdisciplinary approach including dermatologists, internists, cardiologists and pathologists is necessary in order to better recognize this syndrome and manage its sequelae,” Dr. Arias-Santiago says.

Angiography is a very commonly used procedure and can be a very useful diagnostic tool. The technique could “trigger” cholesterol embolism syndrome, however. Therefore, angiography should only be performed in select patients, and clinicians should be vigilant and look out for cutaneous symptoms of cholesterol embolism syndrome such as livedo reticularis.

“Cutaneous abnormalities are usually the earliest and often the only clinical manifestation of this syndrome. Therefore, it behooves the wary physician to keep clinical signs and symptoms such as livedo reticularis in mind when approaching patients with cholesterol embolism,” Dr. Arias-Santiago says. DT

Disclosures: Dr. Arias-Santiago reports no relevant financial interests.
Working world
Responsibility goes beyond patient with occupational dermatitis

By John Jesitus
Senior Staff Correspondent

Melbourne, Australia — When dermatologists encounter a case of work-related contact dermatitis, they should consider the well-being not only the patient, but also of his or her co-workers.

Although treating patients with occupational contact dermatitis can be challenging, “We must embrace that challenge. It’s very rewarding when treatment succeeds,” says Rosemary L. Nixon, M.D., director, Occupational Dermatology Research and Education Centre, Victoria, Melbourne, Australia.

Reasons that occupational contact dermatitis occurs include failure of workplace controls, failure to use appropriate personal protection and, at times, lack of awareness that exposure to certain chemicals can create problems, Dr. Nixon says.

Whatever the reason, Dr. Nixon quotes U.S. Deputy Surgeon General Boris Lushniak, M.D.: “He reminds us that we don’t just have a responsibility to our patients. We have a responsibility to others in the workplace who may also be at risk of the same problem. We see it time and again — someone with an allergy to epoxy resins gets fired, only for another person to take their place and get exposed to epoxy resins inappropriately.”

Dr. Nixon’s tertiary referral patch-testing clinic has treated more than 3,500 patients with contact dermatitis. The vast majority of these patients have at least partially work-related occupational contact dermatitis, she says. Patients in the “partial” category may have atopic dermatitis that something in the workplace aggravates, Dr. Nixon explains.

Treatment parameters
In treating patients with rashes on their hands that could be symptoms of occupational contact dermatitis, Dr. Nixon says it’s critical to make a proper diagnosis. In this regard, she encourages dermatologists to consider endogenous factors such as atopic eczema or hand eczema, as well as licea, psoriasis and rare conditions such as porphyria cutanea tarda.

Diagnosing these patients requires taking extensive histories, she says, because the rash may have resolved by the time the patient sees her.

“Many physicians, including dermatologists, advise patients to change jobs without even taking an exposure history. If you don’t make a diagnosis, you could be asking people to change jobs when, in fact, they’re allergic to gloves, which they’ll encounter in their next job,” Dr. Nixon says.

Tools that can assist with patient history-taking include questionnaires and material safety data sheets that patients bring from their workplaces.

“Sometimes, we have the luxury of going to the workplace,” Dr. Nixon says, but more commonly she relies on photos patients submit through their cell phones.

Patient education
To help patients understand their condition, at 48-hour patch test appointments, Dr. Nixon gives patients a chart that introduces concepts including exogenous and endogenous sources of irritation, plus the potential relevance of positive patch tests.

“If a test is negative, that doesn’t mean it’s not OCD (occupational contact dermatitis). It might just be irritant contact dermatitis (ICD). Then, when we see patients at “We don’t just have a responsibility to our patients. We have a responsibility to others in the workplace who may also be at risk of the same problem.”

Rosemary L. Nixon, M.D.
Melbourne, Australia

96 hours, they have some sort of background, because this is very complex,” she says.

One of Dr. Nixon’s patients, a 20-year-old female kitchen worker with a background of atopic eczema, presented with hand dermatitis and said she never wore protective gloves until after the rash developed.

During patch testing, “She reacted to nickel and fragrance mix,” Dr.
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Nixon says, “Fortunately, she didn’t react to her latex gloves. I diagnosed her with ICD originating from ‘wet’ work.” The nickel reaction ultimately proved unrelated to her workplace, although other nickel items may have played a role, Dr. Nixon adds, saying that she advised this patient to use disposable gloves that would cover her wrists and ideally to change her duties. “She needed some time off work for her skin to heal,” Dr. Nixon says, explaining that she also instructed the patient about optimal skincare, including use of barrier creams and moisturizing creams. However, she says that because the patient waited until after the rash developed to begin protecting her skin, “She had a poor prognosis” and ultimately had to change jobs.

“We’ve known from research done in Europe that ‘wet’ work is a risk factor for ICD (Jungbauer FH, Van Der Harst JF, Schutteelaar ML, Groothoff JW, Coenraads PJ. Contact Dermatitis. 2004;51(3):131-134),” Dr. Nixon says. As a result, she says, Germany has begun to require pre-employment counseling for people at high risk of ICD who are considering “wet” work. High-risk factors include a history of moderate-to-severe atopic eczema with hand involvement, chronic hand eczema and a history of changing jobs due to such problems.

In Australia, “We don’t even have nickel legislation. We have guidelines on the Internet, but unfortunately they’re largely ignored by wet workers and their employers,” she says.

The sentinel sign of ICD is irritation between the fingers, where soap and water accumulate. Because career counselors tend to know little about this topic, Dr. Nixon says her clinic attempts to educate this community.

Dermatologists must remember that in patch testing, “The first mistake many physicians make is to underestimate the role of ICD,” Dr. Nixon says. Dermatologists also should remember that the presence of eczema raises ICD risk, and that patients with a history of eczema must wear gloves preven-}

**Often, workplaces don’t have the systems in place to teach people that they’re at risk.**

*Rosemary L. Nixon, M.D.*

Melbourne, Australia

Such was the case with a 42-year-old male patient who worked extensively with floor coatings but only occasionally wore rubber gloves. Dr. Nixon says she diagnosed the patient with allergic contact dermatitis to epoxy resin. Better gloves for working with epoxies include the laminated Silver Shield 4H glove (North Safety Products) or thick nitrile gloves, she says.

Another case illustrates the difficulties of persistent post-occupational dermatitis (PPOD). Specifically, Dr. Nixon says she treated a patient who had spent nearly 20 years being exposed to photodevelopment chemicals. His occupational contact dermatitis persisted even after a 12-month break from this work.

At that point, “He went to an independent medical examiner, who said, ‘He is not working, and he is not better. Therefore, this can’t be work-related,’ and withdrew his workers’ compensation. This is why we need to understand PPOD,” Dr. Nixon says.

Clinically, “The patient’s dermatitis was like a form of hand eczema. But there was a very definite history of occupational causation” that should not have been ignored, she says.

**PPOD definition**

Initially, experts defined PPOD as an ongoing skin disease that has no obvious present cause but was precipitated by the prior develop-ment of occupational skin disease (Wall LM, Gebauer KA. *Contact Dermatitis*. 1991;24(4):241-243). To refine this definition, Dr. Nixon and her colleagues have added a requirement for clinical follow-up at two time points (Sajjachareonpong P, Cahill J, Keegel T, Saunders H, Nixon R. *Contact Dermatitis*. 2004;51(5-6):278-283).

“You can’t just see these people and make a diagnosis. You may need to re-patch test them to make sure they’re not allergic to something else. It’s a diagnosis of exclusion,” she says.

In an unpublished follow-up study, Dr. Nixon and her colleagues interviewed 119 patients approximately five years after they were diagnosed with occupational contact dermatitis. Using a case-control study design, these authors concluded that many factors previously thought to be significant risk factors for PPOD, such as age, gender and disease duration, were not.

However, high severity scores initially and at follow-up were a seven-fold risk factor for PPOD, she says. For this study, Dr. Nixon and her colleagues used the occupational contact dermatitis disease severity index (ODDI), a scale that they developed using functional criteria (Curr N, Dharmage S, Keegel T, Lee A, Saunders H, Nixon R. *Contact Dermatitis*. 2008;59(3):157-164).

“Among the patients we see in our clinic, about 20 percent fall into this severe category,” Dr. Nixon says. “The implication is that with severe disease, we need to intervene early. These people require time off work — not just modified duties — and may need more aggressive treatment.”

Additionally, Dr. Nixon says it surprised her that her group’s research found smoking to be a highly significant risk factor for PPOD.

Disclosures: Dr. Nixon reports no relevant financial interests.
For the first-line treatment of inflammatory and comedonal acne

Prescribe the #1 BRANDED TOPICAL ACNE PRODUCT AMONG DERMATOLOGISTS

NOW AVAILABLE IN A PUMP!

The only, once-daily adapalene/benzoyl peroxide combination—in a patient-preferred PUMP.

- 79% of acne patients preferred the PUMP over the tube²*
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Measured dose for consistent delivery.

*Survey of 231 patients 12 to 35 years of age who completed a randomized study of Epiduo® Gel tube vs pump after 1 week of treatment with each dispenser.

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.

Please see brief summary of Prescribing Information on next page.
EPIDUO®
(adapalene and benzoyl peroxide) Gel 0.1% / 2.5%

Rx only

For Topical Use Only
Not For Ophthalmic, Oral, or Intravaginal Use.

BRIEF SUMMARY

INDICATIONS AND USAGE

EPIDUO Gel is a combination of adapalene, a retinoid, and benzoyl peroxide, and is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided.

ERYTHEMA, SCALING, DRYNESS, AND STINGING/BUurning may occur with use of EPIDUO Gel.

ADVERSE REACTIONS

Observed local adverse reactions in patients treated with EPIDUO Gel were erythema, scaling, dryness, stinging, and burning. The most common reported adverse events (>1%) in patients treated with EPIDUO Gel were dry skin, contact dermatitis, application site burning, application site irritation, skin irritation.

DRUG INTERACTIONS

Exercise caution in using preparations containing sulfur, resorcinol, or salicylic acid, medicated or abrasive soaps and cleansers, and products with high concentrations of alcohol or astringents in combination with EPIDUO Gel.

Concomitant use of topical products with a strong drying effect can increase irritation. Use with caution.

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with EPIDUO Gel. Animal reproduction studies have not been conducted with the combination gel or benzoyl peroxide. Furthermore, studies such as these are not always predictive of human response; therefore, EPIDUO Gel should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m²/day) the maximum recommended human dose (MRHD) of 2 grams of EPIDUO Gel. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of ≥ 25 mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats; and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day [25-59 times (mg/m²) the MRHD] showed no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

Nursing Mothers

It is not known whether adapalene or benzoyl peroxide is excreted in human milk following use of EPIDUO Gel. Because many drugs are excreted in human milk, caution should be exercised when EPIDUO Gel is administered to a nursing woman.

Pediatric Use

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

Geriatric Use

Clinical studies of EPIDUO Gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, photocarcinogenicity, genotoxicity, or fertility studies were conducted with EPIDUO Gel.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m²/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 (rats) times the MRHD of 2 grams of EPIDUO Gel. In the rat study, an increased incidence of benign and malignant pulmonary adenomas in the adrenal medulla of male rats was observed. No significant increase in tumor formation was observed in rodents topically treated with 15-25% benzoyl peroxide carbopol gel (6-10 times the concentration of benzoyl peroxide in EPIDUO Gel) for two years. Rats received maximum daily applications of 138 (males) and 205 (females) mg benzoyl peroxide/kg. In terms of body surface area, these levels are 27-40 times the MRHD. Similar results were obtained in mice topically treated with 25% benzoyl peroxide carbopol gel for 52 weeks followed by intermittent treatment with 15% benzoyl peroxide carbopol gel for the rest of the 2 years study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years. The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. However, the significance of this finding in humans is unknown.

In a photocarcinogenicity study conducted with 5% benzoyl peroxide carbopol gel, no increase in UV-induced tumor formation was observed in hairless mice treated topically for 40 weeks.

No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects in vitro (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or in vivo (mouse micronucleus test).

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide has provided mixed results, mutagenic potential was observed in a few but not in a majority of investigations. Benzoyl peroxide has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, it has caused DNA-protein cross-links in the human cells, and has also induced a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells.

In rat oral studies, 20 mg adapalene/kg/day (120 mg/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F1 males and females, or growth, development and reproductive function of F1 offspring.

No fertility studies were conducted with benzoyl peroxide.

PATIENT COUNSELING INFORMATION

- Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply EPIDUO Gel as a thin layer, avoiding the eyes, lips and mucous membranes.
- Advise patients not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.
- EPIDUO Gel may cause irritation such as erythema, scaling, dryness, stinging, or burning.
- Advise patients to minimize exposure to sunlight, including sunlamps. Recommend the use of sunscreen products and protective apparel, (e.g., hat) when exposure cannot be avoided.
- EPIDUO Gel may bleach hair and colored fabric.

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Revised: December 2011
P51740-0-BS

Cellulitis

But really, a much more common presentation of erythema migrans is homogenous erythema that can mimic cellulitis. Consultant teams are usually very surprised “that what they suspected was cellulitis is actually Lyme disease.

In another case, she says, “We were called to see a patient who had radiation to her skin years prior for an internal cancer. She was given an antibiotic that caused radiation recall. Usually, we think about that happening with chemotherapy, but we’re seeing it happening with antibiotics as well — particularly the fluoroquinolones.”

Accordingly, it’s becoming a much more common phenomenon because years after radiation treatment, people are more likely to get antibiotics than chemotherapy, Dr. Kroshinsky says, adding that she and her colleagues also have consulted on many suspected cellulitis cases that led to the discovery of cutaneous and internal cancers.

Whereas typical cellulitis is poorly demarcated, erysipelas involves a more superficial process, which leads to more lymphatic involvement and a well-demarcated area of erythema.

Medical literature reveals misdiagnosis or “pseudo-cellulitis” rates of 14 to 33 percent, Dr. Kroshinsky says. “Our own data (unpublished) from Massachusetts General Hospital showed a rate of about 18 percent (Kroshinsky D, Bailey E. Medical Dermatology Society Annual Meeting, February 3, 2011. New Orleans),” she says. “It’s quite variable, depending on whose study you look at.”

Cellulitis studies

The retrospective Massachusetts General study included 390 patients with suspected cellulitis admitted between April and September 2009. Among these patients, the condition most commonly misdiagnosed as cellulitis was stasis dermatitis, Dr. Kroshinsky says. A 145-patient prospective study echoed this finding (David CV, Chira S, Eells SJ, et al. *Dermatol Online J*. 2011;17(3):1).

More profound, Dr. Kroshinsky says, were the findings of a study which revealed that three percent of patients referred for lower-limb cellulitis actually required hospital admission (Levell NJ, Wingfield CG, Garioch JJ. *Br J Dermatol*. 2011;164(6):1326-1328. Epub 2011 May 13). Investigators managed the rest as outpatients with oral or intravenous antibiotics.

Moreover, 28 percent of study patients who had cellulitis also had underlying skin disease, such as a chronic leg ulcer or fungal infection that contributed to the development or recurrence of cellulitis, Dr. Kroshinsky says. Seeing a dermatologist allowed these patients to address the underlying skin disease, which potentially reduced the risk of future admissions, she says.

Variants defined

Cellulitis variants include perianal streptococcal infection, Dr. Kroshinsky says. “In addition to streptococcal infections,” she says, “we’re now seeing a significant proportion of staph infections in that area.”

Whereas typical cellulitis is poorly demarcated, she says, erysipelas involves a more superficial process, which leads to more lymphatic involvement and a well-demarcated area of erythema. “Erysipelas often occurs as a result of some trauma to the skin,” she says. As for periorbital and orbital cellulitis, Dr. Kroshinsky says it’s very difficult to distinguish between the two based purely on clinical inspection of the skin. However, she says, differences in demographics, symptoms and eye findings can help.

For example, research has shown that the mean age of patients with periorbital cellulitis is 21 months, versus 12 years for orbital cellulitis (Givner LB. *Pediatr Infect Dis J*. 2002;21(12):1157-1158. Review). “Periorbital cellulitis tends to be a more benign process,” she says.

Depending on which type is more likely, “The patient should have antibiotic coverage for the organisms that are the most common offenders,” Dr. Kroshinsky says.

More specifically, bacterial causes for periorbital cellulitis are relatively few (*S. aureus* and group A streptococcus in cases involving trauma; *S. pneumoniae* in cases involving bacteremia), she says, adding, “Orbital cellulitis has a greater number that must be taken into consideration.” These include *S. pneumoniae*, group A strep, nontypeable *H. influenzae*, *Moraxella catarrhalis*, *S. aureus* and anaerobes.

In diagnosing typical versus variant versus pseudo-cellulitis, taking a thorough patient history can be very helpful, Dr. Kroshinsky says. Along with the patient’s medical history, dermatologists should consider the patient’s family and social history and medication usage.

“There are diagnostic tests that can be helpful to support your suspicion, but there’s no gold standard for identifying cellulitis and confirming the causative organism,” she says.

Treating immunosuppressed patients requires one to consider a broader range of potential causative organisms (bacterial, fungal, viral, parasitic and mycobacterial), Dr. Kroshinsky says.
Q-switched solution
Certain lasers effective for treating drug-induced hyperpigmentation

By Lisa B. Samalonis
Staff Correspondent

Tucson, Ariz. — Q-switched lasers treat drug-induced hyperpigmentation caused by oral medications, including minocycline, amiodarone and Plaquenil (hydroxychloroquine sulfate; Sanofi-Aventis). Laser therapy for topical hydroquinone-induced hyperpigmentation can be more resistant to treatment, according to Gerald Goldberg, M.D., clinical professor of dermatology, University of Arizona, and in practice in Tucson, Ariz. But lasers can be effective for treating silver-induced hyperpigmentation, he says.

Quality-switched lasers provide high-energy, short nanosecond pulsing and are available in four wavelengths, including the ruby 694 nm wavelength; the alexandrite 755 nm wavelength; the 1,064 nm neodymium:YAG (Nd:YAG) infrared laser; and the 532 nm frequency-doubled, Nd:YAG laser, which gives green light at 532 nm. “The 532 nm is not used in drug-induced pigmentation cases; it is used in tattoo removal,” Dr. Goldberg says. “The three other lasers are the ones that are workhorses for removal of drug-induced hyperpigmentation.”

Oral medicines
The most common cases of drug-induced hyperpigmentation arise with minocycline, the acne antibiotic, according to Dr. Goldberg. “Typically, we see slight areas of a gray-blue hyperpigmentation that occurs on sun-exposed skin more than normal skin and it usually occurs in and around acne scars after several months of minocycline treatment,” he says.

In one recent case, a 63-year-old male patient taking minocycline for rheumatoid arthritis for many years presented at Dr. Goldberg’s office with a coal miner’s slate gray skin color (Fig. 1, 2). “There have been a number of reports of this treatment for minocycline pigment with some specific Q-switched lasers,” he says. “The one we used in this case was the Q-switched alexandrite laser. Typically, it is very responsive. There is some type of photochemical reaction that occurs, so it is an instantaneous change in the color of the skin. Literally, you see the laser pulse and the skin becomes normal as you pulse.”

Treatment was successful and the patient decided to continue on minocycline. Three years later, he returned for a one-session successful treatment, “Literally, you see the laser pulse and the skin becomes normal as you pulse.”

Gerald Goldberg, M.D.
Tucson, Ariz.

but Dr. Goldberg says the hyperpigmentation probably would not have reappeared if he had discontinued use of the medicine. While the method of action is thought to be a photochemical reaction, it is not well understood.

“It changes or disrupts the molecular configuration of the aggregated molecule in the dermis of the skin, thus

**QUICK READ**
In many cases, drug-induced hyperpigmentation can be treated with Q-switched lasers for one-session results. Other cases, such as ochronosis, take more time.

Quotable
“You’re not just treating for the moment. You’re treating for the future.”

Ranella Hirsch, M.D.
Boston

On encouraging at-home skincare regimens
See story, page 54

**DT Extra**
Carbon dioxide laser ablation could be an alternative for managing primary lentigo maligna, according to the November/December issue of Archives of Facial Plastic Surgery. Researchers from the University of Western Ontario, London, compared outcomes using surgical excision, radiation and CO₂ laser in 73 patients, ages 39 to 83 years. Median followup was at 16.6, 46.3 and 77.8 months, respectively. Recurrence rates for the modalities were 4.2, 29 and 6.7 percent, respectively.

Source: physiciansbriefing.com

**Lesion lessons**
Pulsed dye lasers effective for infantile hemangiomas

**Enhanced results**
At-home skincare regimens improve post-laser outcomes

**Hand-held help**
Home-use laser, light devices no substitute for physicians
Indication
Erivedge™ (vismodegib) capsule is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

WARNING: EMBR YO-FETAL DEATH AND SEVERE BIRTH DEFECTS
Erivedge (vismodegib) capsule can result in embryo-fetal death or severe birth defects. Erivedge is embryotoxic and teratogenic in animals. Teratogenic effects included severe midline defects, missing digits, and other irreversible malformations.
Verify pregnancy status prior to the initiation of Erivedge. Advise male and female patients of these risks. Advise female patients of the need for contraception and advise male patients of the potential risk of Erivedge exposure through semen.

Boxed Warning and Additional Important Safety Information

Embryo-Fetal Death and Severe Birth Defects
- Erivedge capsule can cause fetal harm when administered to a pregnant woman based on its mechanism of action.
- Verify pregnancy status prior to the initiation of Erivedge. Advise male and female patients of these risks. Advise female patients of the need for contraception during and after treatment and advise male patients of the potential risk of Erivedge exposure through semen.
- Advise patients to contact their healthcare provider immediately if they suspect they (or, for males, their female partner) may be pregnant.
- Immediately report exposure to Erivedge during pregnancy and encourage women who may have been exposed to Erivedge during pregnancy, either directly or through seminal fluid, to participate in the Erivedge pregnancy pharmacovigilance program by contacting the Genentech Adverse Event Line at (888) 835-2555.

Blood Donation
- Advise patients not to donate blood or blood products while receiving Erivedge and for at least 7 months after the last dose of Erivedge.

Nursing Mothers
- Inform female patients of the potential for serious adverse reactions in nursing infants from Erivedge, taking into account the importance of the drug to the mother.

Adverse Reactions
- The most common adverse reactions (≥10%) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia.
- In clinical trials, a total of 3 of 10 premenopausal women developed amenorrhea while receiving Erivedge.
- Treatment-emergent grade 3 laboratory abnormalities observed in clinical trials were hyponatremia in 6 patients (4%), hypokalemia in 2 patients (1%), and azotemia in 3 patients (2%).

Please see Brief Summary of Prescribing Information on the following page.
Table 1: Adverse Reactions Occurring in > 10% of Advanced BCC Patients

<table>
<thead>
<tr>
<th>Medication Preferred Term</th>
<th>Grade 4 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 1 (%)</th>
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</thead>
<tbody>
<tr>
<td>All BCC Patients (N = 138)</td>
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**NERVOUS SYSTEM DISORDERS**

<table>
<thead>
<tr>
<th>Disorder</th>
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</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10.3%</td>
<td>2.1%</td>
<td>0.6%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13.8%</td>
<td>2.1%</td>
<td>0.6%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>21.9%</td>
<td>3.6%</td>
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<tr>
<td>Diarrhea</td>
<td>28.0%</td>
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<tr>
<td>Fatigue</td>
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**GASTROINTESTINAL DISORDERS**

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<tr>
<td>Nausea</td>
<td>42.0%</td>
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1 INDICATIONS AND USAGE

ERIDGE (vismodegib) capsule is indicated for the treatment of adults with metastatic or locally advanced basal cell carcinoma (BCC); or with recurrent, locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are candidates for radiation.

2 USAGE AND ADMINISTRATION

The recommended dose of ERIDGE is 150 mg taken orally once daily until disease progression or until unacceptable toxicity (see Clinical Studies (14)). ERIDGE may be taken with or without food. Seawall capsules within should not be open or crushed/ broken.

If a dose of ERIDGE is missed, do not make up that dose; resume dosing at the next scheduled dose.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Death and Severe Birth Defects

ERIDGE capsules can cause fetal harm when administered to a pregnant woman or to a woman who may become pregnant (see Pregnancy Exposure to Drugs, Vismodegib, or its metabolites). Women of childbearing potential should have a negative pregnancy test prior to starting therapy. Women of childbearing potential should be advised to avoid becoming pregnant while on treatment with ERIDGE, and to use contraception while taking ERIDGE and for 4 months after treatment discontinuation. Men who are sexually active with women of childbearing potential should be advised to use effective contraception while taking ERIDGE and for 4 months after treatment discontinuation.

7.1 Effects of Other Drugs on Vismodegib

Drug interactions that affect CYP3A4 and/or CYP2C9 may increase the plasma concentrations of vismodegib. Co-administered drugs that inhibit P-gp (e.g., cephalosporins, erythromycin, azithromycin, systemic exposure to vismodegib and incidence of adverse events of ERIDGE may be increased. Drugs that affect Gastric pH

7.2 Effects of Vismodegib on Other Drugs

Results of a drug-drug interaction study in cancer patients demonstrated that the systemic exposure of rezatigib (a CYP2C8 substrate) or oral contraceptives (ethinyl estradiol and norethindrone) is not altered when co-administered with vismodegib. In vitro studies indicate that vismodegib is an inhibitor of CYP2C8, CYP2C9, CYP2B6 and CYP3A4. Vismodegib does not induce CYP1A2, CYP2C8, or CYP3A4 in human liver (see table 1). 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

ERIDGE capsules can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Vismodegib is teratogenic in rats at doses corresponding to an exposure of 20% of the recommended human dose (estimated AUC0-24h, steady-state exposure). In rats, maternities included atrial restraints, open peritoneum, and absent or fused digits. Fetal abnormalities and variations were also observed. Vismodegib is embryotoxic in rats at exposure within the range achieved at the recommended human dose. If ERIDGE is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the embryo or fetus. Report immediately exposure to ERIDGE during pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may have been exposed to ERIDGE during pregnancy, either directly or through seminal fluid, to participate in the ERIDGE pregnancy pharmacovigilance program by contacting the Genentech Adverse Event Line at 1-888-835-2555 (see boxed Warning, Warnings and Precautions (5)).

In an embryo-fetal developmental toxicity study, pregnant rats were administered oral vismodegib at doses of 10, 60, or 300 mg/kg/day during the period of organogenesis (day 6 through day 17 of gestation). Oral and intraperitoneal administration of 300 mg/kg/day (approximately = 2 times the systemic exposure [AUC] in patients on the post-marketing human study), which included early receipt of 10% of the fetuses. A dose of 10 mg/kg/day (approximately = 0.4 times the systemic exposure [AUC] in patients on the post-marketing human study) resulted in maternities including (missing and/or fused digits, open peritoneum and craniofacial anomalies) and retardations or variations (including reduced renal pelvis, sternal uncalcified and incompletely or unskeletonized sternal elements, central of vertebral, or proximal phalanges and clefts).

8.3 Nursing Mothers

It is not known whether vismodegib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ERIDGE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of ERIDGE capsules have not been established in pediatric patients.

In repeat-dose toxicity studies in rats, administration of oral vismodegib resulted in toxicity in bone and teeth. Effects on bone consisted of closure of the epiphyseal growth plate when oral vismodegib was administered for 26 weeks at 30 mg/kg/day (approximately = 0.4 times the systemic exposure [AUC] in rats at the recommended human dose). Abnormalities in growing incisor teeth (including degeneration/ necrosis of odontoblasts, formation of dental lacunae, and root resorption in the root apex of the incisors) and sequestration and/or nuclear disintegration in bone marrow lymphocytes were observed in rats administered oral vismodegib at 15 mg/kg/day (approximately = 0.2 times the AUC in rats at the recommended human dose).

17 PREVENTION COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

• Advise patients that ERIDGE exposure during pregnancy can cause embryo-fetal death or severe birth defects.
• Instruct female patients of reproductive potential to use a highly effective method of contraception while taking ERIDGE and for at least 7 months after the last dose of ERIDGE.
• Instruct all male patients, even those with prior vasectomy, to use barrier methods with spermicides while taking ERIDGE and for at least 7 months after the last dose of ERIDGE.
• Instruct patients to immediately contact their healthcare provider if they (or, for males, their female partner) become pregnant while taking ERIDGE. Request immediate exposure to ERIDGE during pregnancy to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may have been exposed to ERIDGE during pregnancy, either directly or through seminal fluid, to participate in the ERIDGE pregnancy pharmacovigilance program by contacting the Genentech Adverse Event Line at 1-888-835-2555 (see boxed Warning, Warnings and Precautions (5)).

Informed women of the potential for serious adverse reactions in nursing infants from ERIDGE, taking into account the importance of the drug to the mother.

• Advise patients not to donate blood or blood products while taking ERIDGE, because ERIDGE could be present in blood or blood products.

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Q-switched from page 48

producing an immediate color change. It happens instantly,” Dr. Goldberg says.

The oral antiarrhythmic amiodarone is another popular medication that causes drug-induced hyperpigmentation. There have been several reports in the literature in which a Q-switched ruby laser was used to treat this type of hyperpigmentation, Dr. Goldberg says. Treatment is probably effective with any of the three Q-switched lasers.

Plaquenil, an oral antimalarial also used in various rheumatologic disorders (including lupus of the skin), often gives patients the blue-grayish discoloration from the pigment that deposits in the skin. “Plaquenil hyperpigmentation is also responsive to a variety of the Q-switched lasers,” he says.

Topical medicine

Topically applied medication hydroquinone, which is used commonly to bleach brown spots, can cause ochronosis. In a small numbers of patients, particularly dark-skinned patients, tiny 0.5 mm to 1 mm punctate or dark grey-blue hyperpigmentation results.

“I have a patient under treatment and this has been remarkably resistant, as opposed to the other three drug-induced pigmentation types of cases. In my experience, this is very difficult to treat. I would go with the longer of the Q-switched wavelengths, i.e., 1,064 nm or the Q-switched 755 nm typically, because it is a deeper deposit and it is difficult to disrupt. I am trying to disrupt it with a combination of the Q-switched laser in addition to a fractional CO₂ laser as well,” he says.

A recent report¹ showed treatment using those combine modalities. “It was partially successful, and that has been my experience. In resistant pigment problems with the Q-switched laser, the next step is to add concurrently at the same session a fractional CO₂ laser to try and break the pigment up with CO₂ laser treatment,” Dr. Goldberg says.

Silver-induced discoloration

Silver is a popular alternative therapy, Dr. Goldberg says. Pulses from any of the three Q-switched lasers — ruby, alexandrite and 1,064 nm — work successfully to remove silver pigment, typically in one session, he says. The pigment is often deposited in or around eccrine sweat glands.

In one recent case involving a female patient with silver-induced hyperpigmentation, Dr. Goldberg chose the 1,064 nm laser because it left the least injury to the skin’s surface (Fig. 3, 4).

“Treatment causes an instantaneous photochemical reaction, perhaps changing the molecule from a silver sulfide (dark) to sulfate (light). That chemical change creates the color change that is instantaneous. This high-heat-powered, nanosecond-pulsed laser creates that disruption and oxidizes the particles,” he says.

Dr. Goldberg says the patient has stopped ingesting silver, and he will follow to see if discoloration will reappear with sun exposure. DT

Disclosures: Dr. Goldberg reports no relevant financial interests.

References:

(Fig. 1, 2) A 65-year-old male patient who had taken minocycline for 25 years, and presented with hyperpigmentation before (left) and two years after a single treatment.

(Fig. 3, 4) A female patient who had ingested soluble silver for three years, before (left) and immediately after test with three laser types — Q-switched ruby, alexandrite, and Nd:YAG, then after single pass treatment of entire face, accomplished in three “staged” Rx sessions. (Photos: Gerald Goldberg, M.D.)
Lessening lesions
Pulsed dye laser used as monotherapy, adjunct to propranolol for hemangiomas

By Louise Gagnon
Staff Correspondent

San Diego — The pulsed dye laser is being used as monotherapy or as an adjunct to propranolol in the treatment of infantile hemangiomas, and clinicians are contemplating the use of the CO₂ fractionated laser to treat residual scars and textural changes.

While propranolol is not indicated to treat infantile hemangiomas, it is becoming more commonly administered because of its efficacy, according to Lawrence Eichenfield, M.D., F.A.A.D., chief of pediatric and adolescent dermatology, Rady Children’s Hospital, San Diego, and at the University of California, San Diego (UCSD) School of Medicine, and professor of pediatrics and medicine at UCSD.

Patients can have a good clinical response to propranolol therapy, but then attempts to wean them off the therapy are not successful, and laser therapy can be a benefit in those situations, he says.

"With attempts to wean propranolol either before the first year of life or after the first year of life we often see rebound," he says. "In many cases, we will initiate laser treatment either prior to the weaning of propranolol or at the first signs of rebound to try to retain the positive effects of propranolol."

Laser effects
With the evolving use of fractionated CO₂ lasers for improvement of scars, clinicians may look to this modality to diminish remnant scars after hemangiomas have involuted, Dr. Eichenfield says.

"This modality can impact textural changes and minimize the remnant deformity," he says, noting his center is looking at the utility of the CO₂, fractionated laser to minimize scars left after oral propranolol treatment of hemangiomas.

The pulsed dye laser can be a great asset in treating remnant superficial redness and telangiectasia, Dr. Eichenfield says, noting that in some instances the pulsed dye laser “cleans up” the superficial hemangioma remnants after propranolol.

"We still find it useful in our armamentarium for hemangiomas," he says.

Systemic glucocorticoids had been the mainstay of treatment for infantile hemangiomas before clinicians observed a rapid and successful response with propranolol, Dr. Eichenfield says, describing propranolol as very effective in the early treatment of hemangiomas, minimizing the proliferation of hemangiomas, and in later stages, inducing involution.

"We still find lasers can be very helpful in multimodal management," Dr. Eichenfield says. "Very commonly, we will have patients with large facial hemangiomas who will initiate pulsed dye laser treatment several months into their systemic therapy course, allowing for earlier involution of the superficial portion of the hemangiomas."

Unanswered questions
While there are a plethora of articles now describing successful treatment of hemangiomas with propranolol in the medical literature, there remain many unanswered questions with respect to the use of propranolol, Dr. Eichenfield says.

"Many specialists have protocols that they use, but we don't really know how to optimally use this medicine in individual cases, nor how much, how long, and when to stop propranolol use," he says. "We find it incredibly useful to use a multimodal therapeutic model. There is still a place for the pulsed dye laser, there is a still a place for intralesional injections of steroids, and there is still a place for surgical excision in the management of hemangiomas."

“In many cases, we will initiate laser treatment either prior to the weaning of propranolol or at the first signs of rebound.”

Lawrence Eichenfield, M.D.
San Diego

French clinicians first published results of their success with using propranolol to inhibit the growth of infantile hemangiomas in 2008. Since then, the use of propranolol

Lesions see page 58
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**Significant improvement in reduction of acne lesions**

![Graph showing improvement in reduction of acne lesions](image)

[2] Protocol: A 12-week dermatologist controlled, multi-center study; double blind clinical trial to evaluate safety and efficacy of two acne creams in subjects with mild to moderate acne vulgaris. 61 patients, ages 18-50, multi-ethnic skin, all skin types. 2 cell study: Cell 1, 27 patients, [EFFACLAR DUO+] 0.025% Topical Retinoid vs. Cell 2, 34 patients, [leading topical Benzoyl peroxide prescription] + 0.025% Topical Retinoid. Results measured at mean % change from baseline at 12 weeks of use. Application of topical retinoid applied once a day in PM and application of Effaclar DUO or a leading topical prescription Benzoyl peroxide twice a day. Inclusion criteria: ≥ 15 inflammatory lesions and ≥ 20 non-inflammatory lesions.
Fully engaged
Laser procedure results enhanced with at-home topical skincare regimens

By Diane Donofrio Angelucci
Staff Correspondent

Boston — Combining home-care regimens with office laser procedures helps dermatologists achieve better results when targeting almost any skin problem, says Ranella Hirsch, M.D., clinical assistant professor of dermatology, Boston University School of Medicine.

Not only do patients benefit from the laser treatment, the home-care regimen can offer an “extra oomph,” Dr. Hirsch says.

Furthermore, prescribing a skincare regimen engages patients in their own treatment so they become vested in their own care.

“I’m a huge believer that patients do much better when they’re engaged in the process,” she says.

Dr. Hirsch explains that she loves the analogy she learned from an extraordinary colleague, New Orleans dermatologist Mary Lupo, M.D., who likened the relationship between a dermatologist and a patient to that of a trainer and an athlete.

“We’re kind of like a trainer where we can really evoke great things from the athlete, but there’s really still a lot of the homework to be done by them,” Dr. Hirsch says. “They have to still go and do the work.”

Patients vested in their own skincare and skin health are more apt to adhere to routines that will improve results, such as remaining moisturized and applying sunblock, Dr. Hirsch says.

**Broad benefits**
Dr. Hirsch prescribes a complementary topical regimen for almost every office laser treatment she performs. Sunscreen is a requirement across the board.

For example, Dr. Hirsch says she frequently prescribes Vaniqa cream (eflornithine hydrochloride, SkinMedica) after laser hair-removal treatments.

“So you get this double benefit of the product working through its mechanism and also the laser procedure working through its mechanism,” Dr. Hirsch says. “People get better results, are more engaged, and have a better outcome.”

After performing a nonablative laser treatment in the office, she often prescribes a prescription-strength or over-the-counter topical retinoid to be used at home. For patients treated for brown spots or motting, she prescribes a bleaching agent for use at home. When treating acne with light treatments, Dr. Hirsch also prescribes topical treatments.

In addition to involving patients in their treatment outcomes, combining treatments sets the stage for the concept of skincare maintenance, because most laser skincare procedures require a series of treatments, Dr. Hirsch says.

“That is a really great way to sort of set them up with this idea that there’s two parts to it. There’s what we do in the office and then also what’s done as maintenance,” she says.

**Laying the groundwork**
Dr. Hirsch emphasizes the value of beginning skincare treatment regimens before the laser procedure. For example, she prescribes patients a regimen for a month or two before a procedure such as a fractional resurfacing. This not only helps prepare the skin, it also enables her to gauge how well the patient will comply with treatment guidelines, she says.

“If I say, ‘You need to do this every day and apply sunblock every day,’ and they come to me and they are clearly not following that advice, this is something I want to know before I do a major procedure on them,” Dr. Hirsch says.

It’s best to know that a patient will be noncompliant prior to the procedure, Dr. Hirsch says, because compliance is critical in woundcare after a resurfacing treatment.

“You don’t want to find out after-
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Help at hand

At-home laser, light devices won’t replace dermatologic expertise, clinician says

By Lisette Hilton
Staff Correspondent

Omaha, Neb. — The public seems to have a growing fascination with at-home hand-held laser and light devices, as dermatologists try to figure out how and if these products fit into practice, says Joel Schlessinger, M.D.

Dr. Schlessinger, a dermatologist in Omaha, Neb., and director of the Cosmetic Surgery Forum conference, spoke on the topic of hand-held devices at the 2011 Forum in Las Vegas. While available at-home options for hair removal and skin rejuvenation encroach in dermatologists’ fee-for-service offerings, he says, the devices are not strong enough to replace what dermatologists do.

“I think that the hand-held devices are training wheels for people looking to get into these types of treatments. Despite the initial concerns that they would be competitors, I think they are going to be a first step on people’s roads to having a more intense cosmetic experience with the dermatologist,” Dr. Schlessinger says.

What’s out there

There are several hair-removal devices on the market, according to Dr. Schlessinger. Among the more popular are no/no! (Radiancy), a thermal filament device, and Silk’n SensEpil (Home Skinovations), which uses pulsed light.

“The thermal filament device ends up burning or singeing the hair. And that’s not actually even a laser device, but many people mistakenly believe it is based on the company’s promotions,” Dr. Schlessinger says.

While users can treat a small body area, to use today’s hair-removal devices on a large area, such as the leg, would be time-prohibitive, he says.

A hand-held device, the PalOVia Skin Renewing Laser (Palomar Medical) shows more promise in the area of wrinkle reduction, according to Dr. Schlessinger. The device delivers low-level laser energy to the periorcular area.

“PalOVia has a benefit from the standpoint that it is a true diode laser, with the ability for some of that laser energy to actually reach into the skin and penetrate,” he says.

Cleared by the Food and Drug Administration, PalOVia is an at-home laser proven to reduce fine lines and wrinkles around the eyes. PalOVia delivers 250 microns coagulation and 15 mJ. It also has an elaborate safety system, Dr. Schlessinger says, which keeps it from damaging the eye.

Red light, blue light

Another category of products for at-home users is blue light and red light devices. Among those: the Baby Quasar (Quasar Bio Tech), with a red light technology for wrinkles and blue light for acne, as well as the Tanda Luxe (Syneron), which uses LED light to rejuvenate skin.

Dr. Schlessinger questions whether red light devices can make a notice-
Lesions from page 52

has become very prevalent in the pediatric setting to treat infantile hemangiomas, according to Dr. Eichenfield.

"Propranolol has revolutionized the treatment of infantile hemangiomas," Dr. Eichenfield says. "For most hemangiomas that require systemic therapy, my sense is that there is much more propranolol being used than glucocorticoids."

Since infants cannot communicate symptoms that suggest any of the potential adverse events that can occur with propranolol, it is necessary that clinicians pay careful attention to the emergency of any side effects, he says.

Because of the possibility of adverse events such as hypotension, hypoglycemia and bradycardia, clinicians are careful when treating younger infants. For instance, at Rady Children’s Hospital, those infants under 3 months of age are hospitalized, and are carefully monitored during a rapid escalation of propranolol dosing. For infants older than 3 months, they are typically treated on an outpatient basis, with a slower escalation of the drug therapy.

At his center, Dr. Eichenfield says hypotension is more common in younger infants and formerly premature infants.

Early referral is key in minimizing deformity and functional impact of hemangiomas, which are proliferative tumors, for clinical response is more probable with less tumor than more tumor, Dr. Eichenfield says.

A large international study led by Pierre-Fabre aimed at providing answers to optimize the management of infantile hemangiomas with oral propranolol is underway. Infants are being treated with 1 mg/kg or 3 mg/kg per day of propranolol.

Disclosures: Dr. Eichenfield has served as an investigator for Pierre-Fabre, without compensation.

Engaged from page 54

wards the patient doesn’t listen to you,” she says.

Doctor-patient partnership

Everyone wins when dermatologists prescribe an at-home skincare regimen and the patient and physician work together, Dr. Hirsch says.

"I think you get this brilliant synergy when they work together that’s really very, very beneficial.”

Prescribing at-home skincare regimens differentiates dermatologists in a competitive skincare environment.

Dr. Hirsch says. “And you just set these great habits for patients going forward, which I think have real benefit as well.”

“It really lets you stand ahead of the crowd because you’re going to

“You’re going to give someone not just acne treatment with light, but also a prescription strength that’s going to help them.”

Ranella Hirsch, M.D.
Boston

Furthermore, prescribing at-home skincare regimens differentiates dermatologists in a competitive skincare environment where non-dermatologists also provide laser treatments.

“One of the real things we can bring to the table that’s so cogent as dermatologists is the ability to really buffer and supplement what we’re doing with technology with some of the medications and other techniques that we have in home care and skincare,” she says.

Skincare regimens offer dermatologists a distinctive tool.

give someone not just acne treatment with light, but also a prescription strength that’s going to help them,” Dr. Hirsch says. “So you’re not just treating for the moment. You’re treating for the future. You’re treating for prevention.”

Disclosures: Dr. Hirsch reports no relevant financial interests.
urge for people to cleanse themselves better, and this allows them to do that safely without abrading and causing actual damage from their activity.”

Light at the end of the tunnel
Dr. Schlessinger equates the outcomes patients can expect with cosmeceuticals to be similar with what they get from some of these devices. Many of the devices cost between $250 and $500. The cleansing devices tend to cost less. As to whether dermatologists should be concerned about this trend, Dr. Schlessinger says probably not.

“I think if they get to a level that is effective, it might keep them from being approved by the FDA,” he says.

For a slideshow on this by Dr. Schlessinger, please visit: http://www.slideshare.net/drjoelschlessinger. DT

Disclosures: Dr. Schlessinger sells many at-home devices through his practice, including Clarisonic, PaloVia and Neova products. Dr. Schlessinger is a researcher for Galderma and owner of LovelySkin.com.
Lightening and tightening
Products that tackle pigmentation, smooth wrinkles have benefits, drawbacks

What is the most effective ingredient for pigment lightening?

Undoubtedly, the most effective ingredient for pigment lightening is hydroquinone, but hydroquinone is a highly unstable radical capable of producing reactive oxygen species and destroying melanocytes.

Some of the efficacy attributed to hydroquinone is not from interference with tyrosinase, but rather from melanocyte destruction, accounting for the controversy surrounding its incorporation into formulations that have not passed through investigational new drug (IND) Food and Drug Administration pathways. Hydroquinone is converted in the presence of oxygen to melanocyte toxic p-benzoquinone and hydroxybenzoquinone.

Probably the second most effective pigment lightening substance is kojic acid, found in many cosmeceutical formulations. It is used in low concentration because it can be a skin irritant. It is a hydrophilic fungal derivative found in Acetobacter, Aspergillus and Penicillium species, but most kojic acid used in cosmeceutical formulations is mushroom-derived. It functions by binding to copper, a necessary cofactor in the functioning of tyrosinase. In some cosmeceutical formulations, it is combined with glycolic acid as a penetration enhancer to allow the kojic acid access to the viable skin layers where pigmentation can be affected below the stratum corneum.

Kojic acid is usually combined with other pigment lightening ingredients for optimal efficacy. One popular formulation pairs kojic acid with emblica, also known as Indian Gooseberry. Emblica extract is high in vitamin C, tannins, kaempferol, ellagic acid and gallic acid. It is the tannins that inhibit melanogenesis in human melanocyte cultures, while the kaempferol, ellagic acid and gallic acid function as antioxidants. Rarely is one pigment lightening agent used in cosmeceutical formulations, as many lower-concentration pigment lightening ingredients produce fewer side effects than one pigment lightening ingredient used in high concentration.
It is the frequent combination of many skin lightening ingredients that makes it hard to determine which constituent is the most effective. Many companies that manufacture over-the-counter pigment lighteners offer combinations to cosmeceutical producers, making it very difficult to test individual components.

Over time, water evaporates from the hyaluronic acid to the atmosphere ... and the remaining material turns white and flakes from the face in small pieces.

Q How do the wrinkle-reducing, skin-tightening creams that promise results in 15 minutes work?

A It is astounding, and somewhat unbelievable, that any cosmetic product could produce immediate wrinkle reduction, yet it is, in fact, possible with some of the new small-particle hyaluronic acid products.

Hyaluronic acid is well known to the cosmetic dermatologist as a safe and versatile injectable filler that absorbs water when injected into and beneath the dermis. Hyaluronic acid can also be applied topically with much the same effect. Small spheres of hyaluronic acid can be rubbed into the wrinkles around the eyes and deposited at the base of the wrinkle. Here, the sphure can absorb water and physically fill in the wrinkle, creating a smooth surface (much like wood filler can be used to smooth the irregularities in porous wood). These spheres create the illusion of a smooth surface by externally filling in the skin folds, and they can instantly improve wrinkles to the eyes of the observer.

Unfortunately, over time, water evaporates from the hyaluronic acid to the atmosphere, especially under low-humidity conditions, and the remaining material turns white and flakes from the face in small pieces. This has been a common complaint of many consumers who use these products around the eyes. While the immediate effect is quite amazing, the long-term effect is undesirable. As the water evaporates, however, a tightening feeling occurs, which many consumers associate with a decrease in wrinkles. But the flaking effect soon causes problems with the appearance of other facial cosmetics. Many hyaluronic acid products are now sold with a sodium PCA mist that is sprayed over the face to counteract this effect. DT
light on lasers

Dermatology Associates, Joely Kaufman, M.D., practices at Dr. Brandt Dermatology Associates, Coral Gables, Fla., and is a voluntary assistant professor, University of Miami Department of Dermatology & Cutaneous Surgery.

Jeremy B. Green, M.D., practices at Dr. Brandt Dermatology Associates, Coral Gables, Fla., and is a voluntary assistant professor, University of Miami Department of Dermatology & Cutaneous Surgery.

Long and short of it
Long-pulsed 1,064 nm Nd:YAG lasers effective in vein, PWS, other treatments

The 1,064 nm neodymium:YAG (Nd:YAG) laser can be used with a range of pulse widths depending on the clinical target. Last month, we reviewed short-pulsed Nd:YAG systems for indications such as pigmentation, tattoo removal and photorejuvenation. This month, we will examine the uses for long-pulsed Nd:YAG devices, including leg veins and other deep vascular lesions, laser hair removal and laser-assisted liposuction.

The long-pulsed 1,064 nm Nd:YAG laser affords greater depth of penetration than its shorter wavelength and shorter pulse-width counterparts, reaching 5 mm to 10 mm depth when used with epidermal cooling. The invisible 1,064 nm light is 100 times less well absorbed by oxyhemoglobin than the 595 nm yellow light emitted by the pulsed dye laser (Baumler W, Ulrich H, Hartl A, et al. Br J Dermatol. 2006;155(2):364-371). Therefore, higher fluences must be employed with the Nd:YAG than with the pulsed dye laser (PDL) for vascular targets.

Additionally, 1,064 nm infrared light is approximately 10 times more readily absorbed by oxyhemoglobin than by water, the primary chromophore in the dermis. Therefore, selective photo-thermolysis is possible, but 1,064 nm Nd:YAG treatments are less selective than treatments with shorter wavelength visible-light lasers for vascular structures.

The higher fluences and reduced selectivity require that laser practitioners employ the long-pulsed Nd:YAG with caution due to the potential for collateral thermal spread. However, the greater depth of penetration facilitates treatment of deeper lesions that cannot be targeted by the shorter wavelength vascular lasers.

Leg veins
Lower-extremity vascular lesions, including spider veins and varicosities, are a frequent complaint of approximately 40 percent of women. Though the very superficial leg telangiectasias (less than 1 mm) do respond somewhat to the shorter-wavelength vascular lasers in lighter skin types, most leg veins are too large or too deep for these devices.

The long-pulsed 1,064 nm Nd:YAG laser affords greater depth of penetration than its shorter wavelength and shorter pulse-width counterparts.

A comparison of the 532 nm potassium titanyl phosphate (KTP) laser to the long-pulsed 1,064 nm Nd:YAG for leg veins showed that the Nd:YAG outperformed the KTP for all vessel sizes. The KTP was effective for vessels less than 1 mm, but it was not useful in vessels larger than 1 mm (Özden MG, Bahçivan M, Aydin F, et al. J Dermatol Treat. 2011; 22(3):162-166).


Most blue vessels will need to be treated with a deeper-wavelength vascular device, such as the 1,064 nm Nd:YAG. Optimal pulse durations and spot sizes will vary by vessel diameter.

The Nd:YAG heats the vessel more uniformly than the shorter-wavelength 532 nm laser. This even heating allows for more successful vessel closure, yet due to its lower affinity for hemoglobin, the Nd:YAG will need to be used at much higher fluences than the KTP laser (Ross EV, Domankiewitz Y. Lasers Surg Med. 2005;36(2):105-116).

Pulse durations range typically between 10 ms and 100 ms, with short pulse durations (less than 20 ms) causing more purpura and potential for postinflammatory pigmentation alteration (Baumler W, Ulrich H, Hartl A, et al. Br J Dermatol. 2006;155(2):364-371). Shorter pulse durations (less than 40 ms) are often required to close smaller vessels, whereas longer pulse durations are used for larger vessels. Longer pulse durations are safer for darker skin types, as they decrease the potential for damage to the epidermis.

Larger beam diameter can also increase the depth of penetration of the laser and can be useful in deeper vessels. Larger spot sizes are more painful, however. Cooling is critical for epidermal protection in the treatment of leg veins with the Nd:YAG, as high fluences are needed to effectively induce thermal damage to the vessel walls.


Perinasal telangiectasias
Lee et al treated 12 patients who had resistant nasal telangiectasias, defined as patients who had four or
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light on lasers from page 62

more (average 5.8) treatments with the PDL or intense pulsed light without success (Lee JH, et al. J Eur Acad Dermatol Venereol. 2011). They found a 78.3 percent total clearance of vessels after a single Nd:YAG laser treatment.

Vascular ectasia of the lip are frequently seen in the elderly.

One patient experienced vesicle formation and postinflammatory hyperpigmentation due to inadvertent pulse stacking. In contrast to 532 nm or 595 nm lasers, pulse stacking should not be employed for 1,064 nm treatment of facial telangiectasias due to the risk of overheating the vessels and surrounding dermis.

Port wine stains

Port wine stains generally begin as flat purple or red vascular lesions of 30 microns to 150 microns in diameter, but over time they eventually progress to thickened, hypertrophic plaques. Usually, port wine stains and hemangiomas are initially treated with the short-pulse-width vascular lasers, including the 532 nm KTP and the 585/595 nm pulsed dye lasers (Dierickx CC, Casparian JM, Venugopalan V, et al. J Invest Dermatol. 1995;105:708-714). There are many times, however, when these lesions do not clear completely, and sometimes they hardly lighten at all. These treatment-resistant lesions are thought to be the result of the inability of the shorter wavelength lasers to reach the deeper components of the lesion.

Though less well absorbed by hemoglobin, the Nd:YAG offers deeper penetration into the tissue, allowing for effective treatment of “resistant” vascular lesions. Port wine stains on the extremities or the perioral areas are often resistant to short-wavelength vascular lasers, and they often require therapy with an Nd:YAG laser (Kono T, Groff WF, Chan HH, et at. J Cosmet Laser Ther. 2009; 11(1):11-13).

A recent report of four cases highlighted the effectiveness of the Nd:YAG for blebbed port wine stains recalcitrant to pulsed dye laser (Chang HS, Kim YG, Lee JH. Ann Dermatol, 2011;23(supp 1):S75-S78). All patients displayed significant improvement of the blebbed portion of the port wine stain with one to three sessions of a contact-cooling 1,064 nm laser at 130J/cm², 6 mm spot and 30 ms.

Venous lake

Vascular ectasia of the lip are frequently seen in the elderly.

Though mainly a cosmetic issue, some lesions may bleed with trauma. Failure of the shorter wavelength vascular lasers to consistently resolve venous lakes has been documented (Cheung ST, Lanigan SW. Clin Exp Dermatol. 2007;32(4):381-384). The long-pulsed 1,064 nm laser with epidermal cooling is a valid option for treatment of venous lakes.

Bekhor reported a 94 percent complete clearance rate on a series of 34 venous lakes treated with a long-pulse-width Nd:YAG laser (5 mm/140 J/cm²/55 ms). For venous lakes, the long-pulsed Nd:YAG is the laser of choice.

Laser-assisted lipo

The long-pulsed Nd:YAG was cleared for use in laser-assisted liposuction in late 2006. The purported benefits for Nd:YAG during liposuction include additional fat disruption and collagen induction with tissue tightening.

One split-abdomen study examined the degree of skin tightening following liposuction alone versus laser-assisted liposuction. In the 10 patients treated, the author found more skin “shrinkage” at both one and three months post-procedure on the laser-assisted liposuction side (DiBernardo BE. Aesthet Surg J. 2010;30(4):S93-602). The response of fat and subcutaneous tissues to infrared lasers is secondary to the thermal effects on the tissues themselves.

All lasers with wavelengths between 900 and 1,320 nm are able to produce controlled thermal injury to the subcutaneous tissues in order to induce lipolysis and skin contraction (Wassmer B, Zemmour J, Rochon P, Mordon S. Photomed Laser Surg. 2010;28(2):185-188). The exception is the 1,444 nm Nd:YAG, which in porcine and in vitro human fat.

light on lasers see page 67
THE SKIN BARRIER OF ROSACEA PATIENTS IS COMPROMISED

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- Rosacea sufferers surveyed prefer the pump over the tube (69\% vs 31\%; \(N=207\))\(^{2,1}\)

MetroGel\textsuperscript{\textregistered} (metronidazole) Gel, 1\% is indicated for the topical treatment of inflammatory lesions of rosacea.

Important Safety Information

The following adverse experiences have been reported with the topical use of metronidazole: nasopharyngitis, upper respiratory tract infections and headache. Patients may also experience local burning, skin irritation, dryness and transient redness. Although rare, patients may also experience metallic taste, numbness or paresthesia at the extremities and nausea with use of MetroGel\textsuperscript{\textregistered} 1\%, and peripheral neuropathy has been reported with use of metronidazole. MetroGel\textsuperscript{\textregistered} 1\% therapy should be reevaluated if these symptoms occur. Caution should be used when prescribing metronidazole products for patients with blood dyscrasia, and patients using blood thinning agents such as coumarin or warfarin may experience prolonged prothrombin times. MetroGel\textsuperscript{\textregistered} 1\% is contraindicated in patients with a history of hypersensitivity to metronidazole or any other ingredient in the formulation.

Please see next page for brief summary of full prescribing information.

*MetroGel\textsuperscript{\textregistered} 1\% does not further damage the already compromised skin barrier of rosacea patients.

\(^{1}\) Claims are based on a Consumer Preference Study of 207 physician-diagnosed. male and female rosacea patients aged 25 to 60 years. Patients were asked to complete a self-administered Internet survey following video presentations highlighting the steps involved when applying medication from a pump and a tube.

\(^{2}\) Data on file. Galderma Laboratories, L.P.


**MetroGel and Galderma are registered trademarks.©2011 Galderma Laboratories, L.P. Galderma Laboratories, L.P. 1450 N. Freeway Fort Worth, TX 76177 MC1648 Printed in USA 11/11**
METROGEL® (metronidazole) Gel, 1% \[Rx Only\]

For topical use only.

Not for oral, ophthalmic or intravaginal use.

Talk to your doctor or pharmacist to learn more about METROGEL. You can also learn more at www.metrogel.com.

**BRIEF SUMMARY**

**INDICATIONS AND USAGE**

METROGEL® (metronidazole) Gel, 1% is a nitromidazole indicated for the topical treatment of inflammatory lesions of rosacea.

**CONTRAINDICATIONS**

METROGEL is contraindicated in those patients with a history of hypersensitivity to metronidazole or to any other ingredient in this formulation.

**WARNINGS AND PRECAUTIONS**

- Peripheral neuropathy, characterized by numbness or paresthesia of an extremity, has been reported in patients treated with systemic metronidazole. Although not evident in clinical trials for topical metronidazole, peripheral neuropathy has been reported with the post approval use. The appearance of abnormal neurologic signs should prompt immediate reevaluation of METROGEL therapy.
- Metronidazole is a nitromidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia.
- If dermatitis occurs, patients may need to discontinue use.
- Topical metronidazole has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided.

**ADVERSE REACTIONS**

Most common adverse reactions (incidence >2%) are nasopharyngitis, upper respiratory tract infection, and headache.

In a controlled clinical trial, 557 patients used metronidazole gel, 1% and 189 patients used the gel vehicle once daily for up to 10 weeks. The following table summarizes adverse reactions that occurred at a rate of ≥1%.

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>Metronidazole Gel, 1%</th>
<th>Gel Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one AE</td>
<td>N=557</td>
<td>N=189</td>
</tr>
<tr>
<td>Number (% of Patients)</td>
<td>186 (33.4)</td>
<td>51 (27.0)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>76 (13.8)</td>
<td>26 (14.3)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (1.1)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Influenza</td>
<td>6 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (2.3)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>8 (1.4)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14 (2.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vaginal mycotic</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>19 (3.4)</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (0.5)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>4 (0.7)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>18 (3.2)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (2.2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>22 (3.9)</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>6 (1.1)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>38 (6.5)</td>
<td>12 (6.3)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>7 (1.3)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (1.1)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>8 (1.4)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (1.1)</td>
<td>3 (1.6)</td>
</tr>
</tbody>
</table>

Table 2: Local Cutaneous Signs and Symptoms of Irritation That Were Worse Than Baseline

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Metronidazole Gel, 1%</th>
<th>Gel Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dryness</td>
<td>139 (23.4)</td>
<td>63 (34.2)</td>
</tr>
<tr>
<td>Mild</td>
<td>93 (16.7)</td>
<td>44 (23.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>47 (8.2)</td>
<td>20 (10.3)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (0.6)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Scaling</td>
<td>134 (23.6)</td>
<td>60 (32.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>88 (15.2)</td>
<td>32 (17.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>43 (7.9)</td>
<td>21 (11.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (0.6)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>86 (15.8)</td>
<td>35 (19.3)</td>
</tr>
<tr>
<td>Mild</td>
<td>53 (9.5)</td>
<td>21 (11.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>22 (4.0)</td>
<td>13 (7.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>6 (1.1)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Stinging/burning</td>
<td>56 (10.3)</td>
<td>26 (14.3)</td>
</tr>
<tr>
<td>Mild</td>
<td>39 (7.2)</td>
<td>18 (9.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7 (1.3)</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>10 (1.8)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

The following additional adverse experiences have been reported with the topical use of metronidazole: skin irritation, transient redness, metallic taste, tingling or numbness of extremities, and nausea.

**Post Marketing Experience**

The following adverse reaction has been identified during post approval use of topical metronidazole: peripheral neuropathy. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

**DRUG INTERACTIONS**

Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin, resulting in a prolongation of prothrombin time. Drug interactions should be kept in mind when METROGEL is prescribed for patients who are receiving anticoagulant treatment. Although the risk is less likely to occur with topical metronidazole administration because of low absorption.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Teratogenic Effects:** Pregnancy Category B.

There are no adequate and well-controlled studies with the use of METROGEL in pregnant women. Metronidazole crosses the placent and enter the fetal circulation rapidly. No fetotoxicity was observed after oral administration of metronidazole in rats or mice at 200 and 20 times, respectively, the expected clinical dose. However, oral metronidazole has been shown carcinogenic activity in rodents. Because animal reproduction studies are not always predictive of human response, METROGEL should be used during pregnancy only if clearly needed.

**Nursing Mothers**

After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels taken after topical metronidazole applications are significantly lower than those achieved after oral metronidazole a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the risk to the infant.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Sixty-six subjects aged 65 years and older were treated with metronidazole gel, 1% in the clinical study. 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 to the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats, but not in studies involving hamsters.

In several long-term studies in mice, oral doses of approximately 225 mg/kg/day or greater (approximately 37 times the human topical dose on a mg/kg basis) were associated with an increase in pulmonary tumors and lymphomas. Several long-term oral studies in the rat have shown statistically significant increases in mammary and hepatic tumors at doses >365 mg/kg/day (144 times the human dose).

Metronidazole has shown evidence of mutagenic activity in several in vitro bacterial assay systems. In addition, a dose-related increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosomal aberrations in peripheral blood lymphocytes was reported in patients with Crohn’s disease who were treated with 200 to 1000 mg/day of metronidazole for 1 to 24 months. However, in another study, no increase in chromosomal aberrations in circulating lymphocytes was observed in patients with Crohn’s disease treated with the drug for 6 months.

In one published study, using albino hairless mice, intraperitoneal administration of metronidazole at a dose of 45 mg/kg/day (approximately 7 times the human topical dose on a mg/kg basis) was associated with an increase in ultraviolet radiation-induced skin carcinogenesis. Neither dermal carcinogenicity nor phototoxicity studies have been performed with METROGEL or any marketed metronidazole formulations.

**PATIENT COUNSELING INFORMATION**

Patients using METROGEL should receive the following information and instructions:

1. This medication is to be used as directed.
2. It is for external use only.
3. Avoid contact with the eyes.
4. Cleanse affected area(s) before applying METROGEL.
5. This medication should not be used for any condition other than that for which it is prescribed.
7. Patients should report any adverse reaction to their physicians.

US Patent No. 6,881,726 and 7,348,317

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light on lasers from page 64


The first reports on laser-assisted liposuction employed a 100 ms pulse duration, though now, recommended pulse widths are considerably shorter, in the 0.5 ms to 1 ms range. Some devices currently available now pair the 1,064 nm Nd:YAG laser with the 1,320 nm and/or the 1,440 nm for additional fat disruption.

Hair removal

The 1,064 nm Nd:YAG laser offers a viable option for laser hair removal in all skin types. Its relatively poor absorption by melanin affords increased safety for use on tanned or darker skin types. As a consequence, however, this poor affinity for melanin also decreases its efficacy on treating light or fine hairs. The Nd:YAG is an excellent choice for treatment of dark coarse hairs on any skin type.


extended theory of selective photothermolysis described by Rox Anderson, M.D., and colleagues dictates that successful photoepilation requires a significantly longer pulse width than the thermal relaxation time of the target hair shaft to allow for collateral thermal damage of the matrix cells in the hair bulge (Altshuler GB, Anderson RR, Manstein D, et al. Lasers Surg Med. 2001;29(5):416-432).

As with all hair removal devices, cooling of the epidermis is critical. Cooling offered on Nd:YAG hair removal systems include cryogen spray, metal contact cooling, sapphire window cooling and forced-air cooling.

A recent report of six patients demonstrated a subjective and objective

As with all hair removal devices, cooling of the epidermis is critical. Cooling offered on Nd:YAG hair removal systems include cryogen spray, metal contact cooling, sapphire window cooling and forced-air cooling.

trials, the long-pulsed 755 nm alexandrite laser showed greater hair clearance rates than the Nd:YAG (Khoury JG, Saluja R, Goldman MP. Dermatol Surg. 2008;34(5):665-671; (starch iodine test) decrease in axillary sweating following Nd:YAG laser hair removal. Interestingly, though clinical effects were seen, no histologic changes in the eccrine gland were
demonstrated when pre- and post-treatment biopsies were compared (Letada PR, Landers JT, Ubelhoer NS, Shumaker PR. J Drugs Dermatol. 2012;11(1):59-63). Further studies are needed to clarify the reproducibility of these effects in a larger group.

Pulse widths for long-pulsed Nd:YAG hair removal can range from 0.1 ms to 300 ms, but most commonly the devices are used within 3 ms to 100 ms.

With its relatively low absorption by the skin’s three major chromophores, the 1,064 nm Nd:YAG is quite a versatile wavelength. Oxyhemoglobin can be targeted to treat telangiectasias, leg veins and port wine stains, among others. The affinity of 1,064 nm light for water allows its use for nonablative rejuvenation, and the absorption of the Nd:YAG laser light by melanin allows the surgeon to perform photoepilation.

Due to the higher fluences employed, adequate epidermal cooling is paramount. In the hands of an experienced laser surgeon, the 1,064 nm Nd:YAG laser can deliver excellent results safely. DT
Word of mouth

New grading scales focus on perioral aesthetic features

By Cheryl Gutman Krader
Senior Staff Correspondent

Englewood, Colo. — New photographic scales for classifying aesthetic features of the perioral area demonstrate high levels of intra- and inter-rater reliability in validity testing and are a useful addition for clinical research and practice, according to Joel L. Cohen, M.D.

Dr. Cohen, director, AboutSkin Dermatology and Derm Surgery, Englewood, Colo., says he identified the need for developing a validated grading scale to quantify the severity of aesthetic features of the perioral area as he began planning a dose-response study of onabotulinumtoxinA (Botox, Allergan) for treatment of perioral lines with animation.

Working in collaboration with several other physicians and researchers at Allergan, several four-point, lip-specific photographic scales were developed based on review of two-dimensional images of healthy volunteers. One scale rates the severity of vertical perioral lines at rest (POL), a second is for vertical perioral lines at maximum contraction (POLM), and the third describes the oral commissures, including marionette lines (OCS). Each scale includes grades of none, mild, moderate, and severe, and features three exemplary photos for each grade level.

Scale validation

Validation testing of the scales was undertaken in a study during which eight physicians specializing in aesthetic dermatology or plastic surgery used the instruments to rate 55 pre-screened subjects in live reviews. The physicians repeated the task in a second round to assess intra-rater variability, and the physicians were also asked to rate themselves at each round using the severity scales.

Statistical analyses using Pearson correlation coefficient testing showed almost perfect inter-rater agreement for all three scales at both rounds, while intra-rater agreement for each scale was substantial or almost perfect, Dr. Cohen says.

For the subjects’ self-assessment ratings, these study subjects themselves had intra-rater agreement ranging from moderate to substantial, and there was also substantial agreement for all three scales between the subject and physician raters at both rounds, says Dr. Cohen, who subsequently used the POL and POLM scales in a multicenter dose-ranging clinical trial of onabotulinumtoxinA injection into the oris orbicularis muscle that he performed with Steve Dayan, M.D., Chicago, and Sue Ellen Cox, M.D., Chapel Hill, N.C.

“It was an interesting experience to address a gap in our clinical assessment tools — the lack of a perioral rating scale — and it was satisfying to be successful in starting from the ground up and developing scales for the perioral area with good reliability that were subsequently used in the setting of a clinical trial,” Dr. Cohen says.

“Validated rating scales have an important role in supporting claims of efficacy from clinical studies of aesthetic treatments and allow inter-study comparisons,” he says. “However, I also find they are a useful aid in clinical practice, both as a patient education tool pre-procedure, especially for discussing realistic expectations of treatments, and for evaluating or reinforcing to patients their improvement after procedures,” he says.

Dr. Cohen says he was pleased that the validation study found good agreement between the patient and physician ratings. “It’s important for a scale to have good intra- and inter-rater reliability based on physician users,” he says. “However, it’s a bonus to find good consistency between physicians and patients because it indicates that patients can understand treatment-related improvement.

“This suggests the scale can be used...
in counseling to set expectations, but it also indicates that patients will be able to describe their treatment benefit when they share their experience with others after a procedure,” he says.

Dr. Cohen says the POLM scale is the most relevant for rating responses to botulinum toxin injection, as it is a scale at animation, whereas the POL scale that focuses on lines at rest has application for other perioral treatments, including resurfacing and fillers. Existing rating scales for the nasolabial fold incorporate oral commissure prominence.

It was worthwhile, however, to develop a scale focusing exclusively on the oral commissure because while aging changes of these two features are often consistent with each other, there can be a substantial difference in the prominence of the nasolabial fold and oral commissure in some patients, Dr. Cohen says.

Botox first

Discussing the rationale behind his desire to study perioral botulinum toxin dosing in the first place, Dr. Cohen says that in patients seeking rejuvenation for vertical lip lines, he often injects onabotulinumtoxinA prior to a resurfacing procedure. This technique is an extrapolation from published reports on approaches to peri-orbital rejuvenation.

“Anecdotally, different surgeons would report using different doses, and there was also variability in injection sites. Intuitively, because the orbicularis is a sphincteric muscle, I thought it was best to inject the upper and lower aspects, using a lower dose in the lower lip. However, I wanted to have some scientific evidence to support that approach, and in planning to undertake a dose-ranging study, I realized there was a need to create a validated rating scale for vertical lip line severity,” he says. DT

Disclosures: Dr. Cohen has served as a consultant and investigator to Allergan. The research was funded by Allergan.

“Validated rating scales have an important role in supporting claims of efficacy from clinical studies of aesthetic treatments and allow inter-study comparisons.”

Joel Cohen, M.D.
Englewood, Colo.

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Aesthetic endorsements

Physicians tout Asclera for leg veins, call for more research on platelet-rich plasma

By John Jesitus
Senior Staff Correspondent

Las Vegas — Among newer aesthetic treatments, Asclera (polidocanol, Merz) hits a home run, while the so-called “vampire lift,” although intriguing, requires further study, according to physicians who spoke at the 2011 Cosmetic Surgery Forum in Las Vegas.

“I was very happy that Asclera (polidocanol, Merz) finally got Food and Drug Administration approval” in 2010, says Doris Day, M.D. For sclerotherapy, “Polidocanol is my preferred product, and I was eagerly awaiting FDA approval so I could get the product here,” says Dr. Day, a clinical assistant professor of dermatology at New York University Medical Center.

For problematic spider and reticular leg veins, “Patients have treatment options that can help,” she says. “These include compression stockings, sclerotherapy, ambulatory phlebectomy, laser treatments and radiofrequency treatments.” For sclerotherapy, she says dermatologists initially had few options — mainly hypertonic saline, which can burn and lead to scarring if not injected perfectly every time. “Sotradecol (sodium tetradecyl sulfate/STS, Bioniche) came along a few years ago, and it became the standard of care for many years. Now I believe Asclera is the new gold standard for treating leg veins.”

Asclera works by sclerosing the blood vessel lining, which causes the body to clear that vessel, Dr. Day says. Ultimately, “The visible vein disappears.” Asclera is reliable, she says, “But as with all sclerotherapy, it can take a few treatments for optimal results or complete clearance.”

Clinical trials showed that Asclera is similar to STS, Dr. Day says. “But there were a few significant differences. Incidence of injection-site hematomas was significantly lower in the Asclera group. Injection-site irritation, which is an important issue, especially if someone makes the mistake of going into the sun afterwards, and neovascularization, which we really want to avoid, also were significantly lower in the Asclera group.” Conversely, she says incidence of injection-site thrombosis was slightly higher in the Asclera group.

Asclera comes in preservative-free 2 mL ampoules, five per pack, in concentrations of 0.5 percent and 1 percent. Because the product costs $25 to $50 per ampoule in the United States, Dr. Day says, “I usually buy the higher concentration and dilute it down to 0.5 percent or 0.25 percent as I’m using it, depending on the size of the vessels I’m treating.”

Asclera also is stable for up to three years when stored at room temperature, she says, “And it’s easy to use.” Dr. Day says she initially tried to wait four to six weeks between injections because improvements continue to occur up to six weeks after the initial injection. “But often, patients have many different concerns that need treatment. So I can have them come back sooner. I’ll re-treat where I originally treated, then

“I was very happy that Asclera (polidocanol, Merz) finally got Food and Drug Administration approval.”

Doris Day, M.D.
New York University Medical Center

Versus hypertonic saline, Asclera is much less painful and causes very few post-treatment adverse effects, she says. At the time of treatment, “You’ll see a little urticaria or a wheal-like flare,” which indicates that the desired vessel damage has occurred. Some patients present with barely visible leg veins, Dr. Day says, “But they’re very bothered by them.” For treating these veins, “There’s evidence that polidocanol is better than the other agents available. It’s very easy to use, pretty painless, and I find it incredibly safe. That’s what I’m looking for — safety and reliability.”

Aesthetic see page 86
Start your adult female acne patients on ACZONE® Gel

In patients age 18 and older, 80%* of ACZONE® prescriptions are written for women, and 67%* of those prescriptions are for women age 25 and older.¹²

ACZONE® treats her acne gently but firmly. Write the 60-gm tube and start your appropriate patients on a different active ingredient—dapsone gel 5%.

* n = 115,001.
¹ n = 92,054.
² Prescription claim data from SDI Health LLC; 2010.

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.

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 67 days.

Please see brief summary of full prescribing information on the adjacent page.
INDICATIONS AND USAGE

ACZONE® Gel, 5%, is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hematologic Effects

Oral dapsone treatment has produced dose-related hemolytic 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. It is possible that signs and symptoms suggestive of hemolytic anemia occur. 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 oral dapsone and sulfadoxine-pyrimethamine (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. At least some events of peripheral neuropathy were observed in clinical trials with topical ACZONE® Gel, 5% treatment.

Skin

Skin reactions (basic 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 - Suicidal ideation, anorexia, insomnia, dizziness, suicidal ideation, mood changes, behavioral changes, depression, suicidal ideation, and agitation
- 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 2375 patients treated with ACZONE® Gel, 5%, and in 0 of 1660 patients treated with vehicle.

Combined concomitant sensitization/mitigation 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 4 controlled studies for local cutaneous events in 1819 patients. The most common events reported from these studies include oiliness/pooping, 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 (basic 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 (AUC0-24) of dapsone and N-acetyl-dapsone (NAD) were increased by about 40% and 20%, respectively in presence of TMP/SMX. Notably, systemic exposure (AUC0-24) of dapsone hydroxylamine (DAH) 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, folate 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 1600 times the systemic exposure observed in human volunteers), with no result of use of dapsone (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 1163 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 (8%), 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 0.35 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 hematocrit 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 56 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 during 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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U.S. Patents 5,863,760; 6,060,085; and 6,620,435
Pumping up
Volumization major goal in filler injections for facial reshaping

By Cheryl Guttman Krader
Senior Staff Correspondent

Alpharetta, Ga. — Understanding facial anatomy is critical to the safe and effective use of fillers for rejuvenating the aging face. And with the goal of a natural appearance, there are two important factors to consider: 1) Volume loss is the main driver of signs of facial aging, and 2) addressing volume loss requires understanding that facial fat is compartmentalized into deep and superficial components, according to Tiffani K. Hamilton, M.D.

“Aging is accompanied by volume loss that involves not only the dermis, but also of fat, muscle, cartilage, dentition and bone, and it is this loss of volume that leads to the appearance of wrinkles, folds, furrows and bony landmarks. Superficial injection of fillers to address only the wrinkles may make skin texture smoother, but it will fail to create an aesthetically pleasing, more youthful face,” says Dr. Hamilton, owner, Atlanta Dermatology, Vein & Research Center, Alpharetta, Ga.

“Achieving good outcomes with fillers for facial reshaping requires that they be used to replace volume, and the discovery that the fat layer consists of distinct superficial and deep components has led to refinements in filler injection technique that achieve superior results. The injections need to target both layers — the deep fat compartment to obtain the necessary volumization and then the superficial layer for fine-tuning,” she says.

Mid-face pearls
To illustrate these concepts, Dr. Hamilton turns to filler injections for reshaping the mid-face. Whereas it was previously thought that the superficial malar fat pad was the essential determinant of a youthful cheek contour (and that its ptosis was the underlying cause for formation of the tear trough, V-deformity of the lower lid and in the appearance of nasolabial folds), it is now recognized that loss of volume in the deep fat compartment has the more important role in development of these signs of mid-facial aging.

Furthermore, results from cadaver studies indicate that both the superficial and deep fat compartments can be divided into separate compartments defined by the nasolabial fat, superior medial fat and inferior infraorbital fat. Injection of filler into the deep fat compartment medial to the zygomatic muscle will lead to improved midface projection and improvement in the V-deformity of the lower lid and in the appearance of nasolabial folds. In addition, there are other benefits of appropriately targeting the deep fat compartment with the filler, Dr. Hamilton says.

“Proper injection technique produces immediate correction and allows the desired effect to be achieved with a smaller volume of filler than if the material is delivered more superficially. In the past, filler injections into the superficial fat compartment...”

“Superficial injection of fillers to address only the wrinkles may make skin texture smoother, but it will fail to create an aesthetically pleasing, more youthful face.”

Tiffani K. Hamilton, M.D.
Alpharetta, Ga.

Required use of a lot of material but achieved minimal results,” she says. “Furthermore, focusing on the upper fat compartment alone contributed to a doughy appearance because the face no longer moves naturally when the superficial layer is so thick.”

Proper tools
The expansion in the filler market over the past several years has allowed surgeons to harness a new understanding of facial anatomy and achieve better results with use of different types of fillers for superficial versus deep injections. Although hyaluronic acid products can be injected deep, they are best used more superficially for correcting fine lines or wrinkles or for lip augmentation.

Thicker products, either calcium hydroxylapatite (CaHA; Radiesse,
Cosmeceutical cornucopia

Latest research offers abundance of new opportunities, dermatologist says

By John Jesitus
Senior Staff Correspondent

High Point, N.C. — A growing body of research is producing increasingly sophisticated and effective cosmeceuticals, according to Zoe Draélos, M.D.

“There’s a lot of science in cosmeceuticals that goes not only into formulation and development, but also into testing and verification that these cosmeceuticals deliver on whatever claims or skin benefit they’re supposed to deliver,” says Dr. Draélos, a High Point, N.C. dermatologist in private practice and consulting professor, department of dermatology, Duke University School of Medicine, Durham.

Regarding cleansing, she says, “Traditionally, it’s been thought that soaps can only clean the skin but cannot moisturize it.” While that’s still true, she says cleansers called depositing body washes leave behind ingredients such as petrolatum, soybean oil and dimethicone that can minimize the appearance and feel of dry skin.

Consumers must apply body washes using puffs made of woven mesh, which introduces large amounts of air and water into the body wash, Dr. Draélos says. “Most body washes don’t foam because they contain oily substances that will be left behind to moisturize the skin.”

Once a person uses the puff to create suds, she says, “The concentration of water is very low, and the concentration of body wash is very high. When you’re cleansing your skin’s surface, you don’t want to be rinsing the cleanser away.”

Conversely, she says rinsing creates a high concentration of water and a low concentration of body wash. “Then the moisturizing ingredients are left behind on the skin.” Formulations designed for normal, dry or very dry skin use progressively larger moisturizing droplets, Dr. Draélos says. “People wonder how a soap can moisturize, but it’s not just a soap — it’s an emulsion containing oil- and water-soluble ingredients.”

Glycerin goods

Dr. Draélos says people used to believe that moisturizing the skin involved simply putting an “oily slick over the skin surface to retard water evaporation. That’s the main way the skin is moisturized. But it was observed many years ago that glycerin, a common ingredient in many moisturizers, seemed to have an effect on the skin that lasted far beyond the time point when the glycerin was actually present. That was called a reservoir effect.”

However, Dr. Draélos says, “We now know that glycerin does not really have a reservoir effect, but it modulates aquaporins — integral cellular proteins that form pores in the surface of all cells in the body.” Like a spigot, she says, turning aquaporins on allows more water to enter the cell, and vice versa.

The best understood aquaporin, aquaporin-3 (AQP3), is the most numerous aquaporin in the dermis, Dr. Draélos says. It transports water, glycerol and urea. AQP3-deficient mice demonstrate decreased stratum corneum hydration and impaired barrier function (Nakahigashi K, Kabashima K, Ikoma A, et al. J Invest Dermatol. 2011;131(4):865-873. Epub 2010 Dec 30). “Those mice look like they have atopic dermatitis. Therefore, there may be a role for aquaporins not only in keeping the skin smooth and soft, but also for keeping the skin healthy,” Dr. Draélos says, adding that many newer over-the-counter therapeutic moisturizers contain glycerin for the purpose of modulating aquaporins.

“There’s a lot of science in cosmeceuticals that goes not only into formulation and development, but also into testing and verification that these cosmeceuticals deliver on whatever claims or skin benefit they’re supposed to deliver.”

Zoe Draélos, M.D.
High Point, N.C.

Through the AQP3 channel, glycerin is transported to phospholipase D within skin cells, resulting in phosphatidylglycerol, a lipid that signals enzymes of cell differentiation. Improved cell differentiation might improve the appearance of aging skin and possibly reduce symptoms of psoriasis or other...

Cosmeceutical see page 88
Clinical questions
Providing advice to patients when lack of data precludes solid recommendations

By Cheryl Guttmann Krader
Senior Staff Correspondent

Las Vegas — A paucity of data from good clinical trials provides reason to be skeptical about benefits of cosmeceuticals for preventing and reversing the signs of skin aging. Furthermore, the best use of cosmeceuticals by persons wanting to look younger may be for maintaining improvement after treatment with physical modalities, such as resurfacing procedures, fillers, or botulinum toxin injections, rather than as a standalone answer, according to Hilary E. Baldwin, M.D.

And yet, she says that because patients are constantly asking for product guidance, dermatologists should be prepared to give a definitive opinion. Speaking at the 30th Annual Fall Clinical Dermatology Conference, Dr. Baldwin discussed the challenges of demonstrating clinical efficacy of cosmeceuticals, reviewed some clinical research data with a focus on antioxidants, and provided suggestions for answering patients who want advice on topical products that can rejuvenate and protect their appearance.

“Use of topical retinoids available by prescription and obsessive-compulsive application of broad-spectrum sunscreens are the only strategies backed by rigorous science.”

Hilary Baldwin, M.D.
New York

“In vitro” data showing biological benefits of raw ingredients do not necessarily translate into “in vivo” efficacy of the final formulation. Active ingredients must be physically, chemically and photostable in the commercial formulation, and they must be able to penetrate the stratum corneum to reach their target in sufficient concentrations. However, few ingredients are clinically tested for efficacy in the finished product, Dr. Baldwin says.

Another reason for skepticism is the skin with topically applied antioxidants to quench free radicals may prevent further damage and perhaps even enable damage repair, Dr. Baldwin says.

However, there are only limited data for some antioxidants showing that when topically applied, these agents can protect against photodamage. There is even less evidence demonstrating value for repairing previously damaged skin, and not all of the research in this area involves the actives in their finished, commercially available products, she says.

“Use of topical retinoids available by prescription and obsessive-compulsive application of broad-spectrum sunscreens are the only strategies backed by rigorous science.”

Dr. Baldwin, associate professor of dermatology, State University of New York, Brooklyn.

“Limited clinical trial data is better than none, consider products with low allergenic potential, and keep in mind that some cosmeceuticals have a price tag of hundreds of dollars,” she says. “In my opinion, because I am not yet convinced about the definitive efficacy of some of these products, it seems to be in the patients’ best interest to suggest something with a reasonable cost.”

Antioxidant update
Highlighting antioxidants, Dr. Baldwin says she expects there may eventually be conclusive clinical data supporting their value in anti-aging cosmeceuticals. For now, there is good rationale for their use based on solid evidence demonstrating the importance of oxidative stress in photoaging and other skin damage.

Acting through various pathways, oxidative stress can lead to weakening of dermal connective tissue and consequently skin wrinkles, laxity, and fragility; melanosome overproduction, causing mottled pigmentation; slowed production and turnover of new skin cells, resulting in a dull appearance of the skin; and DNA damage with possible malignant degeneration. Since oxidative stress occurs faster than the skin can manage it with its natural antioxidants, in theory, supplementing

Quick Read
In the absence of high-level clinical evidence demonstrating cosmeceutical efficacy, physicians should consider availability of clinical trials, safety and cost.
Easy does it
Collagen-stimulating fillers provide rejuvenating advantages, naturally

By John Jesitus
Senior Staff Correspondent

Seattle — Patients’ desire for more natural treatments extends to specific choices in fillers, according to Wm. Philip Werschler, M.D.

Among newer dermal fillers, “It appears that the trend is to move towards collagen stimulators, to replace naturally the volume that Mother Nature and Father Time have taken away,” says Dr. Werschler, assistant clinical professor of medicine/dermatology, University of Washington School of Medicine.

He says that the new stem cell-based treatment LaViv (afzicel-T, Fibrocell Science) requires sending a skin sample harvested from behind the patient’s ear to a laboratory. There, “The fibroblast stem cells are ‘teased’ out and amplified in cell culture, then freeze-dried.”

Subsequently, whenever the patient wants an injection treatment, his or her physician contacts the company to have some of the freeze-dried stem cells drop-shipped. “The patient comes in, you reconstitute them in saline, and then you inject them into lines and wrinkles. It’s a pure collagen stimulator, except you’re injecting the patient’s own cells” to accomplish this in a local area, Dr. Werschler says.

“That’s not to take anything away from hyaluronic acids (HAs) — they’re wonderful products. But having your own natural collagen — which lasts longer and feels more natural than any dermal filler — is a benefit,” he explains.

**Short-, long-term effects**

With Radiesse (calcium hydroxylapatite, Merz), advantages include immediate correction, “And it has a collagen-stimulation component that allows the body, in response to the calcium hydroxylapatite, to make collagen,” Dr. Werschler says.

Conversely, “The collagen that’s made in response to Sculptra (poly-L-lactic acid, Sanofi-Aventis) injections provides the entire effect,” he says, adding that when injected, poly-L-lactic acid has a consistency similar to water.

“With Radiesse, the collagen production gives it an extended longevity of effect. That’s why Radiesse is commonly said to last nine to 18 months, depending on where it’s used — probably closer to nine months around the mouth, where there’s a lot of movement, and closer to 18 months, maybe even a little more, when used in relatively immobile areas such as the temple,” Dr. Werschler says.

Because calcium hydroxylapatite is a particulate filler, however, “We don’t like to use it in areas that have a lot of concentric movement, such as the lips and eyelids,” Dr. Werschler says. “Particulate fillers have a tendency to aggregate, and as they aggregate, they can form lumps.” Though these lumps are not granulomas, they’re unsightly, he explains.

Radiesse consists of a 70/30 blend of carboxymethyl cellulose (CMC) and calcium hydroxylapatite. When injected, “The immediate correction that patients experience for the first eight to 12 weeks comes from the CMC carrier,” Dr. Werschler says.

However, he says these particles degrade at such a rate that type 1 collagen produced by the body in response to the calcium hydroxylapatite microspheres keeps the injected areas looking as they did immediately postinjection.

**“Having your own natural collagen — which lasts longer and feels more natural than any dermal filler — is a benefit.”**

Wm. Philip Werschler, M.D.
Seattle

In fact, “The correction you achieve immediately looks just like the corrections you have six, 12 and 15 months later,” he says. “But what’s making that correction happen under the skin is a transparent transition from the CMC gel to native collagen.”

Ultimately, he says, the patient has all his or her own collagen providing the correction, adding that calcium hydroxylapatite is the only product that offers this capability.

Artefill (polymethylmethacrylate/PMMA, Suneva) functions somewhat similarly, Dr. Werschler says, but its PMMA microspheres are permanent. Conversely, “Poly-L-lactic acid gives no immediate

**Collagen** see page 89
YOUR RECOMMENDATION

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Contouring challenges

Noninvasive devices a mixed bag for body shaping, skin tightening

By John Jesitus
Senior Staff Correspondent

Las Vegas — As the array of noninvasive fat treatments for skin tightening and body contouring continues to expand, experts who spoke at the 2011 Cosmetic Surgery Forum say scientific data will help to separate clinical reality from hype.

As patients struggle to manage their weight, says Jeanine Downie, M.D., “The noninvasive fat-reduction market is growing rapidly. Shrinking the fat cells with diet and exercise is the best way to lose weight. However, it’s difficult to keep it off.” But removing fat with radiofrequency (RF) devices provides apparently permanent results, says Dr. Downie, a Montclair, N.J., dermatologist in private practice.

Radiofrequency

Currently available RF devices use up to eight poles, says Michael H. Gold, M.D. However, he says it’s unclear whether all these poles are necessary. “Every device has a little bit of a twist. But the question is, do these devices work? If you don’t get heat, pain or discomfort, is that enough?”

If a device includes more than two or three poles, Dr. Gold says, each pole will deliver so little power that dermatologists probably will need to add an adjunctive modality to increase efficacy. He is medical director, Gold Skin Care Center and Tennessee Clinical Research Center, and clinical assistant professor, division of dermatology, Vanderbilt University School of Medicine and Vanderbilt University School of Nursing, Nashville, Tenn.

The first RF device to earn Food and Drug Administration approval for aesthetic use is the monopolar ThermaCool (Solta). “When it works,” Dr. Gold says, “it works exceptionally well.” In one survey of physicians who performed a total of 5,700 treatments with this device, a low-energy, multi-pass treatment regimen delivered immediate tightening of facial skin for 87 percent of patients. Six months post-treatment, 92 percent of patients experienced facial skin tightening (Dover JS, Zelickson B; 14-Physician Multispecialty Consensus Panel. Dermatol Surg. 2007;33(8):900-907). A new, larger tip provides noticeable results for skin tightening of the body, Dr. Gold says.

Conversely, Dr. Gold says the Pellevé (Ellman) monopolar RF device provides highly satisfactory results for the face, but presently it’s rarely used on the body. Instead, he frequently uses the Accent RF device (Alma) for body contouring, sometimes after liposuction. The Accent device offers a wide selection of treatment tips for different indications, he says, although he generally dislikes devices with significant disposable costs.

Also effective is the Venus Freeze (Venus Concept), which combines monopolar RF energy (delivered through eight poles) with magnetic pulses, he says. Pulsed light devices also can provide skin tightening and body contouring, he adds.

The Apollo system (Pollogen) uses TriPollar RF energy to reach multiple levels within the dermis. “It doesn’t hurt as much as some of the other RF devices,” Dr. Gold says, and it’s backed by numerous scientific studies. As such, “This is another alternative dermatologists need to start thinking about for their patients.”

“Shrinking the fat cells with diet and exercise is the best way to lose weight. However, it’s difficult to keep it off.”

Jeanine Downie, M.D.
Montclair, N.J.

Somewhat similarly, he says the Reaction device (Viora) uses CORE technology, which combines three distinct RF modes with a fourth mode that delivers all three treatment modes simultaneously. For appropriate patients, he says, “It works well.”

In fact, Dr. Gold says that in his experience with any of the above devices, good results are possible.
“But you won’t get them always, in every patient. So you must pick and choose what works.”

Another RF device, the Exilis (BTL), essentially heats fibroblasts to stimulate production of new collagen fibers, thereby achieving skin tightening, Dr. Downie says. It’s helpful for areas such as the face, the abdomen and bra-area fat rolls, she says.

In the abdomen, its maker says that a single treatment can achieve an average 1.2 cm reduction. “I haven’t seen that,” Dr. Downie says. “After about four treatment sessions, I’ve seen an average of two inches lost.

And that’s in my patients who are not gaining weight and are exercising lightly and drinking lots of water.”

In a recent case, a patient undergoing Exilis treatment gained 4.5 pounds and lost an inch. To guard against the possibility that such a patient might request extra unpaid treatments, Dr. Downie says she weighs and measures patients at every treatment session.

Ultrasound
Ultherapy (Ulthera) is currently approved for noninvasive brow lifting. However, Dr. Gold says this treatment is under evaluation in approximately 30 clinical studies addressing virtually every part of the body.

When using the Ulthera device, he says, “Once you learn how to control the pain issue — because it does hurt — results can be impressive.” The same can be said of a single treatment with the Liposonix device (Solta), he adds.

The second-generation Liposonix device has been FDA-approved and is now available in the United States, says Jeff Nardoci, vice president of global marketing for Solta. The new version of this device will offer a treatment area 2.7 times the size of its predecessor’s, says Joel Schlessinger, M.D., who has performed clinical trials with the earlier device. He is a dermatologist and cosmetic surgeon in private practice in Omaha, Neb.

“I believe there’s some potential here,” he says. Advantages of Liposonix include its noninvasive nature, “and it’s a relatively easy treatment. The downside of the first-generation device was the pain, and the fact that it required multiple sessions. I am hoping that newer versions will both decrease the pain and the number of sessions required. This will require comparison trials to (substantiate) the efficacy with decreased sessions, however. The same will be important with regard to pain.”

“Body contouring is probably the fastest growing aesthetic treatment market in the world right now.”
Michael Gold, M.D.
Nashville, Tenn.

Mr. Nardoci says the new device’s larger treatment area will indeed reduce the number of treatments required by approximately half.

Popular internationally but not yet cleared in the United States, the Contour 1 (UltraShape) combines low-frequency ultrasound with RF energy. In clinical trials, this device achieved an average waist reduction of 7 cm (Ottini J, unpublished). “These are the kinds of results we’re looking for,” Dr. Gold says.

In the cryolipolysis category, Dr. Gold says, “I like CoolSculpting (Zeltiq) a lot. I use it every day. I always tell my patients, if you can grab it, I can treat it” with this device. It uses vacuum suction to draw tissue into a handpiece that essentially freezes fat cells. However, with this device, it’s important to tell patients they can expect a 20 to 25 percent fat reduction in treated areas per treatment cycle. “You’re not going to make somebody’s belly flat on day one,” he says.

Injectables
As for injectable fat treatments, ATX-101 (deoxycholate, Kythera) will enter phase 3 testing for the submental area in the first half of 2012, says Erica Bazerkanian, senior director of marketing for Kythera.

Already, Dr. Schlessinger says, this product’s clinical trials, in which he is a co-investigator, have made a vital contribution regarding the measurement of fat reductions. “To me, this is the important part — how we’re going to decide whether these modalities are useful or not,” he says.

In clinical trials of the treatment, researchers have used MRI to document noticeable fat reductions up to 24 months post-treatment. Although Dr. Schlessinger says he initially believed MRI would be the best way to measure fat reductions achieved by ATX-101, “Calipers have been shockingly accurate. It’s a simple device that bunches the skin together in a reproducible manner to determine how many centimeters of fat are present. That’s been one of the most surprising things I’ve ever encountered in clinical research,” he says.

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Neurotoxin frontiers

Dermatologists continue to wrestle with dilution, clinical profiles, pricing

By John Jesitus
Senior Staff Correspondent

Las Vegas — Although currently available neuromodulators perform similarly, differences exist regarding recommended dilution, onset of action, field of effect and — perhaps most importantly — price, say physicians who spoke on the topic at the 2011 Cosmetic Surgery Forum meeting.

Corey Maas, M.D., says comparing Botox (onabotulinumtoxinA, Allergan), Dysport (abobotulinumtoxinA, Medicis), and Xeomin (incobotulinumtoxinA, Merz) is somewhat difficult because he considers all these products’ clinical trials flawed. He is a San Francisco facial plastic surgeon in private practice and associate clinical professor, University of California, San Francisco, division of facial plastic surgery.

“Many of the trials were designed incorrectly. And they mimic one another,” he says. For example, trials for all three products used injection points in the middle of the forehead for treating glabellar lines. However, he says, anatomic studies show that the corrugator musculature actually follows parallel to the eyebrow as it extends laterally. “Very rarely does it have a vertical orientation” that one could reach by injecting the center of the forehead, where injecting neuromodulators can produce eyebrow ptosis, Dr. Maas says.

For Allergan’s clinical trials, investigators labeled patient responders if they improved from a two or three rating (moderate or severe wrinkles) to one or zero (mild or no wrinkles). “So all they had to do in theory was improve by one point to be considered a responder. In the later trials for Reloxin/Dysport, the Food and Drug Administration required that there be a two-point change,” Dr. Maas says, adding that this can make comparing results between onabotulinumtoxinA and abobotulinumtoxinA trials difficult.

Similarly, he says, incobotulinumtoxinA’s clinical trials have shown that three months post-treatment, only 60 to 70 percent of patients are still considered responders. “That’s a little deceptive, because investigators are requiring people to move two points on a scale that’s very subjective in terms of severity,” he says.

According to Dr. Maas, bell curves depicting patient response levels to abobotulinumtoxinA over time depict longer-lasting results than onabotulinumtoxinA’s clinical trials produced. “One of the reasons for that, at least in part, is that the Allergan trials didn’t follow patients out long enough. So it’s not a completely fair comparison. But there is a suggestion that Dysport in some patients can last longer. That’s been our impression clinically,” and published results are beginning to bear this out, he says.

Onset of action

Regarding action onset, says Heidi A. Waldorf, M.D., “I look at Botox and Xeomin as having a very sharp beginning, middle and end,” while abobotulinumtoxinA’s efficacy arc forms a more gradual curve.

Accordingly, she says the overlap between the end of one abobotulinumtoxinA injection’s effects and the beginning of another’s could explain why she can accomplish the same clinical goals with perhaps fewer abobotulinumtoxinA injections than onabotulinumtoxinA. She is director of laser and cosmetic dermatology at Mount Sinai School of Medicine, New York.


In a split-face, double-blinded
study of abobotulinumtoxinA versus onabotulinumtoxinA for glabellar lines, both products achieved statistically significant results at rest and maximum contraction two days post-injection, Dr. Maas says. Also at day two, abobotulinumtoxinA showed a trend toward greater improvement than onabotulinumtoxinA, and a statistically significant greater improvement at days four and six in terms of maximal contraction (Yu KC, Nettar KD, Bapna S, et al. Arch Facial Plast Surg. 2011 Dec 19. [Epub ahead of print]).

In this area, “There are visible differences, more than just a numeric difference, when we looked at all the patients,” he says. Publication of long-term study results is pending (Arch Facial Plast Surg).

Overall, “Dysport and Botox perform differently,” Dr. Maas says. “Dysport seems to have a little greater area of effect, so we use it a little more concentrated. I use 1.5 mL for Dysport in a 300-unit vial, and 2 mL for Botox in a 100-unit vial.”

For practical purposes, incobotulinumtoxinA and onabotulinumtoxinA performs nearly identically to onabotulinumtoxinA, Dr. Maas says, as does PureTox (botulinum toxin, Mentor). In clinical trials of PureTox submitted to the FDA, Mentor chose a 30-unit dose for the glabellar area,

**Toxins** see page 84

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“All of the manufacturers want us to get away from ratios. But we have to start somewhere — and everybody’s got Botox as a baseline.”

Corey Maas, M.D.
University of California, San Francisco

**Wrestling with ratios**

As for dilution, Dr. Maas says, “All of the manufacturers want us to get away from ratios. But we have to start somewhere — and everybody’s got Botox as a baseline.” Earlier dosing comparisons suggested using a ratio of 2.5 units of abobotulinumtoxinA to one unit of onabotulinumtoxinA, Dr. Maas says.

More recently, he says, the preponderance of evidence suggests that the ratio of therapeutic equivalence is 3:1. “My impression was that 2.5 units of Dysport — which we used in the clinical trials — worked fine. But it didn’t last quite as long, so we went to three units.”

In a study that Dr. Maas co-authored, investigators randomized patients to receive 60 units of abobotulinumtoxinA injected into the crow’s feet on one side of the face and 20 units of onabotulinumtoxinA on the other side. “At one month, the improvement was better with Dysport, in both the subject and investigator assessments (Nettar KD, Yu KC, Bapna S, et al. Arch Facial Plast Surg. 2011;13(6):380-386. Epub 2011 Jun 20). And these were statistically significant” regarding dynamic lines, he says.
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but only because this dose achieved slightly higher efficacy than 20 units at day 30, he says. "In my mind, 20 units of PuraFox would be the same as 20 units of Botox."

In reconstituting neuromodulators, Dr. Waldorf says, "Everyone will tell you that their way is best. For Botox and Xomin, I use 2 cc for 100 units. For Dysport, I use 3 cc per 100 units." Keeping the math and injection volumes simple facilitates switching patients from one toxin to another when needed, she says.

Longevity and pricing

Reconstituting neuromodulators with bacteriostatic saline provides less painful injections, Dr. Waldorf says. Nevertheless, "We have this sense of comfort that bacteriostatic saline helps prolong our ability to use the products. The truth is, these are self-contained vials. So unless you’re popping the top off, if you’re using sterile technique to get into them, they shouldn’t be growing anything anyway. So bacteriostatic saline really isn’t helping."

"We have this sense of comfort that bacteriostatic saline helps prolong our ability to use the products. The truth is, these are self-contained vials. So unless you’re popping the top off, if you’re using sterile technique to get into them, they shouldn’t be growing anything anyway."

Heidi Waldorf, M.D.
Mount Sinai School of Medicine

There’s also a concern that the benzyl alcohol in bacteriostatic saline reduces neuromodulators’ potency over time, she says. "Could that be one of the reasons that results don’t last as long for some of your patients, though you treat them all exactly the same way with the same product? We need more studies" in this area, she says, though presently she continues to use bacteriostatic saline.

The complexing proteins included in abobotulinumtoxinA and onabotulinumtoxinA also could explain patients’ loss of response to these drugs over time, Dr. Burgess says. Because it’s unclear what role complexing proteins play, "That’s an issue I’m going to look into further. I’m going to see how my patients do" in terms of maintaining response over time with all three neuromodulators. Before abobotulinumtoxinA and incobotulinumtoxinA became available, she says, injecting Myobloc (rimabotulinumtoxinB, Solstice)
Cryo comparisons

Repeat treatment enhances benefits of cryolipolysis, study shows

By Cheryl Guttman Krader
Senior Staff Correspondent

Hong Kong — Cryolipolysis is an effective noninvasive procedure for body contouring in Chinese patients that provides a cumulative effect with multiple treatments, report researchers from the University of Hong Kong.

Samantha Y. Shek, M.D., presented results from a retrospective study including nine women and three men who had a series of two cryolipolysis procedures performed with a commercially available device (CoolSculpting, Zeltiq) using the first available applicator (EZ APP6.3).

Treatment sites were the abdomen and love handles, and the benefit for localized fat reduction was assessed objectively based on caliper measurements obtained at treated and untreated control sites with the patient standing. The two sessions were performed at an average of three months apart, and efficacy was assessed at two months after each treatment.

Study results
The results showed that statistically significant improvements were achieved at both the love handles and abdomen after the first procedure, and there was a further (but relatively lesser) improvement after the second procedure.

The objective findings corresponded with subjective assessments of standardized clinical photographs (Canfield Monostand System) and were not attributed to weight loss since mean body mass index was stable throughout the study period. The procedures were well tolerated, with no patients reporting unusual or severe pain.

“The efficacy of cryolipolysis performed as a single treatment for reducing fat-layer thickness has been reported previously. Our interest was in determining the outcomes of multiple treatments, and the results indicate there is benefit from a second session,” says Dr. Shek, honorary clinical research associate, department of dermatology, University of Hong Kong.

She adds that the results achieved in current clinical practice might differ from those recorded in the retrospective study since a new applicator (EZ APP6.2) subsequently became available.

“The first- and second-generation applicators have identical cooling panel dimensions and treat the same amount of tissue. However, it’s our observation that the newer applicator, which is 1 inch shorter in length as a result of tighter ears, provides a better fit. Suction and contact are improved, particularly when treating the love handles, and as a result, efficacy may also be greater,” Dr. Shek says.

Dr. Shek is the principal investigator for the study and Henry L. Chan, M.D., honorary professor, department of dermatology, University of Hong Kong, is the senior author. All of the treatments were performed with a fixed energy level (CIF 41.6; 73 milliwatts/cm²) for 60

Quick Read

A retrospective study in an Asian population analyzing outcomes after multiple cryolipolysis procedures showed significant benefits after two treatments.

Dr. Chan

A patient before (top, left) and two months after first cryolipolysis treatment. Before a second treatment (bottom, left) and two months after on the same patient, same area.

(Photos: Samantha Shek, M.D.)

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**Vampire facelift**

The so-called “vampire facelift” has generated significant coverage in consumer media. But initially, Julie Woodward, M.D., says she was skeptical of this procedure and the product upon which it is originally based, Selphyl (Aesthetic Factors). Selphyl carries its FDA approval as an off-label use of the Fibrinet autologous platelet system (Cascade Medical Enterprises), which is FDA-approved for orthopedic use, says Dr. Woodward, who is chief of the Oculofacial and Reconstructive Surgery Service in the Duke University Health System, Durham, N.C.

More than two years ago, after meeting with a Selphyl sales representative and researching the product on her own, she says, “I made the educated decision not to use it because there were no peer-reviewed publications.”

Presently, “There are only three published uses for Fibrinet as a cosmetic treatment — all by the same author,” she says. “There are no published studies or multicenter trials as yet. About 300 physicians are actually using the system.”

Dr. Woodward adds that when she further researched Fibrinet, “I found that the FDA sent its manufacturer a warning letter for promoting off-label use of the product (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/ucm271002.htm).”

In her recent research, she also found a lengthy YouTube video in which one physician defined the term “vampire facelift” as trilogy of Platelet Rich Fibrin Matrix (PRFM, Selphyl), hyaluronic acid and “the science of understanding beauty.” He discussed how only physicians trained by him could claim proper skill to perform the procedure, says Dr. Woodward. Selphyl has no relationship with this physician, according to its manufacturer.

She says that upon closer examination, however, she found the science behind the current version of Selphyl’s PRFM very interesting. “It’s called the “vampire lift” because it involves harvesting blood. There are competitors to Selphyl’s PRFM that have been around for years,” namely platelet-rich plasma (PRP) products.

“These have not been known to work well to increase facial volume,” she adds. “Selphyl’s manufacturer states that these companies do not have the technology to produce as pure an injectable product; nor are their products catalyzed into a gel to keep the growth factors in place. Thus they do not work as well.”

Selphyl’s maker is interested in producing quality research, Dr. Woodward says, and company representatives have not been happy about the media hype surrounding the term “vampire facelift.”

“The theory, according to Selphyl’s manufacturer, is that competitors’ products are ‘tainted’ with red and white blood cells, which interfere with the process. Only Selphyl has a technique to get rid of them,” she says.

The Selphyl treatment requires drawing a patient’s blood and then spinning it in a centrifuge tube containing a separator gel that spins out pure platelets and plasma, Dr. Woodward says.

“…for example, the patient’s blood is drawn into an intravenous catheter and placed into a device that uses a centrifuge to spin the platelets apart from the plasma,” she says. “The platelets are then returned to the donor while the plasma is extracted.”

The collected platelets can be used immediately or frozen for future use, she says.

The company has been tainted by this with autologous fat transfers.

Disclosures: Dr. Day is a speaker for Allergan, Medicis and Sanofi-Aventis. Dr. Woodward is a consultant for SkinCeuticals and Lutronic and a speaker for Medicis and Merz.

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Merz) or the biostimulating agent, poly-L-lactic acid (PLLA; Sculptra Aesthetic, Sanofi-Aventis), should be used preferentially for injection into the deep fat compartments to achieve volumization, Dr. Hamilton says.

When using CaHA, Dr. Hamilton says she dilutes it 1:1 with lidocaine 2 percent plus epinephrine (plain lidocaine is used in all dilutions for epinephrine-sensitive individuals). However, it can also be mixed in a 2:1 dilution with lidocaine plus epinephrine to achieve a thinner consistency that gives added versatility in using this product for superficial and deeper injections, she says.

When using PLLA, Dr. Hamilton adds 6 cc bacteriostatic water and 2 cc lidocaine 2 percent plus epinephrine and does the reconstitution at least one day prior to use of the product to ensure complete hydration. At the time of injection, the vial is warmed and shaken vigorously before the filler is drawn into the syringe for injection.

“In contrast to CaHA, which may be used at different depths, PLLA is injected only below the muscle-loose areolar tissue level. PLLA should never be injected into the dermis or superficial subcutaneous space where it can lead to nodule formation,” Dr. Hamilton says.

Disclosures: Dr. Hamilton is an adviser for Sanofi-Aventis; physician trainer for Bioform, Ortho-Neutrogena and Sanofi-Aventis; speaker for Sanofi-Aventis, Bioform, Allergan, Medicis, Ortho-Neutrogena and Galderma; and principal investigator for Sanofi-Aventis and Galderma.
Deborah Longwill, DO
and her mother, Barbara Longwill.

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inflammatory diseases. Theoretically, Dr. Draelos says, “Improved cellular differentiation might reduce the incidence of nonmelanoma skin cancer.”

Nanoparticle news

Among sunscreen ingredients, Dr. Draelos says that a 2007 Food and Drug Administration report expressed concern that nanoparticles of zinc oxide could penetrate the dermis and create a permanent reservoir of zinc oxide in the skin. Manufacturers sprinkle nanoparticles into sunscreens with the idea that they’ll be invisible on the skin’s surface.

“This would allow people who have higher Fitzpatrick skin types like four, five and six to use a zinc oxide sunscreen without it being visible,” she says.

However, nanoparticles tend to aggregate, Dr. Draelos says. “It’s impossible to make an emulsion where every single nanoparticle is able to exist by itself. In addition to aggregation, the nanoparticle clumps tend to stick together (agglomeration) and even settle out in formulations.” That’s why nanoparticle-containing sunscreens are not invisible and don’t pose the absorption risk they once were believed to. Health concerns remain, however.

In the former area, the body is unable to expel inhaled or other nanoparticles, and nanoparticles act as proinflammatory mediators, she says. Nevertheless, “Nanoparticles have become very important in dermatology for drug delivery,” Dr. Draelos says. Examples include chemotherapeutic drugs used to treat Kaposi’s sarcoma. “The nanoparticles can be targeted more directly to certain tissues, allowing chemotherapeutic agents to concentrate in tumors,” thereby sparing other tissues toxicity.

“Nanoparticles have become very important in dermatology for drug delivery.”

Zoe Draelos, M.D.
High Point, N.C.

Rosacea update

As for the innate immune system, Dr. Draelos says it’s known that cathelicidins and defensins essentially kill organisms that attempt to invade the body by blowing apart the organisms and the cells they infect. “Defensin pokes a hole in the cell. Hydrogen peroxide is released, and then the cell dies,” she says.

However, it now appears that rosacea may stem from overexpression of cathelicidins (Yamasaki K, Di Nardo A, Bardan A, et al. Nat Med. 2007;13(8):975-980. Epub 2007 Aug 5). Dr. Draelos says researchers are investigating ways of using the innate immune system to improve skin conditions by removing or reducing inflammatory mediators. For example, “People are trying to develop cleansers that mobilize antimicrobial peptides that are present on the skin’s surface.”

Researchers have rediscovered natural moisturizing factor (NMF), the body’s natural skin moisturizer. Dr. Draelos says, “We’ve known for a couple years that filaggrin breaks down into NMF during the maturation process as the corneocytes move up to the stratum corneum,” she says. “NMF is made up of urea, lactate, amino acids, pyrrolidone carboxylic acid and inorganic salts.

“Those five ingredients have been put together artificially to try to mimic broken-down filaggrin, because many people believe abnormalities in filaggrin lead to the dry skin found in atopic dermatitis and other dry skin conditions,” Dr. Draelos says. DT

Disclosures: Dr. Draelos reports no relevant financial interests.

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that many of the published reports on cosmeceutical products appear in trade magazines for the spa or cosmetic and toiletries industries or in special interest group newsletters. Considering these forums, Dr. Baldwin says she remains suspicious that research with negative findings might be suppressed. Even when studies are published in the medical literature, they are generally too underpowered to draw statistically significant results, as demonstrated by Dr. Baldwin’s literature review. Although some active ingredients or final products were investigated in randomized, controlled studies with independent raters assessing outcomes, the sample size is usually very small.

Dr. Baldwin says rigorous clinical trials of cosmeceutical products may not even be feasible due to difficulty in demonstrating statistically significant differences in efficacy between the treatment and control groups.

“If nothing else, cosmeceuticals are well-made moisturizers that improve the skin in of and themselves, and this creates a challenge for demonstrating efficacy compared to a vehicle control for a cosmeceutical product that is expected to provide only subtle improvements in skin appearance,” she says.

ORAC scoring

Clinicians should also be familiar with the ORAC score (oxygen radical absorbance capacity) that is a measure of the antioxidant capacity of natural substances. What is important to realize is that this metric was developed by the Department of Agriculture to describe the antioxidant activity of ingested foods and supplements. The relevance of this laboratory-derived value to topically applied cosmeceutical ingredients is controversial, Dr. Baldwin says.

Furthermore, antioxidants taken orally do not necessarily provide skin benefits. For example, although vitamins C and E are naturally found in the skin, oral supplementation with these vitamins in safe doses provides no proven cutaneous antioxidant/anti-aging benefit because they do not reach the skin in sufficient concentrations to have any activity, she says.

“GI absorption is the rate-limiting step in the cutaneous delivery pathway for these vitamins, and the transport mechanisms from the GI tract to the skin are inadequate,” Dr. Baldwin explains. “Patients will continue to remain concerned about their appearance. Lay publications will continue to tout products with claims for which there is little scientific proof. Dermatologists need to serve as filters for our patients so that the products with the best combination of scientific rationale, clinical evidence and cost are recommended. We look forward to additional data in the future in this rapidly changing field.” DT

Disclosures: Dr. Baldwin reports no relevant financial interests.
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correction,” he says. Its visible effects virtually disappear the day after injection, “And it’s purely a stimulatory filler. That’s why it takes three to five treatments over six months or more to see the full effect of Sculptra.”

“When you’re injecting into the lips, eyelids and tear troughs, you want soft shaping.”
Wm. Philip Werschler, M.D.
Seattle

Firmness factor
“The utility of Radiesse is sometimes misunderstood,” Dr. Werschler says. Unlike HA, “Calcium hydroxylapatite has much more elasticity and viscosity. It’s a tougher product” in the way that a basketball is firmer than a Nerf ball.

“When you’re injecting into the lips, eyelids and tear troughs, you want soft shaping,” he says. “Calcium hydroxylapatite resists deformation, and it has the ability to bounce back into shape. Therefore, we like to use Radiesse in areas that need lifting and holding. That’s why it’s so effective in the temples and along the cheekbones. “I especially like it in the nasolabial folds, and the canine fossa,” Dr. Werschler adds. “That’s an area where we lose bone as we age — we get an effect of maxillary retrusion there. That area is subject to significant force and weight. By injecting Radiesse there, we can lift the nose, which helps to counteract the drooping of the tip of the nose that comes with age.”

These injections also lift the nasolabial fold, thereby lifting the corner of the lip, effectively rejuvenating that entire cosmetic unit, he says.

Because calcium hydroxylapatite has a labeled indication for mixing with lidocaine, “It gives the physician at the time of injection a great deal of flexibility regarding how much to thin it out,” Dr. Werschler says. “We use it in different ways and different areas, such as the back of the hands.”

At press time, Merz was answering Food and Drug Administration questions regarding study protocols for this potential calcium hydroxylapatite indication, although physicians have long been using it off-label in this area, Dr. Werschler says.

Dr. Werschler says he credits Mariano Busso, M.D., a Coconut Grove, Fla., dermatologist in private practice, for developing the technique to be used in the FDA trial. It involves mixing lidocaine into one syringe of calcium hydroxylapatite then injecting the mixture just under the skin of the dorsal hands.

“You inject it as a bolus, then squeeze it with your thumbs” into the areas it is needed. The same

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A clear message for external genital and perianal warts (EGW)...
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The technique works for the dorsal feet, he adds. In the hands, “Results seem to last from six months to a year or more. We tried using Sculptura in the back of the hands (Sadick NS, Anderson D, Werschler WP, J Cosmet Laser Ther. 2008;10(4):237-241), but there were too many problems with lumps and nodules long-term,” Dr. Werschler says. Conversely, he says that calcium hydroxyapatite’s elasticity and viscosity make it ideal for high-movement, high-force areas. Because calcium hydroxyapatite causes collagen formation, “It fills in the dorsal hand with the patient’s own natural tissue. Therefore, it doesn’t look blue under certain lights. This can happen with HA fillers due to the Tyndall effect.”

Merz has completed hand rejuvenation studies in Europe. Dr. Werschler says. Stateside, “The studies were ready to go, but then the FDA decided to add some range-of-motion testing of the hands before and after injection. That’s delayed the study a bit. But I have no doubt, based on my experience, that one day not too far off, we’ll have approval for using Radiesse in the back of the hands.”

“Radiesse’s safety profile is outstanding. It’s never had any significant issues with granulomas (or biofilm).” Wm. Philip Werschler, M.D.

Seattle

In a recent study, researchers calculated the amount of filler necessary to provide adequate correction in various facial areas. “They found that calcium hydroxyapatite was about 50 percent more effective than collagen, and about 30 percent more effective than HA (Moers-Carpi M, Vogt S, Santos BM, et al. Dermatol Surg. 2007;33 Suppl 2:SI44-SI51),” Dr. Werschler says. “In other words, because of calcium hydroxyapatite’s viscosity and elasticity, you use about one-third less than if you were using HA.”

Moreover, “Radiesse’s safety profile is outstanding. It’s never had any significant issues with granulomas, biofilm” or other serious adverse events.” Dr. Werschler says. “Most people don’t realize that calcium hydroxyapatite is actually the oldest true filler we have.” It was originally approved more than two decades ago as a marker for radiation therapy, then in 2006 for facial wrinkles and folds. DT

Disclosures: Dr. Werschler has been a speaker, investigator and consultant for Merz, but he owns no stock in the company.
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Moreover, he says that because ATX-101 could become the first minimally invasive fat reduction treatment approved specifically for the submental area, “It potentially will help us to bring new patients into the office.”

Market growth

Overall, Dr. Gold says, “Body contouring is probably the fastest growing aesthetic treatment market in the world right now. Outside the United States, it’s growing faster than the neuromodulator market.”

However, he says that to date, manufacturers have not addressed the issue of when to schedule maintenance treatments. “We never talk about this with patients. We just say, come back when you need it. Long-term studies with these noninvasive devices are not that plentiful in the literature. The companies are not going to spend the money doing that. So we’re not going to get the data until we perform the studies ourselves.”

To that end, Drs. Gold and Schlessinger have cofounded the Dermatologic & Aesthetic Surgery International League, which aims to “create a global community for the open exchange of knowledge and innovation by physicians specializing in dermatologic and aesthetic surgery,” according to its website (thedasil.org).

Disclosures: Dr. Downie has received grant/research support from Johnson & Johnson, Allergan, Photocure, Merz and Medicis. She is also a consultant for Johnson & Johnson, Allergan, Merz and Intendis, and a speaker for Allergan, Stiefel, SkinMedica, Novartis and Procter & Gamble. Dr. Gold has received grant/research support from Ulthera. He is a consultant for Syneron, Lumenis, Alma, Sciton, Ulthera and Venus Concept, and a speaker for Alma, Lumenis, Syneron, Sciton, Ulthera, Venus Concept and Jelisy. He is also a Lumenis stockholder. Dr. Schlessinger has received grant/research support from 3M, Abbott, Allergan, Amgen, Fujisawa, Gelderma, Genentech, GlaxoSmithKline, Kythera, Medicis, Mentor, Merz, Perrigo, Pfizer, Valeant and Revance. He is also a consultant for Allergan, Medicis, Mentor and Merz.

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worked for her patients who stopped responding to onabotulinumtoxinA.

Dr. Burgess says that per FDA standards, “Both onabotulinumtoxinA and incobotulinumtoxinA were tested with 2.5 mL of normal saline.” And, like abobotulinumtoxinA, she says, both are approved for the glabellar area and carry a black box warning about potential side effects. “The difference here is that incobotulinumtoxinA costs $425 for a 100-unit vial, and onabotulinumtoxinA costs $525.” AbobotulinumtoxinA costs around $475, she says.

Because patients can get this information online, Dr. Maas says, the first question many will ask their doctor is, "Am I getting the 'cheap Botox'?"

In this regard, Dr. Waldorf says that dermatologists are divided over whether to price neuromodulator treatments by units injected or area treated. “Do what makes sense for you and your population,” she says. However, she cautions that patients who pick practitioners based solely on price don’t appreciate physicians’ expertise and experience. Having a little more profit margin on a safe, effective product is "something we will keep in mind. However, I believe all three toxins are luxury products, and I don’t charge less for one or the other.”

Disclosures: Dr. Maas has received research support from Medicis and Merz; has been a consultant for Medicis, Merz and Allergan; and is a speaker for Allergan and Lumenis and a shareholder in Allergan. Dr. Burgess has received research support from Allergan and GlaxoSmithKline; is a consultant for Allergan, Merz and Sanofi-Aventis; and is a speaker and shareholder for Allergan and Medicis. Dr. Waldorf is a consultant and speaker for Allergan and Merz and a consultant for Medicis.

Cryolipolysis from page 85

minutes per cycle. A treatment consisted of two to four cycles. The treatment sites and locations for caliper placement were identified, assessed and marked by a physician. The caliper readings were taken by a trained nurse using a transparent plastic sheet with markings to identify the treatment site and caliper placement location with reference to anatomical landmarks.

“Although we attempted to standardize the caliper readings, use of the skinfold caliper for efficacy determination is a limitation of the study since the readings are operator dependent and the device performance is subject to spring fatigue and its reliability depends on calibration,” Dr. Shek says.

Analyzing effects

The effects of the cryolipolysis were assessed by analysis of differences from baseline measurements and compared with changes at control sites. Analysis of change from baseline to two months after the second treatment showed no significant change at the control sites for either the abdominal or love handle regions, but there was a significant difference comparing the changes from baseline achieved at the treated versus control sites for both locations.

For the abdomen, the first treatment resulted in a statistically significant, 14 percent mean improvement in caliper readings, and there was a further 7.2 percent improvement after the second treatment (also statistically significant). Data for the love handles showed that the first treatment resulted in a statistically significant, 13.4 percent improvement. After the second treatment, there was a 4.3 percent change, but the effect only trended toward statistical significance.

Due to the small sample size, the results were also analyzed by combining data for the abdominal and love handle regions. In the pooled analysis, a statistically significant reduction in fat thickness was achieved after both the first and second treatments at the abdominal and love handle sites.

Disclosures: Zeltiq provided free consumables to support the study, but the investigators report no other relevant financial interests.
Knowing nails
Intraop dermoscopy reveals diagnostic patterns for longitudinal melanonychia

By John Jesitus
Senior Staff Correspondent

Sao Paulo, Brazil — Intraoperative dermoscopy can help dermatologists and dermatopathologists alike to distinguish between benign and malignant presentations of longitudinal melanonychia (LM), according to a recent study.

Unlike dermatoscopic examination of the nail plate, intraoperative dermoscopy after nail plate avulsion allows direct examination of the nail matrix and bed, says Nilton Di Chiaccio, M.D., Ph.D., head of the Dermatology Clinic at the Hospital do Servidor Público Municipal de São Paulo, Brazil.

Research has not definitively established the mortality rate for subungual melanomas with the clinical appearance of LM (longitudinal brown-black pigmentation of the nail plate), he says. More specifically, most studies of subungual melanomas tend to lump invasive, in situ, and nodular or other subungual melanomas together. As such, these studies have shown five-year survival rates ranging between 16 and 91 percent.

Conversely, Dr. Di Chiaccio says, perhaps the most authoritative publication on this topic showed that in the Sydney Melanoma Unit series, five- and 10-year survival rates were 55 and 44 percent, respectively (Thai KE, Young R, Sinclair RD. *Australas J Dermatol.* 2001;42(2):71-81; quiz 82-83. Review).

As with any melanoma, he says, “The problem is early diagnosis. When the melanoma becomes invasive, the clinical features change from those of LM to a nodular lesion with nail dystrophy and pigmentation in the proximal, lateral and/or distal nail folds.”

Recent research
In one study that examined dermatologists’ accuracy in early diagnosis of melanomas of the nail matrix, “The percentage of right answers was considered low for clinical features, the ABCDEF rule and dermoscopy of nail plate, regardless of the dermatologist’s level of experience (Di Chiaccio N, Hirata SH, Enokihara MY, et al. *Arch Dermatol.* 2010;146(4):382-387),” Dr. Di Chiaccio says. Specifically, these methods yielded accuracy rates of 46 to 55 percent.

However, Dr. Di Chiaccio says, “The percentage of right answers increased to between 71 and 76 percent with dermoscopy of the nail bed and matrix.” Overall, study authors concluded that early excision and pathologic examination of all lesions with suspicious clinical features is presently the only way to avoid misdiagnosis of suspicious LM.

“‘The problem is early diagnosis. When the melanoma becomes invasive, the clinical features change from those of LM to a nodular lesion with nail dystrophy and pigmentation in the proximal, lateral and/or distal nail folds.’

Nilton Di Chiaccio, M.D., Ph.D.
Sao Paulo, Brazil

To establish and validate patterns for intraoperative dermoscopy of the LM see page 94

Quotable
“The combination of both of these technologies results in very specific high resolution images.”

Joseph Malvehy, M.D.
Barcelona, Spain

On using mole mapping with dermoscopy

See story, page 100

DT Extra
Radioactive cream used for BCC

A radioactive cream used to treat basal cell carcinoma kills even deep tumors in just half an hour, the London Telegraph reports. Researchers at the Institut Laue-Langevin in France say a cream using rhenium-188, a radioactive isotope, completely removed tumors in 95 percent of 1,000 patients with just one treatment. Investigators applied a base layer of cream to the skin to protect healthy cells from the isotope, which sits on top of the base to irradiate the skin below it.

Source: telegraph.co.uk
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Acanya Gel is indicated for the topical treatment of acne vulgaris in patients 12 years of age or older. Acanya Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Discontinuation is recommended if significant diarrhea, bloody diarrhea, severe abdominal cramping, or colitis (including pseudomembranous colitis) develops. Clindamycin taken orally or through IV may result in 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 or shortness of breath, they should be instructed to discontinue use and contact a physician immediately. Patients should be advised to avoid contact with the eyes or mucous membranes and to minimize sun exposure following the application of Acanya Gel.

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*Individual results may vary.

**LM from page 92**

nail matrix, Dr. Di Chiacchio and several colleagues analyzed 100 bands of LM that were excised at the Hospital do Servidor Público Municipal de São Paulo (Hirata SH, Yamada S, Enokihara MY, et al. J Am Acad Dermatol. 2011;65(2):297-303. Epub 2011 Apr 29). These investigators first performed nail plate dermoscopy then intraoperative dermoscopy of the nail matrix after partial or total nail plate removal prior to surgical excision. To avoid contaminating the surgical field, the equipment used for the latter examination (DermLite, 3Gen) does not require tissue contact, Dr. Di Chiacchio says.

Next, investigators grouped the images obtained from nail plate dermoscopy and those obtained from intraoperative dermoscopy into four patterns: regular gray lines (hypermelanosis), regular brown lines (benign melanocytic hyperplasia/leointi), regular brown lines with gobules or blotches (melanocytic nevi), and irregular (melanoma). They subsequently reached a consensus among five examiners to define a final pattern for each case, which they compared to the corresponding pathological diagnosis. Investigators checked for agreement.

**LM see page 102**

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**DOSAGE AND ADMINISTRATION**

Apply a pea-sized amount of ACANAYA Gel to the face once daily. Use of ACANAYA Gel beyond 12 weeks has not been evaluated.

ACANAYA Gel is not for oral, ophthalmic, or intravaginal use.

**CONTRAINDICATIONS**

ACANAYA Gel is contraindicated in patients with a history of regional extents, ulcerative colitis, or antibiotic-associated colitis.

**WARNINGS AND PRECAUTIONS**

Colitis Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. When significant diarrhea occurs, ACANAYA 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.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibiotic drug clinically effective against C. difficile colitis.

**Ultraviolet Light and Environmental Exposure**

Minimize sun exposure following drug application. (See NONCLINICAL TOXICITY.)

**ADVERSE REACTIONS**

**Clinical Studies 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. Because clinical trials are also conducted under wider and varying conditions, adverse reactions observed in the clinical trials of a drug cannot always be directly compared to rates in the clinical trials of another drug. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use and for approximating rates.

The following selected adverse reactions occurred in less than 0.2% of patients treated with ACANAYA Gel: application site pain (0.1%); application site irritation (0.1%), and application site infection (0.1%).

During clinical trials, patients were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning and stinging. Most local skin reactions increased and peaked around week 4 and continually decreased over time reaching near baseline levels by week 12. The percentage of patients that had symptoms present before treatment, the maximum value recorded during treatment, and the percent with symptoms present at week 12 are shown below.

**Local Skin Reactions—Percent Patients with Symptoms Present. Combined Results from the Two Phase 3 Trials (N = 776)**

| Disposition Instructions for the pharmacist | Dispense ACANAYA Gel with a 10 week expiration date. Specify “Store at room temperature up to 25°C (77°F). Do not freeze.” | Storage and Handling | PHARMACIST: Prior to dispensing, store in a refrigerator, 2°C to 8°C (36°F to 46°F). | **HOW SUPPLIED** | ACANAYA Gel is supplied as a 50 g pump (NDC 13548-132-50). |

**Drug Interactions**

**Erythromycin**

ACANAYA Gel should not be used 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 vivo antagonism is not known.

**Concomitant Topical Medications**

Concomitant topical therapy should be used with caution because a possible cumulative irritant effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

**Neuromuscular Blocking Agents**

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ACANAYA Gel should be used with caution in patients receiving such agents.
Special attention

Only problematic lesions in pediatric patients require close observation

By John Jusit
Senior Staff Correspondent

Rome — Because melanoma in children occurs very rarely, dermatologists should prioritize only those types of melanocytic nevi that can pose problems: Spitzoid nevi and large congenital melanocytic nevi (CMN), according to Elvira Moscarella, M.D.

The estimated annual incidence of melanoma in children 10 years old and younger is 0.8 per 1 million (Ferrari A, Bon A, Baldi M, et al. Pediatrics. 2005;115(3):649-654). But the incidence of melanoma rises with age, says Dr. Moscarella, a dermatologist in the department of oncologic dermatology at San Gallicano Dermatological Institute in Rome. This rate peaks in people age 40 and older, she says, but at the other end of the age spectrum, melanoma is virtually nonexistent in young children — although melanoma incidence and prevalence rates begin increasing at puberty.

“A high number of nevi correlates with a higher incidence of melanoma,” and vice versa, she says. Except for children born with congenital nevi, however, “Nevi are also rare in children.”

Nevertheless, Dr. Moscarella says that proportionally speaking, “We excise a lot of benign nevi in children. Instead, we should probably focus our attention mainly on lesions that are problematic, such as very large congenital nevi and lesions that are sometimes difficult to differentiate from melanoma, such as Spitzoid lesions.”

A matter of size

Present since birth by definition, congenital nevi are divided into small (< 1.5 cm), medium (1.5 cm to 20 cm) and large (> 20 cm) categories. Experts subdivide the latter group into three "giant" classifications: G1 (20 cm to 30 cm), G2 (30 cm to 40 cm) and G3 (> 40 cm), Dr. Moscarella says.


In this category, “Melanoma incidence is also low. It is reported mainly within the first years of life,” Dr. Moscarella says. “In these cases, melanoma arises deep within the nevus, so it’s very difficult to detect at an early stage. It usually starts from the dermis. It’s not superficial spreading melanoma, but usually a nodular melanoma from the beginning. And it can have a very worrisome impact on life expectancy.”

Conversely, Dr. Moscarella says the risk of melanoma development with small and medium-sized congenital nevi is low. “It is thought to be up to 1 percent over a lifetime (Tannous ZS, Mihm MC Jr., Sober AJ, Duncan LM. J Am Acad Dermatol. 2005;52(2):197-203), although this is controversial,” she says.

Perhaps more importantly, Dr. Moscarella says, “This risk rises with increasing age and nevus size. Therefore, we recommend following up with these young patients annually,” possibly using dermoscopy or digital dermoscopy. It’s also important to explain to these children’s parents that although the lesion can grow over time, it should always remain proportional to the growth of a child, she says.

With small and medium-sized congenital nevi, “It’s usually possible to detect early melanoma, which arises from the dermal-epidermal junction,” Dr. Moscarella says. “So it’s visible when we look at the nevus with the naked eye or dermoscopy.”

Spitzoid, Reed nevi

In contrast, Spitzoid lesions prove particularly difficult to diagnose because they share many features with melanoma, Dr. Moscarella says. Classical Spitz nevi appear as pink or flesh-colored nodules or papules on the lower extremities. These amelanotic or hypopigmented lesions include vascular patterns composed of dotted vessels, which give the lesion its pinkish color.

Children see page 104
LM highlights

Topical imiquimod, staged excisions reduce morbidity in difficult-to-treat cases

By Ilya Petrou, M.D.
Senior Staff Correspondent

Tampa, Fla. — The treatment of lentigo maligna (LM) with topical imiquimod 5 percent cream followed by conservative staged excisions can significantly reduce surgical morbidity and represents a solution for difficult-to-treat lesions, according to Glen Bowen, M.D., co-director, Multidisciplinary Melanoma Clinic, and associate professor, department of dermatology, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City. Dr. Bowen spoke at the 2011 International Melanoma Congress in Tampa, Fla.

LM can be challenging to treat because lesions frequently occur in cosmetically sensitive areas such as the head and neck. They also occur in a much older patient population for which larger surgeries may not be considered ideal. Therapeutic options can include surgical and nonsurgical approaches or a combination of both, Dr. Bowen says, and the choice of therapy is based on several factors such as the size and location of the lesion and the age and general health of the patient.

According to Dr. Bowen, the widely accepted standard of care for treating LM is staged excisions with confirmation of histologically negative margins before surgical repairs are performed.

“Though this approach has greatly reduced the rate of local recurrences, it is associated with significant morbidity. Pre-treating LM with imiquimod can help shrink the lesion, after which staged excisions could be performed,” Dr. Bowen says.

**Initial procedure**

In his patients with LM, Dr. Bowen says he first views the lesion with a Wood’s lamp and outlines the borders on a plastic transparent template (to be used again before the staged excision). After placing a small India ink tattoo in the center of the lesion, he then removes the visible pigment of the LM using a Dermablade. Removing visible tumor first can help to ensure that there is no invasion of the tumor, he says.

“Even after careful staged excisions, many lentigo maligna lesions will show a nidus of invasion in up to 16 percent of cases,” he says. “Removal of the visible part of the pigmented lesion with a Dermablade before using topical imiquimod can be beneficial in helping to identify invasion.”

After the Dermablade procedure, Dr. Bowen will treat the area with imiquimod 5 percent cream five times a week for two to three months. Though patients apply the cream at home, Dr. Bowen says he follows patients monthly to monitor treatment progress because patients can have varied responses to imiquimod.

In those patients with a mild local inflammatory response to the cream, Dr. Bowen says he adds a topical retinoid such as tazarotene 0.1 percent gel to the treatment regimen, to be applied twice a week. The retinoid will disrupt the stratum corneum and help induce inflammation in the area in minimally responsive lesions, he says.

Dr. Bowen says he allows the inflammation to subside and the area to heal after completion of imiquimod therapy for approximately two months. It may be advantageous to postpone surgery for this period because the overabundance of lymphocytes resultant from the inflammation caused by the topical therapies may obscure the histologic picture and hide the melanocytes, he says.

**LM can be challenging to treat because lesions frequently occur in cosmetically sensitive areas such as the head and neck. They also occur in a much older patient population for which larger surgeries may not be considered ideal.**

**Surgical excision**

Just before the staged surgical excision, Dr. Bowen says he realigns the center of the original template that was taken of the lesion (with the India ink tattoo on the biopsy) and retraces it onto the patient. He then re-excises around the original template with 2 mm margins around
the lesion and does radial frozen sections, performing immunohistochemical staining with MART-1 until negative margins are confirmed.

“Using this technique, we have found the recurrence rates of LM to be extremely low, around 1.6 percent, which is not higher than what you would expect following much larger surgeries.”

Glen Bowen, M.D.
University of Utah School of Medicine

Radial sections allow the physician to see the devolution of the tumor from the center to the perimeter, Dr. Bowen says, making the whole histologic image much less ambiguous.

Dr. Bowen says it can be extremely difficult for a pathologist to histologically determine where LM stops and atypical junctional melanocytic hyperplasia on sun-damaged skin starts. One of the benefits of imiquimod is that it removes a lot of the melanocytic hyperplasia that confounds the histologic picture, leading to a clearer and histologically definitive diagnosis, he explains.

“Using this technique, we have found the recurrence rates of LM to be extremely low, around 1.6 percent, which is not higher than what you would expect following much larger surgeries,” he says. “Moreover, in the vast majority of cases, we are able to remove the LM with negative borders after only one conservative stage of surgery, not requiring a second stage.”

Without imiquimod, surgeons would have to remove an average margin of 7.1 mm to get a negative border for LM, Dr. Bowen says. If imiquimod is used prior to any surgery, the average margin required to get a negative border (including the lesions that did not get a complete inflammatory response) is 3.2 mm, allowing for a much smaller surgery in the majority of patients, he adds.

Without imiquimod, surgeons would have to remove an average margin of 7.1 mm to get a negative border for LM, Dr. Bowen says.

**Melanocytic blush**

According to Dr. Bowen, the melanocytic blush typically seen around LM is what frequently pushes surgeons to take multiple sections around the lesion in order to get a negative margin. Imiquimod can treat that blush, he says, allowing the surgeon to ultimately remove the LM with a much smaller defect without compromising recurrence rates.

“The conundrum is to try to figure out a way to not put the patient at risk, but at the same time not disfigure them by pursuing larger aggressive surgeries with flaps, grafts and other techniques. The imiquimod approach we use could be a good treatment option that can achieve this goal,” Dr. Bowen says. DT

Disclosures: Dr. Bowen reports no relevant financial interests.
Digital age
Role of automated imaging technologies expanding in dermatology

By John Jesitus
Senior Staff Correspondent

Stamford, Conn. — In the not-too-distant future, computer vision and automated image processing will play an important role in dermatology practices, says Rhett Druge, M.D., a Stamford, Conn., dermatologist and cosmetic surgeon.

As electronic health records (EHRs) and social media continue to facilitate the sharing of information throughout the world, “We are quickly moving beyond simple doctor-to-doctor communications,” Dr. Druge says. Image processing for dermatology records will facilitate this transition, he says.

Mole mapping
The Melanoscan system, which Dr. Druge developed, tracks lesion development and texture over time. With this information, his practice specializes in managing patients with high-risk melanoma, basing diagnoses and ongoing care partly on follow-up imagery gleaned from the Melanoscan.

The Melanoscan is an upgrade of the Daavlin 3 Series and is approved by the Food and Drug Administration, Dr. Druge says.

With Melanoscan, “You can flicker between the images and evenly light the skin to find changes which reveal melanoma,” Dr. Druge says. The system’s serial scanning capabilities also allow users to track melanoma growth and identify invasive melanomas early.

Thanks to these capabilities, “We’ve been able to dramatically reduce the death rate from melanoma, if you believe that Breslow depth predicts death, which I believe it does,” he says.

In a 55-patient study Dr. Druge co-authored, comprehensive cutaneous photography with Melanoscan showed a sensitivity of 75 percent and a specificity of 73.70 percent in determining malignant lesions (Druge RJ, Nguyen C, Gliga L, Druge ED. Dermatol Online J. 2016;16(3):1).

Additionally, “Our clinical group recently finished a study of 257 melanomas in situ (MIS), introducing the MIS to invasive melanoma ratio,” Dr. Druge says. “In this study, three private practice clinics found melanomas on average at a later stage than did the clinic with the Melanoscan device, which can detect change but provides no diagnosis. In the clinic with the Melanoscan device, 8 percent of MIS were tiny — 3 mm and smaller — while in the other three clinics, 4.1 percent of MIS were tiny (Stricklin SM, Stoeker WV, Malters JM, et al. J Am Acad Dermatol. 2012 Jan 7. [Epub ahead of print]).”

Additional tools
Dr. Druge says he has concerns about some other melanoma diagnostic tools. In its pivotal trials, the MelaFind device (Mela Sciences) was said to identify melanomas and high-grade lesions with 98.3 percent biopsy sensitivity, and a biopsy specificity of 10.8 percent (versus 5.6 percent for dermatologists).

He says that the sensitivity figure may be overstated because investigators used the clinical diagnoses of extremely accomplished dermatologists to verify which lesions identified by MelaFind were actually melanomas. In contrast, he says, studies involving the Melanoscan device, including the latest Journal of the American Academy of Dermatology article, use the pathological diagnosis of melanoma as an endpoint, he says.

“What would happen if we were to send our pathology samples to a lab which would evaluate them for the presence or absence of melanoma with about 10 percent specificity and no mention of any alternative diagnosis? That’s not exactly what I want a laboratory to tell me,” Dr. Druge says.

A $1.99 smartphone application (MelApp, Health Discovery Corporation) captures an image of the lesion in question and sends it to a server, as MelaFind does. “The server analyzes it then spits out an answer,” he says.

When he informally tested the application using images he downloaded from the Internet, it found only one of five melanomas, he says. “It was

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“We’ve been able to dramatically reduce the death rate from melanoma, if you believe that Breslow depth predicts death, which I believe it does.”

Rhett Druge, M.D.
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Joining forces
Mole mapping, total body photography unite to form powerful diagnostic tool

By Ilya Petrou, M.D.
Senior Staff Correspondent

Tampa, Fla. — Modern diagnostic skin evaluation tools such as dermoscopy and mole mapping with total body photography (TBP) have proven very useful in the diagnosis of suspicious cutaneous lesions and early recognition of malignant melanoma (MM). The combination of these two technologies can result in even more accurate assessment of the lesions viewed, according to Joseph Malvehy, M.D., coordinator, Melanoma Unit, Department of Dermatology, Hospital Clinic DIBAPS, Barcelona, Spain, at the 2011 International Melanoma Congress.

“Melanoma can be clinically and dermatoscopically indistinguishable from benign melanocytic nevi, sometimes making an early recognition of melanoma challenging, particularly in fledgling lesions. The implementation of diagnostic techniques such as mole mapping and dermoscopy are particularly useful in higher-risk patients, such as those with dysplastic nevus syndrome or with a personal and/or familial history of melanoma.”

Joseph Malvehy, M.D.
Barcelona, Spain

QUICK READ
Combining mole mapping and dermoscopy can augment dermatologists’ ability to diagnose MM early and accurately.

The implementation of diagnostic techniques such as mole mapping and dermoscopy are particularly useful in higher-risk patients, such as those with dysplastic nevus syndrome or with a personal and/or familial history of melanoma.”

“Melanoma can be clinically and dermatoscopically indistinguishable from benign melanocytic nevi, sometimes making an early recognition of melanoma challenging, particularly in fledgling lesions. The implementation of diagnostic techniques such as mole mapping and dermoscopy are particularly useful in higher-risk patients, such as those with dysplastic nevus syndrome or with a personal and/or familial history of melanoma,” Dr. Malvehy says.

Mole mapping techniques combined with TBP can help the clinician detect new lesions, Dr. Malvehy says, as well as observe and follow the changes in pre-existing lesions by providing a comparative reference point of areas of skin for future skin exams. According to Dr. Malvehy, dermatoscopic documentation of melanocytic lesions for the comparison of current and previous images in search of subtle changes over time, known as digital follow-up (DFU), has been shown to be helpful in the diagnosis of early melanomas for which specific criteria for MM may not yet be present.

When performing a skin exam in higher-risk patients, Dr. Malvehy follows a “two-step” diagnostic approach using the MoleMax (Derma Medical Systems) device, which produces both mole mapping and dermoscopic images. Though both of these diagnostic modalities are useful in visualizing melanocytic lesions and detecting the changes that they may undergo over time, Dr. Malvehy says the combination of these techniques is far more superior in the accuracy of lesion evaluation, compared to their accuracy when used separately.

“The combination of both of these technologies results in very specific high resolution images that can identify very small malignant tumors with a higher specificity and accuracy, compared to macroscopic clinical evaluation. The integrated dermoscopy function in the system is important because one can detect changes in the moles which can not be seen with the mole mapping technique, and vice versa,” Dr. Malvehy says.

The “two-step” technique can more effectively recognize changes in a given lesion, he says, and alert the clinician to more meticulously scrutinize red-flagged lesions.

Study details
Dr. Malvehy recently published a study of his group’s 10-year experience using the “two-step” technique with the MoleMax device (Salerno G, Carrera C, Lovatto L, et al. J Am Acad Dermatol. 17 Jun 2011 [Epub ahead of print]). The DFU study included 618 patients who considered a high risk of developing melanoma. Between 1999 and 2008, participants underwent DFU analysis that included a total of 11,396 lesions (approximately 18 per patient) during a median follow-up of 96 months.

Results showed that an early detection of melanoma was possible with a low rate of excisions. Long-term follow-up was required to allow the detection of slow-growing melanomas. A total of 1,152 lesions were excised, of which almost 70 percent (798) were lesions previously registered at least twice, and 30 percent (396) were detected and removed in the same visit.

In the long-term follow-up, 98 melanomas (8.5 percent of excised lesions) were diagnosed in 78 patients (12.6 percent). Fifty-three of the melanomas (53.3 percent) were in situ while 45 were non-ulcerated invasive melanomas, all
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between examiners of the intraoperative dermoscopy images, as well.

Ultimately, investigators determined the sensitivity and specificity of nail plate dermoscopy to be 0.73 and 0.51, respectively, versus the following levels for intraoperative dermoscopy, respectively: regular gray lines pattern: 0.95, 1.00; regular brown lines pattern: 1.00, 0.95; regular brown lines with globules or blotches: 1.00, 1.00; irregular pattern: 0.87, 1.00.

The fact that intraoperative dermoscopy yielded higher rates of sensitivity and specificity means that “intraoperative dermoscopy is better than dermoscopy of the nail plate, and can be considered an important tool for the diagnosis of LM,” Dr. Di Chiaccio says.

Conversely, he says that the value of nail plate dermoscopy in the differential diagnosis of nail melanoma has not been established. “When an LM is dark, it means that there is a large amount of pigment, and it doesn’t allow one to define the diagnosis” merely by looking at the nail plate.

“In our study,” he says, “nail plate dermoscopy identified the brown regular line pattern, which is described as a benign nail plate dermatoscopic pattern, in four of 15 melanoma cases.” This contrasts with the findings of another recent study that showed that in 44 cases of nail melanomas — including 29 that presented with LM — 70 percent of cases presented with the irregular line pattern, versus just one case with a regular line pattern (Phan, Dalle S, Touzet S, et al. Br J Dermatol. 2010;162(4):765–771. Epub 2009 Nov 18).

“In our study, nail plate dermoscopy identified the brown regular line pattern, which is described as a benign nail plate dermatoscopic pattern, in four of 15 melanoma cases.”

Nilton Di Chiaccio, M.D., Ph.D.
Sao Paulo, Brazil

**Treatment options**

As for treatment of possible melanomas presenting as LM, Dr. Di Chiaccio says that a recent case series and literature review showed very good results with conservative surgical management.

In particular, retrospective analysis of a French melanoma registry found seven cases of in situ and minimally invasive subungual melanoma treated between 2004 and 2009. All these patients underwent surgical excision of the entire nail unit with a 5 mm to 10 mm safety margin without bone resection. At a mean follow-up of 45 months, investigators observed no recurrences. Additionally, full-thickness skin grafts provided satisfactory aesthetic and functional outcomes (Sureda N, Phan A, Poulalhon N, et al. Br J Dermatol. 2011;165(4):852–858. Epub 2011 Aug 4).

The authors’ literature review identified only two recurrences in 69 reported cases of subungual melanomas treated with conservative surgical management. However, Dr. Di Chiaccio says, one of these recurrences was reported to have a Breslow thickness of 4 mm. “In my mind,” he says, “it should have been treated with amputation because it was not an in situ melanoma.”

Additionally, four patients included in the literature review ultimately required amputation of the affected digit — three because of persistent positive margins and one because of local recurrence 18 months after the initial surgery.

Overall, Dr. Di Chiaccio says, this study shows that “A nonamputative conservative treatment of subungual melanoma at an early stage — diagnosed as an isolated melanonychia striata — offers a safe and functionally efficient alternative to amputation.” Because early stage subungual melanoma is the stage when it presents as LM without nail plate dystrophy or nodules, he adds, “It is the best stage for the diagnosis and treatment of subungual melanomas.”

Moreover, he says that intraoperative dermoscopy enables the surgeon to see nail area pigmentation, which may be difficult to detect with the naked eye. "Identifying the pattern guides the surgeon in establishing the surgical margins.”

**Diagnostic**

having a Breslow of less than 1 mm.

“Using the two-step technique of total body photography and digital dermoscopy with DFU, we found that melanomas can be diagnosed at any time. This suggests that in a population at high risk for developing melanoma, DFU should be maintained over time,” Dr. Malvéhy says.

**Experience needed**

According to Dr. Malvéhy, the DFU procedure is not only time-consuming; it requires training and specific equipment. In the United States, mole mapping is more readily used than digital dermoscopy, Dr. Malvéhy says, and in contrast, digital dermoscopy is the method more often used in European and Australian centers.

The combination of both of these screening techniques not only can help the clinician in the early detection of melanoma, Dr. Malvéhy says; it can also help to avoid unnecessary biopsies. According to Dr. Malvéhy, higher-risk patients who are not in such screening programs or not compliant with follow-up are at risk of developing melanoma that goes unnoticed, which can have far-reaching consequences.

“In higher-risk patients, clinicians should consider such follow-up screening technologies, as these are highly superior in the early diagnosis and correct clinical management of suspicious lesions and melanoma. I believe that when possible, it is the obligation of the physician to offer this diagnostic option to their high-risk patients,” Dr. Malvéhy says. DT

**Disclosures:** Dr. Malvéhy reports no relevant financial interests.
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**Children** from page 95

Reed lesions are heavily pigmented, brownish-black macules or papules, typically located on the lower extremities, Dr. Moscarella says. In these lesions, globules typically are large and regularly distributed at the periphery of the lesion, or, as with classical Spitz nevi, surrounded by reticular depigmentation (regularly intersecting white lines).

Under dermoscopy, Spitz/Reed nevi have been shown to demonstrate six patterns: vascular, starburst, globular, particular, atypical and homogenous. Dr. Moscarella says, however, that most of these patterns simply correspond to different phases of the natural evolution of a Spitz nevus (Pizzichetta MA, Argenziano G, Grandi G, et al. *J Am Acad Dermatol.* 2002;47(1):137-139).

Spitzoid lesions occur very commonly in children up to puberty, Dr. Moscarella says, and they can be considered normal in this age group. As long as Spitzoid or Reed nevi remain relatively small and appear clinically and dermoscopically, “They can be followed in children up to puberty.”

Dr. Moscarella says she recommends seeing these children every three to six months.

“But after puberty, if we find a Spitzoid lesion, we usually excise it. Some features found in Spitzoid nevi — such as redness, lack of melanin or heavy black or brown pigmentation — are the same as we find in melanoma,” she says.

Whether the lesion is a Spitzoid nevus or melanoma, “The lesion tends to grow very rapidly,” Dr. Moscarella says. “These lesions tend to start out very small, and in two to three months, they can double their size.”

Even with an otherwise typical presentation, Spitzoid nevi, like melanoma, can present with worrisome characteristics such as ulcerations. “So sometimes we cannot be 100 percent sure” which one the lesion really is, she says.

“Sometimes it’s also difficult from a histopathological viewpoint,” Dr. Moscarella says. “The dermatopathologist cannot be sure whether the lesion is benign or malignant. It’s a gray zone in dermatology.” If a dermatologist has any doubt about whether a lesion is benign or malignant, “We recommend excision.”

To increase diagnostic and prognostic sensitivity, some researchers have proposed that in addition to wide excision, physicians consider sentinel lymph node biopsy of melanocytic neoplasms of uncertain behavior measuring more than 1 mm thick (Kelley SW, Cockerell CJ. *J Am Acad Dermatol.* 2000;42(3):527-530). However, Dr. Moscarella says, this recommendation is controversial.

In five published case series, no patients with primary ambiguous Spitz tumors and positive lymph nodes died of metastatic melanoma during the period when these studies were conducted, she says.

**Research recap**

Dr. Moscarella says she and her colleagues have noticed increasing interest in melanoma screening for children. However, very little research addresses the accuracy of melanoma detection in children, she says.

“We don’t know much about the natural evolution of nevi — how they can change, and what changes can be considered normal at this age or not,” she says.

Something that might be considered a signal for malignancy in an older patient might not be as dangerous if it occurs in children, Dr. Moscarella says.

“Maybe we have to apply different rules for the different age groups.”

To help determine the accuracy of melanoma detection in children, Dr. Moscarella and her colleagues recently completed a study in which they examined data regarding excised melanocytic lesions in patients up to age 19 treated at the Medical University of Graz, Austria over a 10-year period (submitted for publication).

“In this study, we found a very low number of melanomas compared to the high number of benign melanocytic nevi excised,” she says. Findings did not depend on the expertise of clinicians, “Because we were working with a dermatology database in an academic dermatology department.” Therefore, she says, diagnoses were not being made by non-dermatologists, such as general pediatricians.

As such, Dr. Moscarella says, “Maybe clinicians are not sure about the situations in which they must focus their treatment. Or maybe we must increase our threshold for malignancy in children.”

Disclosures: Dr. Moscarella reports no relevant financial interests.

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**Digital** from page 98

unable to render a decision on the other melanomas. So I don’t understand how people are going to get much out of that application.”

In contrast, he says that for a bedside diagnostic system, “Confocal scanning laser microscopy provides 98 percent sensitivity and 99 percent specificity for melanoma diagnosis and addresses a broad differential diagnosis.” He says the device is cumbersome, however.

**Light boxes and more**

There’s much more to dermatologic image processing than mole mapping, Dr. Druge says. At his practice, “We’ve converted the phototherapy booths into multifunction machines with which we’re not only detecting skin cancer, but also treating psoriasis. Most likely, we can transform a lightbox into a photodynamic therapy machine which treats people with very sensitive nonmelanoma skin cancers,” though this project is in very early stages.

Going forward, he says, such machines could perform systematic full-body analysis and use automated scoring systems to assess and track a host of issues such as acne and hair loss, as well as treatment response. “Similarly, for the eyes, you can capture upper-lid ptosis, which would be very useful for physicians who specialize in blepharoplasty,” Dr. Druge says.

Dr. Druge’s Melanocan images display the curve of the anterior neck, the abdomen and other contours and
import them to the patient’s EHR. Such images could be helpful not only in cosmetic consultations, but also to identify the presence of other medically significant conditions such as risk for sleep apnea and goiter, he says.

Image processing depends heavily on statistical methods such as edge detection, pixel recognition, 3-D reconstructions, elastography and calculations of sensitivity/specificity, he says. Presently, Dr. Drugge says, visual grading schemes can be applied by trained experts to classify images by recognizing visible symptoms of Bell’s palsy or fetal alcohol syndrome, for example.

“Through video analysis of how patients are feeling, we can have lie detectors for patient compliance.”

Rhett Drugge, M.D.
Stamford, Conn.

On a broader scale, Dr. Drugge says that computer analysis of facial expressions and body gestures one day will transform dermatologists’ clinics. In the pain management field, he says, studies show that by recognizing visual cues on videos of patients, physicians can tell how much pain a patient is truly experiencing, whereas a patient himself may over- or understate his pain level.

“Through video analysis of how patients are feeling, we can have lie detectors for patient compliance,” he says. Video analysis also can assess psychosomatic disorders, patient satisfaction, or, to help prevent medical errors, a physician’s level of fatigue.

Already, the Xbox 360 Kinect relies on body-part recognition. “It sees where your limbs are and what your hands are doing” and incorporates your movements into a video game, Dr. Drugge says. “This is not the future — this is now. And it’s rushing towards us.”

Soon, similar technologies could perform healthcare functions such as monitoring home physical therapy or a patient’s range of motion, he says.

Mixed augmented reality surgery systems can help surgeons decide where to incise by projecting, through a computer, the location and appearance of organs beneath the skin, Dr. Drugge says. Somewhat similarly, the Vein-View (Christie Medical Holdings) uses near-infrared light to produce a digital image of a patient’s veins and project it onto the skin to improve vascular access procedures.

“We in dermatology would be very well advised perhaps in the future to use these systems to predict where nerves and blood vessels might be,” and to understand patients more accurately through images of their bodies and internal organs, Dr. Drugge says.

Because such technology will prove particularly helpful in dermatology, “It’s very important for dermatologists to take charge of this visible person that imaging processing technology is creating,” he says. DT

Disclosures: Dr. Drugge is inventor of Melanoscan, a patented device for total immersion human photography.

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Meaningful use revisited

Important action items, deadlines to consider for earning incentives in 2012

It’s just over a year since the federal government’s Electronic Health Records (EHR) Incentive Program opened for business. Eligible professionals yet to enter the program still have time to get going, but the window of opportunity to earn incentives of up to $63,750 for meaningful use of a certified EHR system gets narrower with each passing day.

Fund ed at the federal level, the program actually consists of two distinct tracks — the Medicare EHR Incentive Program and the Medicaid EHR Incentive Program. Physicians are eligible to receive incentive payments through Medicare or Medicaid; nurse practitioners and select physician assistants can participate in the Medicaid program only. Eligible professionals must choose one or the other, but it is not necessary for every provider in a practice to choose the same program. A dermatology practice may have providers in either or both programs.

The choice of EHR systems is expansive — the government has certified more than 1,100 systems for the ambulatory environment. (See the list of certified systems by visiting http://onc-ctcpl.force.com/ehrcert) In contrast, being a meaningful EHR user — the key objective of the program — allows few choices.

Achieving ‘meaningful use’

As defined by the Centers for Medicare and Medicaid Services, meaningful use of an EHR consists of 25 elements, 15 of which are required and 10 that formulate a menu from which five must be chosen. The elements range from simple tasks — recording demographic data, for example — to those that require a change in workflow, such as distributing clinical summaries to all patients seen in the office.

Participants in the Medicare EHR Incentive Program must comply with the meaningful use criteria for 90 days in the initial payment year. If you successfully participated in 2011, subsequent years, including 2012, require participation throughout the entire year. For Medicaid participants, initial-year qualification includes only proof of adopting, implementing or upgrading to a certified system. Compliance with meaningful use is required in subsequent years for participants in the Medicaid program.

With a year under our belts, now is an opportune time to review the highlights — and challenges — of this important initiative and what they may mean to you.

It’s not too late. Although the program opened last year, there’s still plenty of time to participate and receive the maximum payment. For the Medicare EHR Program, eligible professionals need to report the meaningful use criteria for 90 days in the initial payment year, but that gives you until October to begin. Don’t feel like you need to wait until the start of a quarter, however. The 90-day period can consist of any consecutive 90 days; just make sure to start no later than October because you need to get under way in 2012 to gain the full $44,000 payment from the Medicare EHR Incentive Program. Participants in the Medicaid program have until 2016 to join and still gain the maximum payment of $63,750.

The window of opportunity to earn incentives of up to $63,750 for meaningful use of a certified EHR system gets narrower with each passing day.

Don’t sweat Stage Two... just yet. The government announced a significant delay in December. As initially unveiled in 2009, CMS wanted to implement the program in three stages. When the program opened last year, professionals were asked to comply with the agency’s “Stage One” criteria for meaningful use — including the 25 elements. Early adopters (those who successfully participated in the program in 2011) were told that they would need...
to comply with yet-to-be-defined Stage Two criteria in 2013. Then the government put the brakes on its plans; in late 2011, the Department of Health and Human Services revealed that the implementation of Stage Two criteria would be delayed until at least 2014. This means that physicians and other participating professionals can stay focused for now on the 25 criteria that define meaningful use today.

For the Medicare EHR Program, eligible professionals need to report the meaningful use criteria for 90 days in the initial payment year, but that gives you until October to begin.

The check might not be in the mail. Although the Medicaid program is unrelated to charges, the Medicare program relies on a payment-based computation: successful participants receive a bonus equal to 75 percent of their allowed charges, up to an $18,000 ceiling during the calendar year — specifically, professional, fee-for-service Medicare-allowed charges. In order to gain access to the initial-year bonus of $18,000, a physician needs to have booked $24,000 in allowed charges. Thus, despite the fact that CMS promises payment four to eight weeks after a successful attestation, the check is actually processed when the physician hits the allowed charges target.

By the fall, most physicians participating will likely have reached that mark, but it’s not uncommon to see those who begin their initial 90-day attestation period in the spring to wait longer for that check.

Medicare managed care is excluded. The initial-year target of $24,000 allowed charges target.

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Your state may not be prepared. While CMS is operating the primary online portal to register — the Medicare & Medicaid EHR Incentive Program Registration and Attestation System (https://ehrincentives.cms.gov/hitech/login.action) — each state has been given the authority to operate its own EHR Incentive Program for Medicaid participants. Even with the federal government funding the program, placing the administrative tasks in the hands of states (several of which are woefully unprepared) inevitably brings challenges to professionals participating in the Medicaid EHR Incentive Program.

According to a survey recently published by the National Center for Health Statistics, many states are far behind in accommodating participants. Florida and business consult see page 108

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References:
Texas ranked at the bottom of states in terms of preparations for the program. In addition to issuing unclear directions about applying, developing cumbersome (if not broken) registration processes and confusion about the public health-related meaningful use criteria that rely on the state’s acceptance of data, some states haven't even opened their programs to interested participants. View a list of state contacts and starting dates at https://www.cms.gov/apps/files/statecontacts.pdf.

For an audit. Remarkably, the EHR Incentive Program is based solely on good faith. Successful participation is predicated on logging on to a website and attesting that you have performed a series of actions. There is no interface between your EHR system and the government’s computers, nor does such a link-up appear to be coming in the near future. Until such time as there are more robust reporting systems, the government has to rely on the fact that you’re telling the truth. CMS will provide “incentives” for honesty by conducting periodic audits. Retain all relevant documentation supporting their meaningful use attestation for at least six years.

You may have to give up another government bonus. The bonus payment for Medicare's eRx Incentive Program in 2012 is 1 percent of all of the provider’s Medicare fee-for-service allowed charges. Physicians who participate in the EHR Incentive Program through Medicare relinquish their rights to receive that bonus. Even so, you’ll want to participate in the eRx Incentive to avoid future reimbursement penalties. This conflict of programs does not apply to another CMS program, the Physician Quality Reporting System (PQRS) — you can earn bonuses from both the EHR and PQRS programs. Furthermore, participants in the Medicaid EHR Incentive Program can earn bonuses from all three programs if they qualify and participate successfully.

The EHR Incentive Program is based solely on predication on logging on to a website and attesting that you have performed a series of actions.

It still may not be worth it. Don’t let the allure of that check and the tasks of participating successfully erode your revenue. Most who adopt EHRs do see a short-term decline in productivity, usually during the initial few months as they adapt to the system. A significant drop in patient volume, even on a short-term basis, and particularly if it lasts a lengthy period of time, will erode any financial gains offered by the program. Don’t mistake these cautions about the programs for negativity. There’s plenty of good news about the EHR Incentive Programs. Participation through Medicare in 2012 still allows you the opportunity to gain the full bonus payment of $44,000 per participating provider. For Medicaid, you actually have until 2016 to participate and receive the program’s full payment of $63,750.
EHR experiences

Electronic systems deliver advantages, but no product is perfect, experts say

By John Jesitus
Senior Staff Correspondent

National report — Electronic health records (EHRs) provide advantages ranging from streamlining work flows and improving patient safety to capturing government bonus payments. Nevertheless, there’s still no perfect package for dermatology, says Doris Day, M.D., clinical assistant professor of dermatology at New York University Medical Center.

Dr. Day says her EHR system (Criterions Medical Suite, Criterions) allows her to access her entire database swiftly and securely from a PC or an iPad. “When you’re looking for a patient, you can look them up by the last four numbers of their Social Security number, their date of birth or phone number. You can’t lose a patient in there,” she says.

The system also integrates with mole mapping technology and social media. In the latter area, “My patients get phone calls and emails to remind them of their appointments,” Dr. Day says.

These reminders also prompt patients to log into the practice’s website and enter or update their demographic and other basic information. “Their pharmacy phone numbers, their allergies — everything goes in before they even get to the office. So by the time they come in and I look at their chart, half of the note is already done,” Dr. Day says, adding that she fills in the rest by handwriting on a computer template.

“And when I take pictures, I can integrate them seamlessly, as well. I store images mostly in a cloud, although I have backup servers,” she says. Once a photo is stored electronically, “You can search for it in a variety of ways.”

Similarly, “When I do fillers, Botox (onabotulinumtoxinA, Allergan) or another neuromodulator treatment, I just bring up that template,” Dr. Day says. “It has a picture of the face, and I can draw what I injected where, even in different colors.” To mark a mole or other lesion, “I can just draw it on the map or take a picture to show exactly where it is.”

Dr. Day says her system also allows her to store laser parameters used for each patient in that patient’s EHR. “When I do a laser treatment, I just look up which one I used, and that note is done automatically” using the pre-stored parameters.

Dr. Day’s patients sign all consent forms digitally on a computer so that these forms can be automatically stored within their charts. During appointments, “The system even tells which room patients are in,” or which room the patient is in a queue for, she says. “I know who is where, where I have to go and what I have to do. It makes it very easy. Most things are done with one click.”

Altogether, Dr. Day says, the above capabilities have freed up her staff. “Every time there’s a phone call, I want every assistant I have to be a patient coordinator, to help that patient make an appointment — not handling tedious tasks that could be handled by the computer. That makes it fun for my staff.”

Seamless efforts

With the EHR system, “Nobody does anything tedious — nobody has to call to confirm patient appointments. Patients can choose how they get reminded of their appointments, and I can send them other notes” or emails as well, Dr. Day says.

“Every time there’s a phone call, I want every assistant I have to be a patient coordinator, to help that patient make an appointment — not handling tedious tasks that could be handled by the computer. That makes it fun for my staff.”

Doris Day, M.D.
New York University Medical Center

For example, “When I send out newsletters or have specials or if I’m doing a study, I have 40,000 charts of my in-house patients to draw from,” EHR see page 112

EHR experiences — Electronic systems deliver advantages, but no product is perfect, experts say

Two physicians well-versed with the implementation and use of electronic health records discuss ways in which dermatologists can benefit most from such systems.

Quick Read

March 2012 | DermatologyTimes.com
The DF Board of Trustees greatly appreciates the vision, leadership and exceptional generosity of the individuals listed here. Their contributions will help nurture the brightest new minds in dermatology who will pursue countless opportunities to improve patient care and help keep the specialty progressive.
she says. “It’s all done pretty seamlessly, and any of my staff members can do this. Nobody has to be specifically trained for it.”

Additionally, “The computer learns as you go. So as we add to it, it learns what we like” and makes performing that task easier each time it’s done, she says.

Integrated with her billing system, the EHR system also tells Dr. Day what coding level she can bill for based on the parameters she enters during a patient visit. “And if there’s anything special that I can charge for mole mapping, that gets done as well.”

Ultimately, Dr. Day says, the EHR system creates a “superbill.” “My biller is in Florida, but she can dial into the system, check the modifiers and send out all my claims,” she says.

The system also provides a chronological summary. “Every patient, every visit and everything else is documented on one page, so you can see when their last visit was, what their main problems were and how they were treated,” Dr. Day says.

Dr. Day’s EHR system also automatically stores lab results. “All lab reports that come in go directly into the patient’s charts, then into a workflow,” so that staff can track them (she also uses a paper logbook as backup here). If she refers a patient elsewhere, “I can send out their consult note, or pictures of a spot or skin cancer that I want removed” to the practitioner via email, she says.

Likewise, “My requisitions also go out right away electronically. We’re saving trees; we’re being maximally efficient.”

“My requisitions also go out right away electronically. We’re saving trees; we’re being maximally efficient,” says Dr. Day, who sees 60 to 80 patients daily with a five-member staff.

Dr. Day does concede that the EHR system took some time to get used to. “Adapting to any new technology takes some time. We’re all still learning, and for all the ways that it makes life so much better, sometimes these things slow you down a tad” during the learning curve, she says.

“It’s been a process to get to this point. No system is perfect. But what I like about this system is that if you’re a handwriting person, you can write on the screen. If you’re a typer, you can type. If you’re a clicker, you can click. And if you’re a scanner, you can scan,” she explains.

**Ongoing evolution**

When it comes to technologies such as EHRs, says Allan S. Wirtzer, M.D., “One of the problems we have as dermatologists is that we act like lemmings sometimes. Whether it’s a new laser, cosmeceutical or liposuction machine, if somebody says it’s great, we run to do it. I believe the same thing is happening with EHRs. There are reasons we should be active” in adopting this technology.

Dr. Wirtzer uses an EHR system in his Sherman Oaks, Calif., private practice. He says, however, that the ongoing evolution of EHR standards makes waiting to see how the field shakes out an equally reasonable approach.

“Here’s the reality: for solo practitioners and dermatologists in smaller groups, so few systems are in place that can talk to each other that EHRs are not going to affect safety,” he says.

E-prescribing may prove helpful for practices of all sizes because it relies largely on the already-existing Internet, Dr. Wirtzer says. However, “Record templates, which are so important in effectively using EHRs, can adversely affect patient care. Half the time, the templates are worthless” because they don’t reflect what dermatologists actually do during a patient visit, he says.

Disclosures: Dr. Day is a speaker for Allergan, Medicis and Sanofi-Aventis. Dr. Wirtzer reports no relevant financial interests.
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Owning it

Take control of your online reputation by generating positive content

By John Jesitus
Senior Staff Correspondent

International report — Successfully managing and defending one’s online reputation requires taking a proactive approach, remaining vigilant for negative reviews and taking a deep breath before responding to them, according to Arthur Huntley, M.D., and Barry Lycka, M.D.

Sites that allow consumers to rate physicians include rateMDs.com, Healthgrades.com and yelp.com.

However, Dr. Huntley says that much of what appears on these sites “has nothing to do with the ability of the doctor or the accuracy of the diagnosis or treatment.” He is clinical professor of dermatology, University of California, Davis.

Some complaining patients are genuinely dissatisfied, usually with the reception or bill they received, he says. “Because these reviews are anonymous,” Dr. Huntley says, “they also provide an opportunity to people in this world who like to safely cause discomfort to others.” With the ubiquity of social media, he says, a negative rating or review is all but inevitable.

Dr. Lycka adds, “As an occupational hazard of being in this business, you must expect that you’re going to have people write bad things about you. You must learn to accept it, deal with it and go on. Don’t let it ruin your day.” He is associate clinical professor of dermatology, the University of Alberta, Canada.

Dr. Lycka says it’s vital to combat negative reviews because nowadays, “Many people use the Internet as a means of determining whether you’re good or not. They use Google, YouTube, Bing, Yahoo and everything else out there to ‘search’ you, even before you have.”

Therefore, he says that a negative review — accurate or not — can steer patients away from your door.

Owning it

When business-rating sites first began, Dr. Huntley says people who had received negative reviews would spend substantial sums to hire lawyers and write to the sites, demanding that the offending material be excised.

However, he says, “The best way to do it is to own your own reputation. This might be harder for the older generation of doctors than the younger generation, but you need to create your own online content that will essentially overwhelm any bad comments that people post.”

“When people click on your name to see who you are, you want them to see at least one page — and probably more — of great information that paints you and your practice in a positive, accurate light,” he says.

“Remember,” Dr. Lycka says, “most people only read the first three things on a page. So if you keep your positive material up top, you’ll do well.”

To stack the deck, he says, “Take out a pay-per-click ad, because that’s the first thing that comes up” on a typical Web search. “That pushes everything else down the page.”

Secondly, he and Dr. Huntley suggest regularly producing fresh Web content. “Google, Bing and Yahoo love fresh content. They need it all the time,” Dr. Lycka says.

As one means of feeding the search engines, he says, “Always work on your halo.”

Nearly all dermatologists are involved in charity work, he says, but they rarely publicize it via press or video releases. “Get this news out there, and people will love you for it,” Dr. Lycka says.

To help ensure that your Facebook page comes up as the first item on a relevant search, Dr. Lycka adds, “Post there every day. I don’t have time to Facebook,” but he has someone who manages his Facebook site weekly rather than daily.

“As long as you’ve got fresh content out there, your page comes up much higher” than it otherwise would, he says.

“As an occupational hazard of being in this business, you must expect that you’re going to have people write bad things about you. You must learn to accept it, deal with it and go on.”

Barry Lycka, M.D.
University of Alberta

Dr. Huntley says, “Facebook has an increasing presence in the commercial world.” As such, he says, it’s also useful for telling patients about special offers and other timely information.

A practice’s Facebook page should be a professional-oriented page, “not your personal Facebook Reputation see page 116.
Monodox®
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Reputation from page 114

In any visual medium, he states, “Probably the best thing you can do is to use professional photography. Any images of you should be flattering,” not poorly lit, blurry or overly busy.

Moreover, he says, “You’ll notice that the images you see on well-done sites aren’t all of the doctor.” Rather, Dr. Huntley recommends spotlighting images of “whom patients want to see in themselves when they look at your site,” and of staff members with whom patients will be interacting.

To manage various social media well, Dr. Huntley says, “It takes a very active production on your part — or the part of your staff.” To that end, he suggests planning in advance what your various sites will say on a variety of subjects each day.

“You’ll notice that the images you see on well-done sites aren’t all of the doctor.”
Arthur Huntley, M.D.
University of California, Davis

“This is a lot of work. It’s probably not what you went to medical school for, so you may want to have a full-time staff member doing this,” or help from an outside firm.

Fighting back
As for specific cyber-slams, Dr. Lycka says, “When somebody writes a criticism of you, you should respond to it.” Perhaps the most compelling reason to do so is because most rating sites will post such a response after the review, he says.

It’s also helpful to have staff members respond, saying something like, “This is not exactly what happened,” because it can lend credibility to the physician, he says.

However, Dr. Lycka emphasizes, “Don’t get into a mud-throwing competition. It doesn’t work.” Neither does reacting out of anger, he says.

In this regard, “Never post anything you wouldn’t want your mother to see,” he says. To that end, he suggests showing your prospective response to colleagues before posting it. “But do respond — otherwise people will think you have something to hide.”

Additionally, he says it’s important to remember, “Most people have more people that love them than hate them. So how do you use that? Ask your clients, when they’re happy, to write a good review about you.”

He suggests being specific — telling patients exactly how to get onto the site and supplying suggested verbiage that you perhaps crafted before they left the office.

Granted, “It must come from their IP address — not your office IP address. Otherwise it will be considered spam,” he says.

“Most people have more people that love them than hate them.
So how do you use that?
Ask your clients, when they’re happy, to write a good review about you.”
Barry Lycka, M.D.
University of Alberta

Above all, Dr. Lycka says that for ongoing self-defense, “Generate lots of online material — press releases, videos, blogs, Facebook, Twitter, LinkedIn — they’re all important.”

Disclosures: Dr. Lycka reports no relevant financial interests. Dr. Huntley is founder of RxDerm-L and DermChat but reports no financial interests in these services.
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Audit sagas
Fraud, abuse and overpayments: It’s not about ‘if,’ but ‘when’

The government and private insurers are cracking down on healthcare fraud, and for many medical practices, the question is when — not if — audits and allegations of fraud arise. Dermatologists need to know how to prevent fraud allegations in the first place, and what actions to take should they be confronted with such an allegation.

Under the broad definition of fraud are many violations, including the offering or acceptance of kickbacks, and the routine waiver of co-payments.

According to a survey by the Health Insurance Association of America of private insurers’ healthcare fraud investigations, overall healthcare fraud activity broke down as follows: fraudulent diagnosis, 43 percent; billing for services not rendered, 34 percent; routine waiver of patient deductibles and co-payments, 21 percent; other, 2 percent.

For Medicare, the most common forms of fraud include billing for services not furnished as billed; misrepresenting the diagnosis to justify payment; soliciting, offering or receiving a kickback (this applies most in pathology-related charges); misrepresenting the provider of care (such as in incident to scenarios or billing under the name of one physician for services provided by another who is not yet credentialed); misrepresenting the place of service; unbundling or “exploding” charges (misuse or abuse of the modifier 59).

Avoiding allegations
So, how do you avoid allegations of fraud? I think the answers are quite simple. First, have all the providers in the practice certified in dermatology coding. A simple online dermatology-specific course that the provider can take, on his or her own schedule, arms the provider with so much information — it not only helps them avoid improper coding and misrepresentation of services provided, it helps them understand the medical necessity criteria for certain code groups, as well as proper documentation to support services rendered.

The course does the following, as well:

- Increases practice revenue by understanding which codes to use for which services, especially the differences in the levels of E/M services;
- Shows intent to auditors that providers are interested in quality and compliant coding;
- Becomes an inherent part of the practices’ compliance program;
- Assures that all providers are “on the same page.”

Variances between providers impact practice goodwill if providers charge differently for the same services and patients see multiple providers in the same group.

For information about the Inga Elzey Dermatology Institute’s online coding course, contact 800-318-3271, or visit our website at www.ipeg.com. This course is accredited for 30 CEUs by the American Health Information and Management Association.

Another way to avoid allegations of fraud is to purchase a quality electronic medical record (EMR) system for your practice. No single piece of technology will affect your medical record documentation in the future as a state-of-the-art, dermatology-specific EMR. Not only will the right system for your practice save your providers time, freeing them up to see more patients, it can accomplish so much more:

- Capture information of services provided during the E/M encounter that often go unbilled;
- Significantly improve the correct selection of the E/M service;
- Support, through quality and legible documentation, the level of care billed;
- Guard against cloned records (that’s something to watch for in choosing that perfect system for your practice);
- Help to reduce or eliminate over- and under-coding for E/M visits and services;
- Allow for more photography, which can greatly assist in audits;
- Eliminate transcription costs and the worry about non-legible chart notes.

Inga Elzey recommends EMA by Modernizing Medicine. Call 866-799-2146 to set up a no-obligation demo or go online to the Modernizing Medicine website for an instant 30-minute free demo. This program was written by a dermatologist for dermatologists on a platform that documents like dermatologists practice. (Disclaimer: Inga Elzey has no financial interest in this company other than contracting for services for billing service clients. All clients of the Inga Elzey Billing Services get EMA free during the life of the contract as a billing service client.)

Another way to avoid fraud allegations is to have professionals do your billing. Whether you do billing in-house or outsource your services to a company specializing in dermatology, you need to make sure your billing entity is comprised of the best and the brightest. All the billers should be certified in dermatology coding. The billing supervisor should not be working on the billing processes, but rather supervising staff and auditing them for quality and compliance. Internal audits should be performed for claims quality and also physician documentation. And there must a process in place that carefully
monitors carrier requests for information or audit requests to assure timely and quality responses.

**Adequate staffing**

It’s also critical to make sure you have enough staffing to do the work. Some providers tell me they cannot afford to hire any more help, but their accounts receivables (A.R.) are over 90 days and in the hundreds of thousands of dollars.

You cannot afford not to have adequate staff — just do the math. Let’s say you have 1,477 claims that are presented over 90 days but they are all 2011 dates of service. That means that they have a chance of getting paid if worked … soon! If an employee can work without interruption, they can work on an average of 60 claims per day. Let’s assume that you have 1,477 claims that are presented in the over 90-day A.R. Based on the 60-claims-per-day scenario, it would take one full-time person doing nothing but working the old accounts 24.63 days to work the entire report. The average month has 21 working days, so in actuality, it would take one month and four days to work the entire A.R. report over 90 days. This, of course, does not include working the A.R. that is 31 to 90 days old.

In today’s age of electronic filings, electronic remittance and electronic funds transfer, you should have most claims paid in less than 30 days. Claims that are in the 31- to 90-day buckets need to be followed for status. Let’s say that represents another 1,400 claims. That adds another 23 days to the time line, so it would take one full-time person dedicated solely to working the A.R. two months and one week to get through the entire A.R. If there is no one working those claims on a dedicated clock, then about 25 percent of those claims will end up in the over 90-day bucket. Your A.R. will continue to get higher and higher … and eventually out of control.

Now, let’s assume your average claim is worth $134. You hire one more person who devotes 100 percent of their time to A.R. You pay them $18/hour plus benefits, so bottom line is $21/hour. If they can collect 80 percent of the money out over 91 days, that’s $158,400. The staffer costs you $45,000. That’s a pretty good return on your investment. You can’t afford not to hire that extra person. And we are not even talking about all the money in the 31- to 90-day buckets that will go unpaid if no one is there to work the unpaid claims.

It’s also critical to hire the best and the brightest. Develop relationships with the finest vocational schools in the area and have them send their best students to do their required six-week externships. This gives your practice great insight into their personalities, work ethic and in what departments they would be most successful. By the end of the six weeks, you can hire the cream of the crop, and they start already trained, tested and accredited to your company’s philosophy and mission statement. What could be a better win-win scenario?

If you think that only Medicare is auditing like crazy, think again. The vast majority of the audits that I am involved in right now are from commercial carriers. The biggest payback request was from a commercial carrier, not Medicare.

**Recovery audit contractors**

Medicare has contracted with four companies (to cover four regions of the United States) to conduct its provider audits. They are:

1. **Diversified Collection Services Inc.** (DCS) of Livermore, Calif. (Region A). **Region A:** Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Washington, D.C.
   - www.dcsrac.com
   - 1-866-201-0580

2. **CGI Federal** (CGI) of Fairfax, Va. (Region B). **Region B:** Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio and Wisconsin.
   - http://racb.cgi.com; racb@cgi.com
   - 1-877-316-7222

3. **Connolly Inc.** (Connolly) of Wilton, Conn. (Region C). **Region C:** Alabama, Arkansas, Colorado, Florida, Georgia, Louisiana, Mississippi, New Mexico, North Carolina, Oklahoma, Puerto Rico, South Carolina, Tennessee, Texas, U.S. Virgin Islands, Virginia and West Virginia.
   - www.connollyhealthcare.com/RAC
   - RACInfo@connollyhealthcare.com
   - 1-866-360-2507

4. **HealthDataInsights Inc.** (HDI) of Las Vegas (Region D). **Region D:** Alaska, American Samoa, Arizona, California, Guam, Hawaii, Idaho, Iowa, Kansas, Missouri, Montana, Nebraska, Nevada, North Dakota, Northern Mariana Islands, Oregon, South Dakota, Utah, Washington and Wyoming.
   - http://racinfo.healthdatainsights.com; racinfo@emailhdi.com
   - Part B: 1-866-376-2319
Solo provider: 10 records each 45 days; two to five providers: 20 records each 45 days; six to 16 providers: 30 records each 45 days; 16 or more providers: 50 records each 45 days.  

RAC audits are conducted post-payment and limited to the services that have been approved by CMS (source: http://www.cms.gov/Recovery-Audit-Program/01_Overview.asp#TopOfPage).

Demand letters  
This is different from the informational letter, as this is the decision letter sent after the RAC has reviewed the provider’s records against the claim requested in the informational letter. Demand letters will contain detailed information, including:  
1. The coverage, coding or payment policy that was violated;  
2. A reason for conducting the review;  
3. A description of the overpayment situation;  
4. Recommended corrective actions;  
5. An explanation of the provider’s right to submit a rebuttal statement prior to recoupment of any overpayment.

What’s on the Office of Inspector General’s fraud ‘hit list’?  

- Medical documentation issues — Requested medical records were not submitted (no response from office, incomplete records sent, illegible notes).  
- Documentation did not support a face-to-face encounter by the performing physician — Incident to rules were not met, misrepresentation of the provider of care (not credentialled), date of service is incorrect.  
- Documentation did not support the service was rendered on the DOS reported — incorrect ICD-9 code, incorrect CPT code, medical necessity, no documentation at all (frequently seen in my chart audits).  
- Submitted documentation contained insufficient information to determine whether the service reported was actually rendered — no lesion size, no date of service, no patient identification included (name, date of birth), procedure not identified.  
- Signature requirements were not met — physician signatures were either missing or illegible. If the signature is illegible, the provider’s name should be stamped or printed below the signature.  
- Submitted documentation did not capture all of the E/M key components — New patient: Must support all three key components: History, exam and Medical D decision making; Est. patient: One of the three key components can be eliminated but the other two must be met in their entirety.  
- Level of E/M code reported exceeded documented needs for the patient’s condition and the physician’s work required to treat the patient (e.g., medically unnecessary) — This involves asking same questions again in close visit proximity, doing same level of detailed exam in short time frame, or using diagnoses that are not addressed or do not need to be addressed (Personal history of skin cancer; dry skin; sun damage and SPF; lentigos and scattered SKs).  
- Billing new patient visits when seen by another member of the same specialty group — When a patient is seen by one member of the group, the patient is established to all other members of the same group for the next three years. The exception is consultations. You cannot bill a new patient visit if another member of the group has seen the patient within the three-year period.  
- Incorrect use of modifier 25 — i.e., no procedure was reported, E/M was performed in a global period, there was no significant and separately identifiable service rendered over and above that for just the procedure itself. (Note: In the future, carriers will NOT accept an E/M visit on the same DOS for an established patient visit if there are not two separately diagnoses.)  
- Failing to report and document the level of E/M service’s key components appropriate to treat the patient’s presenting problem(s).

Enough is enough  
When you receive a demand letter for payment, you will need to decide whether you should pay it or fight it. Review the claims in question and compare your findings to those of the auditor. You can argue the demand on a claim-by-claim basis. Hire an attorney if the amount is high.

Here is what you can do immediately if you are charged with fraud or have a large payback request. The allegations of fraud are hard to prove, as the carrier must prove intent. That is difficult, so it usually comes down to how much money the carrier will end up getting.

Hire an attorney qualified and experienced in healthcare fraud and audits. The attorney will most likely engage the services of a qualified consultant well-versed in dermatologic coding, billing and documentation issues and can help you determine how to fight their overpayment decisions. They are usually engaged by the attorney so that attorney-client privilege prevails. Note: Any and all consultants should be retained by the lawyer under attorney-client privilege. This individual or team will give their unbiased input regarding whether the findings of the auditor are flawed, partially flawed or correct. Most of the time it’s a combination of provider billing errors as well as sloppy auditing by the carrier’s auditor.

Learn from the audit experience. The audit experience should be educational and result in the practice fine-tuning the areas of deficiency. If you learn from your mistakes, chances are you won’t have as much to worry about should there be a next time. DT
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A new range of cosmeceuticals has been engineered to address problematic skincare issues. Auspect MD is designed to protect, nurture, revitalize and cosmetically restructure the face. Auspect MD implements chirally-corrected ingredients so that products will penetrate and work at a cellular level to change the skin. Chiral correction involves purifying the active ingredients in each formula. In a product range where chiral correction has occurred, there is less chance of irritation, inflammation, free radical production and pain. There is a significantly faster uptake of the ingredient to the skin cells, according to the company.

Auspect MD skincare solutions are designed to address and support all skin conditions such as acne, rosacea, sun damage, aging and hyperpigmentation. Auspect MD is free of parabens, artificial fragrances, chemical dyes and hormones, the company states. The collection includes a Pro Clean daily facial cleanser, Gentle Pro sensitive skin facial cleanser, X-fol-ator exfoliating serum, Trouble Control problem skin serum, Red-Less skin calming serum, Pro-C skin brightening serum, Pro-B extreme damage control serum, Pro-A Retinol facial serum, Pigment Eze Pro skin tone corrector, Resveratrol Pro daily moisturizer, Hydra Pro dry skin moisturizer, Pro-Screen SPF 17 hydrating lotion, and Eye Lift eye cream.

*For more information: www.auspectmd.com*

**LA ROCHE-POSAY**

Sunscreen comes in aerosol form
La Roche-Posay delivers advanced sunscreen protection in a new alcohol-free aerosol spray lotion format. Anthelios Ultra Light Sunscreen Lotion Spray is a cosmetically elegant alcohol-free lotion that provides advanced broad-spectrum protection with Cell-OX Shield antioxidant technology, the company says.

Now in a 360-degree spray lotion application, Anthelios Ultra Light Sunscreen Lotion Spray delivers a controlled application with a visible lotion. The spray provides coverage at every angle for protection with minimal flyaway and waste, plus the rub-in formula ensures gapless and even application. This new spray also boasts no alcohol, parabens, fragrance nor isobutane. Plus, the innovative multi-resistance texture is water-resistant for up to 80 minutes for lasting protection during heavy outdoor activity such as swimming, sweating, etc. The moisturizing formulation, which is appropriate for all skin types and tones, is fast absorbing and dries to a matte, silky finish.

Formulations with CELL-OX Shield provide dual protection against exposure to harmful UV rays. This two-pronged approach delivers a combination of sun filters and antioxidants to further protect skin down to the cellular level.

*For more information: www.laroche-posay.us*

**MIDMARK**

LED exam light is energy-efficient
The Ritter 250 Exam Light is an improvement to the Ritter 152 Halogen Exam Light, and incorporates an LED light engine and enhanced power supply. With the introduction of the Ritter 250, the Ritter 152 will be discontinued, according to the company.

The Ritter 250 offers a flexible gooseneck to allow practitioners to easily adjust the lamp to closely observe the patient, as well as a sturdy base to prevent tipping. The Ritter 250 is the eco- and budget-friendly alternative to less efficient halogen and incandescent lighting. It boasts “green” benefits that can save a practice money. The Ritter 250 LED lasts 12 times longer than a halogen light and 10 times longer than an incandescent light. In addition, the new light is 20 percent brighter than its halogen counterpart, and consumes 45 percent less energy, the company states.

*For more information: www.midmarkclinicalsolutions.com*

**LEO PHARMA**

Topical AK therapy approved by FDA
The Food and Drug Administration has approved Picato gel (ingenol mebutate 0.015 percent, 0.05 percent) for the topical treatment of actinic keratosis (AK). Picato 0.015 percent gel is used once daily on the face and scalp for three consecutive days, and Picato 0.05 percent gel is used once daily on the trunk and extremities for two consecutive days.

In four phase 3 clinical studies of more than 1,000 patients with actinic keratosis, a significantly higher proportion of those treated with Picato gel saw complete clearance of AKs in the field of treatment as compared to placebo, according to the manufacturer. The most common adverse events were local skin reactions, including erythema, flaking/scaling, crusting and swelling.

*For more information: www.leo-pharma.us*

**CELLURE**

Eye treatment tightens skin
Cellure Rework eye treatment noticeably tightens skin around the eye area and improves the appearance of fine lines, wrinkles and overall texture. Sheer and light, it’s easy to wear day or night, even under makeup. Cellure is reportedly the first skincare line introduced to the United States that uses adult human stem cell technology, designed to recode the degenerative, physiological process of aging, according to the company. The key ingredient, Lipotein, is a natural and pure protein complex developed from highly concentrated adult human stem cells.

The Cellure system marries with skin’s normal functions, dispatching powerful proteins that seek out damaged areas to help repair skin and restart its inherent regeneration. The product line includes a skin cleanser, balancing toner, serum booster, eye treatment, day cream and night cream.

*For more information: 855-CELLURE (235-5873) www.cellureskincare.com*

**NAILA MD**

Tinted moisturizer hydrates skin
The new Suncare Essentials skin-perfecting tinted moisturizer is a three-in-one sunscreen to hydrate, protect and provide sheer, tinted coverage. The product is available in a medium shade, which is suitable for most skin tones and types, including acne and rosacea-prone skin, the company says.

This moisturizing sunscreen offers SPF 20 protection in a paraben-free formula featuring a natural, mineral pigment to protect the skin from damage by blocking harmful UVA and UVB rays. An oil-free moisturizing option, the face cream uses octinoxate and titanium dioxide to help protect delicate skin from free-radical damage, environmental stressors and damaging rays.

Providing an even, natural skin complexion with a sheer tint of color, this oil-free cream leaves the skin smooth with a matte finish. Working to bind moisture to the skin by calibrating with the skin’s hydration system, this weightless finish formula works to hydrate, protect and provide coverage and is suitable for most skin types.

*For more information: www.nailamd.com*
Army Lt. Col. Dore J. Gilbert, M.D. (left), with his youngest son, Marine Corps Cpl. Kevin Gilbert, in Camp Leatherneck, Afghanistan, in October 2011, just before Kevin’s return home after a seven-month deployment. (Photo: Dore J. Gilbert, M.D.)

Just do it

California dirm takes his training to a whole new level to serve his country

By Lisette Hilton
Staff Correspondent

Nearly 60 years old, Newport Beach, Calif., dermatologist Lt. Col. Dore J. Gilbert, M.D., said he felt good about having served his community.

“I was on the school board for 29 years. I coached Little League, football and hockey,” he says.

But he hadn’t served his country, and that bothered him. There was still time to join the military, but at Dr. Gilbert’s age, not much.

“To join the Army, you can’t be over 40, unless you’re a physician. Because the Army is in such dire need of physicians, they extended that out to age 60,” he says.

After jumping a few hoops, including signing waivers because of his advanced years and agreeing not to be part of the military’s retirement program, Dr. Gilbert finally swore his oath and took commission as a lieutenant colonel in the Medical Corps of the Army Reserve on July 24, 2010.

Then, like everybody else who joins the Army, he left for a month of basic training. “That was more mentally challenging for me than it was physically challenging,” Dr. Gilbert says. “Here I am, leaving Newport Beach, going to … the middle of the Texas scrub. I’m living in a tent with 10 other guys. My room is theirs in their 20s. I’m sleeping on a cot, with one guy and 12 inches on either side. There’s no place to store your clothes other than in your duffle bag. No showers. No bathrooms, though, we had Porta-Johns.”

The pity party lasted about four days, according to Dr. Gilbert.

“Then I got over it. From that point on, it was fantastic. I absolutely loved it,” he says. “It was a great bonding experience with the other soldiers. Because of my age, I became one of the platoon leaders.”

Getting to work

Dr. Gilbert’s goal was to go Afghanistan. He had to wait until July 2011 for the assignment. In the meantime, he worked full-time at his dermatology practice and went for monthly weekend military drills to ready for deployment.

When the day came to leave the comforts of home for active duty, the destination was Camp Phoenix, an Afghan base with about 2,000 soldiers. While his title was brigade surgeon, his role wasn’t to do surgery; rather, he was to oversee the healthcare for the approximately 9,600 soldiers in the Kabul base cluster.

“I had to make sure that all of these soldiers were being properly taken care of, that there were the right medical assets on every base. And if there was a problem, I had to solve it,” he says.

The Kabul cluster is composed of eight operating bases, each four or
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Amy Stankiewicz, Editor-in-chief of Dermatology Times and Cosmetic Surgery Times, will meet with readers of these magazines during the AAD 70th Annual Meeting in San Diego.

Amy will welcome your comments and ideas at booth # 3041 at The San Diego Convention Center on Saturday, March 17, from noon to 2 pm, and Sunday, March 18, from noon to 2 pm.

Amy will be at our booth # 3041 at the San Diego Convention Center to meet with you. No appointment is necessary.

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John Strasswimmer, MD
Delray Beach, Florida

Milan Anadkat, MD
Washington University School of Medicine
St. Louis, Missouri

Jeffrey Callen, MD
University of Louisville
Louisville, Kentucky

Richard Carvajal, MD
New York, New York

Thomas Darling, MD
Uniformed Services
Bethesda, Maryland

Frank Glass, MD
Tampa, Florida
American Society for Mohs Surgery

Upcoming CME Activities

Annual Clinical Symposium – Dermatologic Surgery: Focus on Skin Cancer

Memorial Day Weekend, May 24-27, 2012
Sheraton Wild Horse Pass Resort & Spa – Chandler, Arizona

Top experts in the field will provide updates on a wide range of dermatologic surgery and Mohs surgery topics. Separate interactive panels will discuss appropriate repair strategies for a variety of surgical wounds and innovative approaches to melanoma treatment. Both Mohs and non-Mohs cases will be featured in the microscope laboratory. Mohs nursing staff, technicians and other Mohs support personnel will increase their knowledge of skin cancer treatment and develop a greater appreciation for their unique roles in supporting high quality dermatologic care.

AMA PRA Category 1 Credit Available

For additional information regarding ASMS educational activities, membership opportunities, and patient resources, please contact:

Novella Rodgers, Executive Director
American Society for Mohs Surgery
5901 Warner Avenue, Box 391
Huntington Beach, CA 92649-4659
Tel: 800-616-2767 or 714-379-6262
Fax: 714-379-6272
www.mohssurgery.org
execdir@mohssurgery.org

Closures Course and Fundamentals of Mohs Surgery

November 5 - 7, 2012 – Closures Course for Dermatologists
Course prerequisite is basic experience in cutting and sewing skin, and program is designed to take dermatologists to the next level of dermatologic surgery practice. This is an intense 2-day experience in closure considerations for the surgeon with a primary interest in closing surgical defects. It will feature practical techniques, site specific discussions, and numerous reconstruction “pearls,” based upon presenters’ extensive derm surgery experience.

November 8 - 11, 2012 – Fundamentals of Mohs Surgery for Dermatologists and Mohs Technicians
Developed as a comprehensive introduction to Mohs surgery, the course provides an overview of Mohs indications, mapping techniques, office set-up and instrumentation, and interpretation of Mohs histopathology. Instruction in key concepts is facilitated by lectures, “pearls” discussions, interactive Q&A sessions, video microscope demonstrations, and challenging microscope electives.

The Mohs technician program will feature hands-on training in Mohs laboratory techniques and incorporate important safety and regulatory guidelines and updates. A high faculty-to-student ratio helps ensure rapid skill development and advancement, and allows for discussion of critical troubleshooting techniques relative to tissue processing and slide preparation.

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“If you have a mature practice, loyal patients and somebody who can cover your practice for you, this is very doable.”

Lt. Col. Dore J. Gilbert, M.D.

Dr. Gilbert did more than his assigned tasks to improve soldiers’ healthcare. Always a dermatologist, he started a skin cancer-screening clinic.

What next?
Dr. Gilbert says he signed up for three years of active reserve and five years of inactive reserve. Having returned from Afghanistan in November 2011, he plans to deploy again, but he is not sure when.

In the meantime, he’s practicing general and cosmetic dermatology and is an associate professor of dermatology at the University of California, Irvine.

The now 62-year-old is also busy honing his skills as a soldier, taking such challenging courses as air assault school and flight surgeon school.
**INDICATIONS AND USAGE**

**ORACEA** is a dosage form for the treatment of only inflammatory inflammatory lesions (papules and pustules) of rosacea in adult patients.

The treatment of ORACEA differs from that of doxycycline used to treat infections. To reduce the development of resistant bacteria as well as to maintain the effectiveness of other antibiotic drugs, **ORACEA** should be used only as indicated.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

**ORACEA** capsules are not bioequivalent to other doxycycline products.

**Drug Interactions**

Concurrent use of an oral retinoid and a tetracycline should be avoided. Use of ORACEA may result in overdosage of VRACELA. The concurrent use of isotretinoin and tetracyclines may cause fetal toxicity at all doses that were examined in this study, even at the lowest dosage tested (50 mg/kg/day). A statistically significant reduction in sperm velocity, nitroglutentia, and motility induced reproductive toxicity at all dosages that were examined in this study, even as the lowest dosage tested (60 mg/kg/day) is administered. This adverse reaction is more common during long-term use of the drug but has been reported to occur independently of time or amount of drug administered. This adverse reaction is more common during long-term use of the drug but has been reported to occur independently of time or amount of drug administered.

**INDICATIONS**

**Abscess**

**ORACEA** has been studied in children of any age with regard to safety and efficacy, therefore use in children is not recommended.

**ADVERSE REACTIONS**

**Adverse Reactions in Clinical Trials of ORACEA**: In controlled clinical trials of adult patients with mild to moderate rosacea, 687 patients received ORACEA or placebo over a 16-week period. The most frequent adverse reactions occurring in these studies are listed in the table below.

<table>
<thead>
<tr>
<th>Incidence (%) of Selected Adverse Reactions in Clinical Trials of ORACEA (n=687) vs. Placebo (n=687)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORACEA</strong></td>
</tr>
<tr>
<td>Nanopharyngitis</td>
</tr>
<tr>
<td>Throat/Hypopharyngeal Pain</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Nasal Congestion</td>
</tr>
<tr>
<td>Transient Infection</td>
</tr>
<tr>
<td>Influenza</td>
</tr>
<tr>
<td>Diarrhea</td>
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<tr>
<td>Abdominal Pain Upper</td>
</tr>
<tr>
<td>Abdominal Discomfort</td>
</tr>
<tr>
<td>Abdominal Pain</td>
</tr>
<tr>
<td>Stomach Discomfort</td>
</tr>
</tbody>
</table>

**Note**: Percentages based on total number of study participants in each treatment group.

**Adverse Reactions for Tetracyclines**: The following adverse reactions have been observed in patients receiving tetracyclines at high, antimicrobial doses.

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphonia, enterocolitis, and inflammatory lesions (with vaginal candidiasis) in the anogenital region. Hepatotoxicity has been reported rarely. Instances of esophagitis and epigastric ulcerations have been reported in patients receiving the capsule forms of the tetracyclines. Most of the patients experiencing these reactions had evidence of other serious disease or were being treated with other potentially hepatotoxic drugs

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (see WARNINGS section).

**Renal toxicity**: Rises in BUN have been reported and is apparently dose-related. (see DOSAGE AND ADMINISTRATION section).

**Skin**: Skin rash has been reported but is uncommon. Photosensitivity is discussed above. (see WARNINGS section).

**OVERDOSE**

**In case of overdose, discontinue medication, treat symptomatically, and institute supportive measures.**

**DOSAGE AND ADMINISTRATION**

**The dose of ORACEA differs from that of DOXYCYCLINE used to treat infections; therefore the recommended dosage may result in an increased incidence of side effects including the development of resistant microorganisms.**

One ORACEA-Capsule (40 mg) should be taken once daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals.

**Efficacy** beyond 16 weeks and safety beyond 9 months have not been established.

**Administration** of adequate amounts of fluid along with the capsule is recommended to wash down the capsule to reduce the risk of esophageal irritation and ulceration. (see ADVERSE REACTIONS section).

**HOW SUPPLIED**

**ORACEA** (beige opaque capsule printed with COP 40) containing doxycycline, USP in an amount equivalent to 40 mg of antimicrobial base contained in a blister pack of 28 capsules (909-2).

**Storage**: All products are to be stored at controlled room temperatures of 15°C-30°C (59°F-86°F) and dispensed in light-resistant containers.


**ORACEA** is a registered trademark of Collaborative Pharmaceuticals, Inc.

Manufactured by: Goldermans Laboratories, L.P.

Marketed by: Goldermans Laboratories, L.P.

139-401

**CONTRAINDICATIONS**

**Drug Interactions**

**Pharmacodynamics**: Photosensitivity may be manifested by an exaggerated sunburn reaction has been observed in patients receiving tetracyclines. There have been reports of pseudotumor cerebri (see WARNINGS section).

**Contraindications**

The concurrent use of tetracycline and a tetracycline should be avoided. Use of ORACEA may result in overdosage of VRACELA. The concurrent use of isotretinoin and tetracyclines may cause fetal toxicity at all doses that were examined in this study, even at the lowest dosage tested (60 mg/kg/day). A statistically significant reduction in sperm velocity, nitroglutentia, and motility induced reproductive toxicity at all dosages that were examined in this study, even as the lowest dosage tested (60 mg/kg/day) is administered. This adverse reaction is more common during long-term use of the drug but has been reported to occur independently of time or amount of drug administered. This adverse reaction is more common during long-term use of the drug but has been reported to occur independently of time or amount of drug administered. This adverse reaction is more common during long-term use of the drug but has been reported to occur independently of time or amount of drug administered.

**PRECAUTIONS**

**Safety of ORACEA beyond 9 months has not been established.**

As with other pharmacological preparations, the use of ORACEA may result in overgrowth of nonsensitive microorganisms. A superinfection can occur. Use of ORACEA should be discontinued and appropriate measures taken.

**Patients**: All products are to be stored at controlled room temperatures of 15°C-30°C (59°F-86°F) and dispensed in light-resistant containers.

**Lactic acidosis and death**: These adverse reactions have been reported rarely. Instances of esophagitis and epigastric ulcerations have been reported in patients receiving the capsule forms of the tetracyclines. Most of the patients experiencing these reactions had evidence of other serious disease or were being treated with other potentially hepatotoxic drugs.

**Gastrointestinal**: anorexia, nausea, vomiting, diarrhea, glossitis, dysphonia, enterocolitis, and inflammatory lesions (with vaginal candidiasis) in the anogenital region. Hepatotoxicity has been reported rarely. Instances of esophagitis and epigastric ulcerations have been reported in patients receiving the capsule forms of the tetracyclines.

**Skin**: Skin rash has been reported but is uncommon. Photosensitivity is discussed above. (see WARNINGS section).

**Adverse Reactions in Clinical Trials of ORACEA**: In controlled clinical trials of adult patients with mild to moderate rosacea, 687 patients received ORACEA or placebo over a 16-week period. The most frequent adverse reactions occurring in these studies are listed in the table below.

**Gastrointestinal**: anorexia, nausea, vomiting, diarrhea, glossitis, dysphonia, enterocolitis, and inflammatory lesions (with vaginal candidiasis) in the anogenital region. Hepatotoxicity has been reported rarely. Instances of esophagitis and epigastric ulcerations have been reported in patients receiving the capsule forms of the tetracyclines. Most of the patients experiencing these reactions had evidence of other serious disease or were being treated with other potentially hepatotoxic drugs.

**Skin**: Skin rash has been reported but is uncommon. Photosensitivity is discussed above. (see WARNINGS section).
DID YOU KNOW...

Rosacea is a common and chronic inflammatory condition of the facial skin that is estimated to affect more than 16 million Americans—and most of those who experience its signs and symptoms don’t even know they have it! The prevalence seems to be increasing in the United States, possibly due to the fact that the “baby boomer” generation is aging and this condition most frequently occurs in those between the ages of 30 and 50 years old. Rosacea may also be underdiagnosed for several reasons:

- Patients may not want to discuss their symptoms with their physician.
- Patients have no knowledge of the condition or how to recognize it.
- Some physicians may not be familiar with the disorder and may overlook it. We know that rosacea is not a life-threatening condition, but the facial redness and blemishes it produces can have a deep impact on your patients’ self-esteem and quality of life.

Because rosacea develops gradually, many patients don’t realize they have a treatable skin condition. In its earlier stages, patients may assume the facial flushing, papules, and pustules are adult acne, sun or wind burn, or the normal effects of aging. But regardless of what they believe it to be, rosacea affects their personal appearance and can significantly impact how they feel about themselves and how they are viewed by those around them.

ROSACEA MAY CAUSE SIGNIFICANT PSYCHOLOGICAL, SOCIAL, AND OCCUPATIONAL PROBLEMS IF LEFT UNTREATED.1

Surveys conducted by the National Rosacea Society with rosacea patients uncovered that:

- 76% said their rosacea had lowered their confidence and self-esteem.
- 88% of those with severe rosacea symptoms said it adversely affected their professional interactions.

In another survey of women with rosacea—44% would give up chocolate and 33% would give up makeup for 1 year in exchange for clearer skin.

EFFECTIVE TREATMENT CAN HELP

This suffering may be greatly reduced when rosacea is properly diagnosed and effectively treated in most patients. Rosacea results from an inflammatory process but the cause remains unknown. There is no cure, but there are treatments available that help control the signs and symptoms of this potentially life-disrupting condition.

ORACÆ® HAS BEEN SPECIALLY FORMULATED FOR AN EFFECTIVE ANTI-INFLAMMATORY RESPONSE

Oracea® is a modified-release, 40-mg dose of doxycycline that remains below the antimicrobial threshold. Unlike antibiotic doses of doxycycline 100 mg, Oracea® has been shown to effectively treat the inflammatory lesions of rosacea without significant side effects and with no evidence of bacterial resistance in a 9-month safety study.5,7

- In a noninferiority trial comparing Oracea® to doxycycline 100 mg, the anti-inflammatory dose demonstrated equivalent efficacy to an antimicrobial dose of doxycycline 100 mg at week 16.
- Incidence of treatment-related gastrointestinal (GI) adverse events (AEs) were 5x less (5% vs 26%) than doxycycline 100 mg (generally nausea, diarrhea, and vomiting).
- In other clinical studies, there were no reports of vaginal candidiasis or photosensitivity with Oracea®. (See below for additional Important Safety Information.)

Important Safety Information

Oracea® is indicated for the treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients. In clinical trials, the most common adverse events reported were nasopharyngitis/pain, gastrointestinal upset, hypertension, and nasal congestion/sinusitis. Oracea® should not be used to treat microbial infections, and should be used only as indicated. This drug is contraindicated in people who have shown hypersensitivity to any of the tetracyclines, and, like other tetracycline drugs, may cause fetal harm when administered to a pregnant woman. Oracea® should not be used during pregnancy, by nursing mothers, or during tooth development (up to the age of 8 years). Although photosensitivity was not observed in clinical trials, Oracea® patients should minimize or avoid exposure to natural or artificial sunlight. All contraindications, warnings, and precautions associated with tetracyclines must be considered before prescribing Oracea®. The efficacy of Oracea® beyond 16 weeks and safety beyond 9 months have not been established.

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.

Please see brief summary of Prescribing Information on next page.

References:

The Effects of Rosacea Go Deeper Than You Think