A Supplement to
Skin & Allergy News®

Skin Disease
Education Foundation

Roundup on Cosmetic Dermatology

SPRING 2006

TOPIC HIGHLIGHTS:

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Produced in affiliation with the 30th Hawaii Dermatology Seminar and the Cosmetic Dermatology Seminar.

LUSTRA-ULTRA is indicated for the gradual treatment of ultraviolet-induced dyschromia and discoloration.

LUSTRA-ULTRA is contraindicated in any patient that has a prior history of hypersensitivity or allergic reaction to hydroquinone or any of the other ingredients. Hydroquinone is a depigmenting agent which may produce unwanted cosmetic effects if not used as directed.

Warning: LUSTRA-ULTRA contains sodium metabisulfite which may cause serious allergic reactions (eg, hives, itching, wheezing, anaphylaxis, severe asthma attack) in certain susceptible persons.

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

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New Options Spur Interest in Combination Treatment

The emergence of new options for cosmetic dermatology procedures has created a great potential for combining different modalities to achieve the best possible result.

Two of the newest technologic developments are light-emitting diode (LED) treatment and topical antiaging agents that contain growth factors. These new treatment modalities can be combined with lasers, intense pulsed light, or other technologies to achieve cosmetic results that are more tailored to individual patient needs.

"The general trend in cosmetic dermatology is to have a synergistic approach involving a variety of different agents," said David J. Goldberg, M.D., J.D., Clinical Professor of Dermatology and Director of Laser Research and Mohs Surgery at Mount Sinai School of Medicine in New York. "The synergy might come from combining lasers with LED technology or, perhaps, with botulinum toxin, fillers, or effective new topical creams."

David J. Goldberg, M.D., J.D.

The evolution of LED technology has given rise to a unique new approach to skin treatment. In contrast to lasers, LED devices do not heat the skin and, as a result, do not cause any pain.

Instead, the devices achieve cosmetic benefits by modulating biologic activity inside various types of cells in the skin.

Within the field of cosmetic dermatology, LED technology currently comprises four wavelengths, each of which has different effects on the skin and can be used for different cosmetic applications. Blue light and red light are both used to treat acne. Red and near-infrared light are used to achieve antiaging effects. Yellow light has found a niche in the treatment of rosacea.

"Each type of light has a different mechanism of action, but they have in common the fact that they do not create any heat," said Dr. Goldberg. "Generally, a treatment can last anywhere from half a minute to 20 minutes. The treatments do not take very long, and there is no wound."

The ultimate role of LED technology in cosmetic dermatology remains to be determined, Dr. Goldberg added. Continued clinical experience with the technology eventually will demonstrate whether LED devices have a place as sole therapy for dermatologic conditions or as an adjunct to other technologies and treatments.

"In the real world of dermatology practice for acne, for example, we often use a laser to shrink the oil glands by heating them and combine that with red LED light, which decreases the bacteria involved in acne," said Dr. Goldberg. "For rosacea, we might use intense pulsed light, which produces heat, and combine it with yellow LED light, which also is used to treat rosacea."

Future experience also will define the role of new-generation topical agents, but the growth factor–containing creams have several advantages over conventional topical treatments. Conventional lotions and creams either fail to penetrate the skin or achieve concentrations that are too low to produce any meaningful effects. In some cases, exposure to air and light causes a cream or lotion to oxidize in its container and lose whatever therapeutic potential it might have had.

The newest additions to the topical armamentarium contain multiple types of growth factors developed by means of stem-cell technology. Originally developed to aid healing of burns and other wounds, the new agents have found a role in cosmetic dermatology because of their antiaging effects.

"These new topical agents are sort of like fertilizer for the skin," said Dr. Goldberg. "They differ from other topical agents in that they can actually get into the skin, they are packed with growth factors, and they can achieve very nice improvement in the skin."

Cosmetic dermatologists have already begun to use the growth-factor agents in combination with other technologies that can achieve antiaging effects in the skin. The experience to date suggests that combination treatment offers the potential to achieve better cosmetic results than does single-agent treatment. ■

DR. GOLDBERG *has received funding for clinical studies from Photo Therapeutics, Cynosure, Inc., Neocutis Swiss Technology, Inamed Corporation, Thermage, Inc., and Cutera, Inc. He is also a consultant to Bioform Medical, Inc., Lumenis Ltd., and Juva Medical Inc.*

Preventive Skin Care Forms Basis for Battle Against Sun and Aging

Advances in skin rejuvenation techniques have not lessened the importance of good preventive care to ward off the effects of sun exposure, climate, and aging.

"An ounce of prevention is worth a lot," said Christopher B. Zachary, F.R.C.P., Chair and Clinical Professor of Dermatology at the University of California, Irvine. "Good preventive skin care can delay aging and reduce the risk of keratoses, cancer, and wrinkling. In fact, a good combined skin care regimen can provide as much benefit in terms of appearance as do many of the new nonablative lasers."

Christopher B. Zachary, F.R.C.P.

Good skin care comprises four principal components: sun block, moisturizer, retinoid, and bleaching agent, such as hydroquinone. Among those components, a good moisturizer often is overlooked, thereby depriving the skin of a treatment that can prevent a significant degree of wrinkling, according to Dr. Zachary.

Providing a "California perspective" on skin aging, the Irvine cosmetic dermatology specialist said geographically defined differences in climate can have a profound impact on the speed and extent of skin aging. As an illustration, he described hypothetical twins, one of whom lived in Glasgow, Scotland, and the other in sunny southern California. By 50 or 60 years of age, sun exposure will have taken a substantial toll on the Californian's skin.

"If you put the twins side by side, you wouldn't have to ask which one lived where," said Dr. Zachary. "Genetically speaking, the two would be very similar. The difference would be in exposure to ultraviolet light, which gives rise to wrinkling, keratoses, lentigines, and loss of elasticity, such that one would probably have silky smooth skin, and the other would be wrinkled like a California raisin."

Good prophylactic skin care can help minimize the harmful effects of exposure to ultraviolet light. Even people who have neglected preventive care can benefit from a combined skin care program, which "sometimes can be more effective than lasers," said Dr. Zachary. "Before discussing a nonablative rejuvenation procedure, a patient should first try a good skin care regimen."

When rejuvenation is indicated, a good initial choice for many patients is intense pulsed light (IPL). Although not a laser, IPL can achieve many of the same benefits for skin that exhibits signs of premature aging, including telangiectasias, lentigines, and wrinkling. IPL is absorbed well by pigment and blood vessels and improves skin tone and texture. Three or four treatment sessions can lead to "dramatic improvement in the color, texture, and tone of the skin," said Dr. Zachary, "although I am not so impressed with its effects on early wrinkling."

Prominent among lasers developed for skin rejuvenation procedures are the CoolTouch (CoolTouch, Roseville, Calif.) and Smoothbeam (Candela Corp., Wayland, Mass.) devices. Both have demonstrated the ability to improve wrinkling and acne scarring.

The latest addition to dermatologic laser technology is fractional resurfacing, represented by the Fraxel, 1,550-nm laser (Reliant Technologies, Inc., Palo Alto, Calif.). Fractional resurfacing represents a new approach to laser skin treatment. Whereas traditional lasers penetrate the skin in a horizontal layer, fractional resurfacing creates multiple tiny cylinders of penetration that extend to a depth of 200 to 500 microns in an orientation at right angles to the skin surface.

"The key to the success of this technology is that it treats only about 15% to 20% of the skin," said Dr. Zachary. "There is no exudation and very little chance of scarring. The treatment results in an internal structure of damage that heals by laying down new collagen and other skin components."

Fractional resurfacing has demonstrated the ability to improve wrinkling, acne scarring, and pigmentation defects. However, Dr. Zachary pointed out that chemical peels and IPL also can be used to treat pigmentation problems, and either technique represents an appropriate initial choice of treatment for a patient whose sole reason for treatment is a pigmentation problem.

Dermabrasion effectively treats acne scarring, but the evolution of newer, less-invasive techniques has greatly diminished dermabrasion's use in cosmetic dermatology. Carbon dioxide and erbium-YAG lasers offer effective options for scarring but are less frequently used now that the performance of nonablative devices has improved substantially.

"Many patients and physicians prefer nonablative devices," said Dr. Zachary.

"They maintain that as much benefit can be obtained with 6 to 12 treatments with the Smoothbeam, CoolTouch, or Fraxel as can be achieved with the erbium-YAG or carbon dioxide laser. If that is true, then I think the day of nonablative rejuvenation and nonablative treatment of acne scarring has finally arrived, even for skeptics like myself."

Radiofrequency techniques offer additional technologic options for cosmetic dermatology procedures. Manufac-

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For Quick Results, Think Nonablative Resurfacing

Non- or minimally-ablative facial resurfacing offers patients the results they desire without extended downtime, said several presenters at the annual fall meeting of the American Academy of Facial Plastic and Reconstructive Surgery.

"Most of my patients want nonsurgical treatments with no downtime," said Elizabeth Rostan, M.D., a cosmetic dermatologist in Charlotte, N.C. "In my community, I can't give away a CO_2 laser resurfacing."

Most of Dr. Rostan's fractional resurfacing patients are women who want treatment for photoaging, acne scars, or melasma. "Many of these patients are the ones for whom you might consider intense pulsed light. It would burn off the pigmentary lesions, but it would not give you the same improvement you see in fine wrinkling."

In terms of both efficacy and recovery, fractional resurfacing falls between nonablative and ablative techniques.

Elizabeth Rostan, M.D.

"The results we get are better than what we would see with a nonablative technique, but not quite as good as what we would see with an ablative resurfacing," she said. "However, with the fractional resurfacing, patients aren't experiencing the 2 weeks of downtime that they would with a CO_2 laser resurfacing, either."

The device directs its energy along the path of a computer-generated pattern, producing about 2,000 tiny holes (microthermal injury zones) per square centimeter. Because the areas of injury are so tiny, "you are treating about 20% of the skin surface, leaving 80% to renew and heal," Dr. Rostan said.

The laser intensity can be varied for different applications. The 8-J/cm^2 setting penetrates about 300 micrometers, and is good for pigmentary lesions. For acne scars or rhytids, the more intense energy of the 20-J/cm^2 setting is necessary; this level penetrates about 700 micrometers.

Patients require a topical anesthetic, which takes about 1 hour to achieve maximum effect. The actual resurfacing procedure lasts about 20 minutes, she said. However, three to five treatments, spaced about a week apart, are usually necessary to achieve the desired result.

Afterward, there is mild erythema and edema. "Patients are usually pink for 2 days, but it can sometimes last as long as 4 days," Dr. Rostan said. "But they can easily cover it with makeup and be back to work the day after the procedure."

Fractional resurfacing is also a good alternative for elderly patients or for those with health issues that might compromise wound healing in an ablative resurfacing, she said. "I've done a healthy 87-year-old, as well as a transplant patient, with no adverse effects."

But she said she would carefully consider patients with scleroderma or rheumatoid problems. "Anyone who you'd have concerns about for laser resurfacing, you would also have to think about for fractional resurfacing."

The in-office erbium laser provides a one-time minimally ablative resurfacing with results similar to a whole course of intense fractional resurfacing, said James Newman, M.D., a facial plastic surgeon from San Mateo, Calif.

"I began using office-based laser treatments in response to patients' wanting a treatment without much downtime or prolonged healing, but who also didn't want to come into the office four or five times to treat a brown spot," he said.

The small erbium lasers are also relatively inexpensive (about $30,000), which allows the physician to rapidly recoup the investment and offer patients a modestly priced treatment. "For the removal of brown spots from the face or hands, it would be about $300, and for a perioral regional resurfacing, maybe $1,000 or less," he said.

The small, portable lasers have lower fluences (about 5-7 J/cm^2) and smaller spot sizes (about 6 mm) than do their larger counterparts.

"They also have a pulse duration of about 300 milliseconds, and because they are lower powered, they can't go as fast. The maximum repetition rate is about 2 Hz," Dr. Newman said.

This makes the in-office erbium laser good for localized or regional (perioral or periorbital) resurfacing, but not appropriate for a full-face procedure, he said.

The main indications for this device are solar lentigines, early elastosis of periorbital skin, sebaceous hyperplasia, scar modification, and epidermal keratosis, Dr. Newman said. Downtime is 4-7 days, "similar to what you would expect with intense fractional resurfacing or a medium-depth chemical peel."

"If they can come in and get it over with in one treatment, and then put up with a week at most of healing, patients will be very happy with this," he said.

The plasma resurfacer gives similar results, without the epidermal sloughing that the erbium laser generates, said Edgar Fincher, M.D., a dermatologic surgeon in Los Angeles.

These devices feature a nitrogen canister that pumps the gas into a handpiece, where a radiofrequency generator heats it and delivers it through a nozzle to the skin surface. They can deliver energy ranging from 1 to 4 J/cm^2 and can be used in single or multipass mode.

Like a CO_2 or erbium laser, the plasma resurfacer causes an immediate zone of thermal damage, with heat dissipation into the deeper tissues, stimulating fibroblast action.

The difference with the plasma resurfacer, Dr. Fincher said, is that the lower fluences preserve the epidermis until reepithelialization is complete. "It does not vaporize the epidermis, which accelerates wound healing. About 4 days later, you have reepithelialization and necrotic keratinocytes moving up

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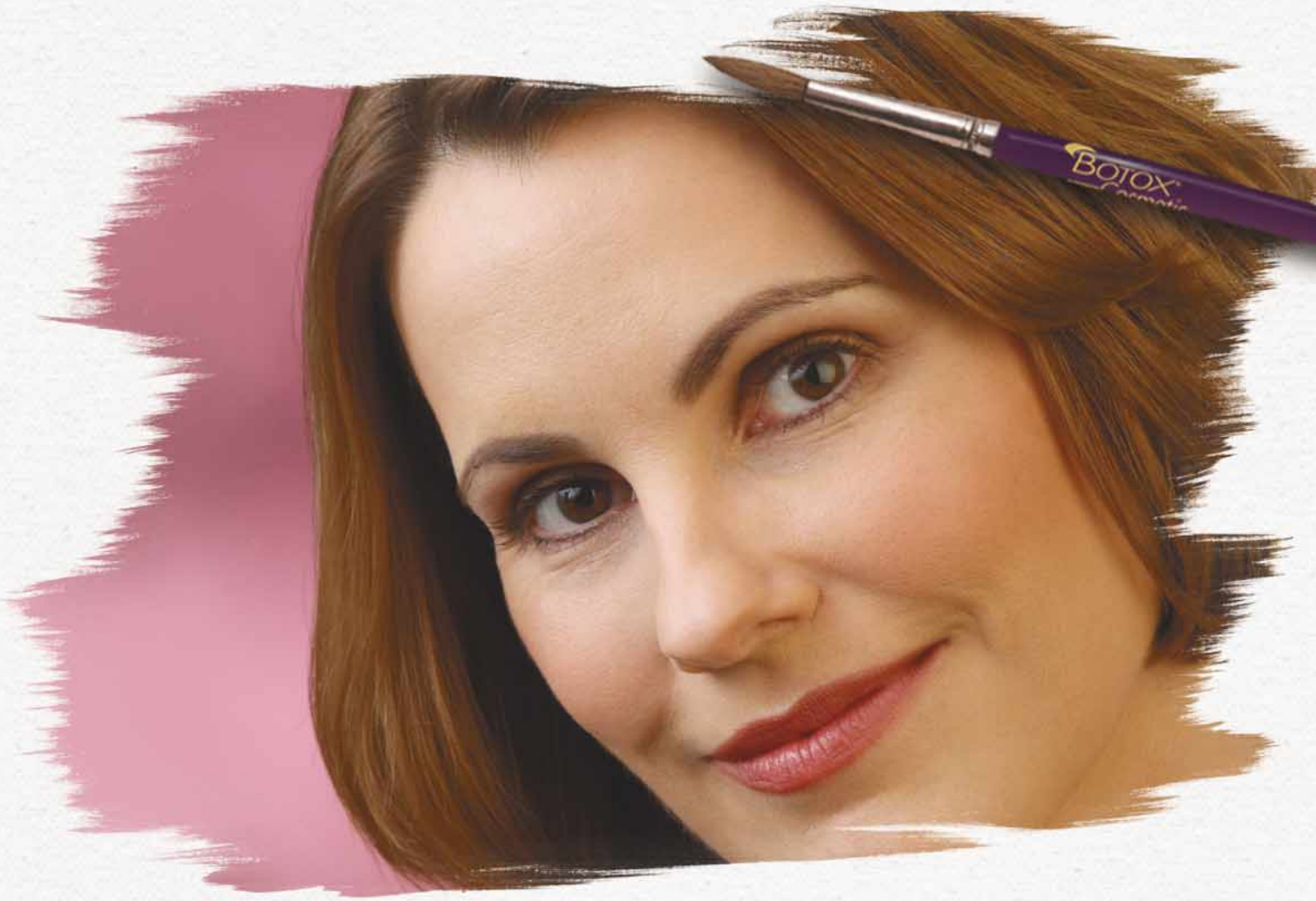
For the temporary treatment of moderate to severe glabellar lines in patients 18 to 65 years of age



Trusted tool of aesthetic artistry

BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in patients 18 to 65 years of age.

Important Safety Information: BOTOX® Cosmetic is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation. There have been rare reports of adverse events involving the cardiovascular system. Serious and/or immediate hypersensitivity reactions have been reported rarely. These reactions include anaphylaxis, urticaria, soft-tissue edema, and dyspnea.

The most common adverse events following injection include blepharoptosis and nausea. Less frequently occurring (<3%) adverse reactions include facial pain, erythema at the injection site, paresthesia, and muscle weakness. Patients with neuromuscular disorders such as ALS, myasthenia gravis, or Lambert-Eaton syndrome may be at increased risk of serious adverse events.

Please see brief summary of full prescribing information on following page.

BOTOX® Cosmetic
Botulinum Toxin Type A

By prescription only

BOTOX® COSMETIC (Botulinum Toxin Type A) Purified Neurotoxin Complex

INDICATIONS AND USAGE

BOTOX® COSMETIC is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age.

CONTRAINDICATIONS

BOTOX® COSMETIC is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

WARNINGS

BOTOX® and **BOTOX® COSMETIC** contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of **BOTOX®** also have the potential to be associated with the use of **BOTOX® COSMETIC**.

Do not exceed the recommended dosage and frequency of administration of **BOTOX® COSMETIC.** Risks resulting from administration at higher dosages are not known.

Hypersensitivity Reactions

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

Pre-Existing Neuromuscular Disorders

Caution should be exercised when administering **BOTOX® COSMETIC** to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX® COSMETIC**. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

Dysphagia

Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There is also a case report where a patient developed aspiration pneumonia and died subsequent to the finding of dysphagia.

Cardiovascular System

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

Human Albumin

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

PRECAUTIONS

General:

The safe and effective use of **BOTOX® COSMETIC** depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX® COSMETIC** must understand the relevant neuromuscular and/or orbital anatomy of the area involved, as well as any alterations to the anatomy due to prior surgical procedures and avoid injection into vulnerable anatomic areas. Caution should be used when **BOTOX® COSMETIC** treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

Reduced blinking from **BOTOX® COSMETIC** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. In the use of **BOTOX®** for in the treatment of blepharospasm, one case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

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

Caution should be used when **BOTOX® COSMETIC** treatment is used in patients who have an inflammatory skin problem at the injection site, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart as these patients were excluded from the Phase 3 safety and efficacy trials.

Needle-related pain and/or anxiety may result in vasovagal responses, (including e.g., syncope, hypotension) which may require appropriate medical therapy.

Injection intervals of **BOTOX® COSMETIC** should be no more frequent than every three months and should be performed using the lowest effective dose (See Adverse Reactions, Immunogenicity).

Information for Patients

Patients or caregivers should be advised to seek immediate medical attention if swallowing, speech or respiratory disorders arise.

Drug Interactions

Co-administration of **BOTOX® COSMETIC** and aminoglycosides[1] or other agents interfering with neuromuscular transmission (e.g., curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should only be performed with caution as the effect of the toxin may be potentiated.

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

Pregnancy: Pregnancy Category C

Administration of **BOTOX® COSMETIC** is not recommended during pregnancy. There are no adequate and well-controlled studies of **BOTOX® COSMETIC** in pregnant women. When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL (No Observed Effect Level) of **BOTOX® COSMETIC** was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification.

In a range finding study in rabbits, daily injection of 0.125 U/kg/day (days 6 to 18 of gestation) and 2 U/kg (days 6 and 13 of gestation) produced severe maternal toxicity, abortions and/or fetal malformations. Higher doses resulted in death of the dams. The rabbit appears to be a very sensitive species to **BOTOX® COSMETIC**.

If the patient becomes pregnant after the administration of this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations that have been observed in rabbits.

Carcinogenesis, Mutagenesis, Impairment of fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential of **BOTOX® COSMETIC**.

The reproductive NOEL following intramuscular injection of 0, 4, 8, and 16 U/kg was 4 U/kg in male rats and 8 U/kg in female rats. Higher doses were associated with dose-dependent reductions in fertility in male rats (where limb weakness resulted in the inability to mate), and testicular atrophy or an altered estrous cycle in female rats. There were no adverse effects on the viability of the embryos.

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

Pediatric use: Use of **BOTOX® COSMETIC** is not recommended in children.

Geriatric use

The two clinical studies of **BOTOX® COSMETIC** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, the responder rates appeared to be higher for patients younger than age 65 than for patients 65 years or older. (See: CLINICAL STUDIES)

There were too few patients (N=3) over the age of 75 to allow any meaningful comparisons.

ADVERSE REACTIONS

General:

BOTOX® and **BOTOX® COSMETIC** contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of **BOTOX®** also have the potential to be associated with the use of **BOTOX® COSMETIC**.

The most serious adverse events reported after treatment with botulinum toxin include rare spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, pneumonia, and/or other significant debility. There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. (See: WARNINGS). New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established. Additionally, a report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

In general, adverse events occur within the first week following injection of **BOTOX® COSMETIC** and while generally transient may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema and/or bleeding/bruising may be associated with the injection.

Glabellar Lines

In clinical trials of **BOTOX® COSMETIC** the most frequently reported adverse events following injection of **BOTOX® COSMETIC** were headache*, respiratory infection*, flu syndrome*, blepharoptosis and nausea.

Less frequently occurring (<3%) adverse reactions included pain in the face, erythema at the injection site*, paresthesia* and muscle weakness. While local weakness of the injected muscle(s) is representative of the expected pharmacological action of botulinum toxin, weakness of adjacent muscles may occur as a result of the spread of toxin. These events are thought to be associated with the injection and occurred within the first week. The events were generally transient but may last several months or longer.

(* incidence not different from Placebo)

The data described in Table 4 reflect exposure to **BOTOX® COSMETIC** in 405 subjects aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of **BOTOX® COSMETIC** in the improvement of the appearance of glabellar lines (See: CLINICAL STUDIES). Adverse events of any cause were reported for 44% of the **BOTOX® COSMETIC** treated subjects and 42% of the placebo treated subjects. The incidence of blepharoptosis was higher in the **BOTOX® COSMETIC** treated arm than in placebo (3% vs. 0).

In the open-label, repeat injection study, blepharoptosis was reported for 2% (8/373) of subjects in the first treatment cycle and 1% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49% (183/373) of subjects overall. The most frequently reported of these adverse events in the open-label study included respiratory infection, headache, flu syndrome, blepharoptosis, pain and nausea.

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 be predictive of rates observed in practice.

TABLE 4.

	Percent of Patients Reporting Adverse Events	
Adverse Events by Body System	**BOTOX® Cosmetic (N=405) %**	**Placebo (N=130) %**
Overall	44	42
Body as a Whole Pain in Face	2	1
Skin and Appendages Skin Tightness	1	0
Digestive System Nausea Dyspepsia Tooth Disorder	3 1 1	2 0 0
Special Senses Blepharoptosis	3	0
Musculoskeletal System Muscle Weakness	2	0
Cardiovascular Hypertension	1	0

Adverse Events Reported at Higher Frequency (>1%) in the BOTOX® COSMETIC Group Compared to the Placebo Group

Immunogenicity

Treatment with **BOTOX® COSMETIC** may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments with **BOTOX® COSMETIC** by inactivating the biological activity of the toxin. The rate of formation of neutralizing antibodies in patients receiving **BOTOX® COSMETIC** has not been well studied.

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

Rx Only

Based on package insert 71711US13S revised January 2005

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

Reference:

1. Wang YC, Burr DH, Korthals GJ, Sugiyama H. Acute toxicity of aminoglycoside antibiotics as an aid in detecting botulism. *Appl Environ Microbiol* 1984; 48:951-955.

Plasma Energy Harnessed for Damaged, Aging Skin

One of the newest trends in nonablative skin rejuvenation is the use of plasma energy to rid patients of sun damage, fine lines, and wrinkles.

The advantage of plasma energy technology is in the conduction of uniform and efficient thermal energy to the dermis without epidermal vaporization or charring, reported Alan T. Lewis, M.D., at the Fourth International Academy of Cosmetic Dermatology World Congress, Paris.

"Unlike CO_2 lasers where you're taking away the epidermis and the protection that it affords, the epidermis is left behind with this device," he said. The intact epithelium provides posttreatment protection and speeds healing, resulting in less downtime.

One-year clinical histology studies show continuing regeneration and improvement over time. Elastosis is reduced, and there is a widening of the collagen band at the dermoepidermal junction. There have been no reports of scarring or hypopigmentation in clinical studies to date, according to Rhytec Inc., which markets the plasma energy device, Portrait PSR^3.

The Portrait PSR^3 system generates plasma energy by passing ultrahigh frequency energy through nitrogen gas. Plasma is formed in the device's handpiece and delivered to the dermis in millisecond pulses without contact, about 5 mm from the skin.

Topical anesthesia, with or without oral medication, is used.

The Portrait PSR^3 system is approved for the treatment of facial rhytides, superficial skin lesions, and actinic keratoses. But is also helpful in improving skin tone and texture, and reducing laugh lines, he said.

It can be used for people with darker skin tones without affecting skin color because the energy absorption is not chromophore dependent.

The device can deliver either low- or high-energy treatments, said Dr. Lewis, Director of Mohs Micrographic Surgery and Cutaneous Oncology at Tulane University Hospital and Clinic in New Orleans.

Full-face rejuvenation using low-energy typically requires three 15-minute sessions spaced 21 days apart. There is no skin sloughing, minimal erythema, and little downtime, he said. Patients undergoing a single high-energy treatment may notice tight skin after the treatment and sloughing at about 7 days.

Another trend in nonablative facial rejuvenation is to "stack," or combine, different laser treatments to elicit a response in different layers of the skin, he said.

The approach takes a little more time but results in greater patient satisfaction.

Dr. Lewis cited a study in which 10 women who received five treatment sessions with a 595-nm pulsed dye laser immediately followed by a 1450-nm diode laser had overall better and faster results than did 20 women treated with either laser alone (*Dermatol. Surg.* 2004;30:1292-8).

The 6-month clinical outcome was best for patients receiving the combination treatment, followed by those treated with the 1450-nm diode laser and the 595-nm pulsed dye laser, respectively.

When stacking lasers, it's important to use the 595-nm laser first because infrared lasers can cause a good deal of redness that can become quite problematic if followed with a vascular laser. ■

By Patrice Wendling, IMNG News Service. Reprinted from Skin & Allergy News, *December 2005. Based on a presentation at the Fourth International Academy of Cosmetic Dermatology World Congress, Paris.*

Nonablative Resurfacing

Continued from page 6

and beginning to slough." By day 10, histology shows a fully reformed stratified epidermis and increased number of active fibroblasts generating collagen, he said.

These devices have received U.S. Food and Drug Administration approval for use in single-pass, low-energy repeat treatments and single-pass, high-energy treatment of facial rhytids, and for the treatment of superficial skin lesions.

Dr. Fincher has used a plasma resurfacer for about 2 years, with no incidence of scarring or hypopigmentation. He has seen some transient hyperpigmentation, however, and two patients have had prolonged (4-6 weeks) erythema.

"We tell people that, pretty reliably, they will be back to normal in 10 days," he said.

A full-face treatment can be done in about 15 minutes. Patients who are being treated for dyschromia or photodamage will probably require two or three treatments about 1 month apart. These low-energy treatments are usually performed with a topical anesthetic, although nerve blocks may be necessary for some patients. The high-energy treatments necessary for treating acne scars usually require local anesthetic or IV sedation.

"We still have a CO_2 laser and use it occasionally, but this has replaced it as our workhorse resurfacing device," Dr. Fincher said. ■

By Michele G. Sullivan, IMNG News Service. Reprinted from Skin & Allergy News, *December 2005. Based on a presentation at the annual fall meeting of the American Academy of Facial Plastic and Reconstructive Surgery.*

Horse Chestnut

There are 15 known species of horse chestnut, which is found as both a tree and a shrub in the temperate regions of Europe, Asia, and North America. Believed to have originated in northern Greece and the Balkan region, the European horse chestnut (*Aesculus hippocastanum*) is the species most often used in medical applications. It is not known whether other horse chestnut species have been thoroughly evaluated for their potential medicinal value. The European horse chestnut is not related to the more familiar sweet chestnut (*Castanea vesca*).

Leslie S. Baumann, M.D.

Most of the aerial sections of the European horse chestnut tree—including the seeds, leaves, and bark—have been traditionally utilized in medical treatments. As early as the 1500s, nuts from the horse chestnut tree were used to treat persistent fever; later, they were used for hemorrhoids, varicose veins in the leg, and phlebitis.

Modern horse chestnut formulations are derived from seed extracts, which are high in the active component aescin (also known as escin). The seeds also contain hydroxycoumarins, flavonoids, tannins, sterols, saponins, and glycosides.

Today, oral administration of standardized horse chestnut seed extract (HCSE) is a well-established treatment for chronic venous insufficiency (CVI) and edema. CVI is characterized by enlarged veins near the skin surface, edema, and leg fatigue. The extract is also effective when used in a sitz bath for the treatment of hemorrhoids. In addition, HCSE is used as an astringent and an anti-inflammatory.

Horse chestnut is a common ingredient in lotions, creams, massage oils, and other skin care products, often in combination with other herbal ingredients. Most such topical products tout the capacity of horse chestnut to combat varicose veins, swelling, and water retention, but some of the newer products ascribe antioxidant potency to horse chestnut and purport to combat wrinkling.

Traditional Chinese medicine uses horse chestnut (*Aesculus chinensis,* known as tien shi li) as an astringent, anti-inflammatory, diuretic, and expectorant, as well as for a wide range of ailments, including circulatory problems and viral infections.

Mechanism of Action

HCSE may work by inhibiting leukocyte activation (*Arch. Dermatol.* 1998;134:1356-60). A natural bioflavonoid and saponin, aescin is believed to foster normal, healthy tone in vein walls by inhibiting enzymes that attack vein interiors (*Arzneimittelforschung.* 1994;44:25-35). Aescin facilitates the contraction of elastic fibers in blood vessel walls, thereby elevating the flexibility of the vessels (*Dtsch. Med. Wochenschr.* 1986;111:1321-9; *Lancet.* 1996;347:292-4; *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines.* Philadelphia: Lippincott Williams & Wilkins, 1996).

Researchers also have shown that aescin inhibits elastase and hyaluronidase in vitro. Both enzymes have roles in the degradation of proteoglycans, an important element in the extravascular matrix and a component of endothelium. It is speculated that aescin alters the equilibrium between proteoglycan synthesis and degradation, resulting in the prevention of vascular leakage (*Arch. Dermatol.* 1998;134:1356-60).

Aescin is associated with the release of prostaglandin F_2 from veins, an antagonism to histamine and 5-hydroxytryptamine, and a decreased catabolism of tissue mucopolysaccharides (*Pharmacol. Res.* 2001; 44:183-93).

Rutin, which is believed to strengthen fragile capillaries, is another active ingredient in horse chestnut seeds. Many researchers in Europe claim that aescin and rutin work synergistically with other active components to enhance circulation and ease inflammation.

The leaves of the horse chestnut tree purportedly have antioxidant properties that may slow skin wrinkling; such claims, however, have not been confirmed by controlled clinical trials.

Chronic Venous Insufficiency

Copious, strong evidence supports the effectiveness of oral HCSE for the treatment of CVI. In a thorough review of placebo-controlled studies, researchers found that HCSE was superior to placebo in all cases. The reviewers noted reductions in lower-leg volume and in leg circumference at the calf and ankle, as well as improvement in symptoms such as leg pain, pruritus, fatigue, and tension, with only mild adverse reactions occurring rarely. The same study found equivalence between horse chestnut and *O*-(β-hydroxyethyl)rutosides against a reference medication, as well as equivalence between horse chestnut and compression therapy (*Am. J. Clin. Dermatol.* 2002;3:341-8; *Arch. Dermatol.* 1998;134:1356-60).

In a different literature review of six placebo-controlled trials assessing leg pain, investigators observed a significant improvement in the groups treated with HCSE compared with placebo. They concluded that horse chestnut is safe and effective for short-term CVI therapy, but that more rigorous, randomized, controlled trials are necessary to evaluate long-term efficacy (*Cochrane Database Syst. Rev.* 2002;1:CD003230).

Others have noted that oral horse chestnut therapy is adequate for treating the early phases of CVI as a result of its capacity to close venular endothelial gaps, but that compression therapy remains indicated for later stages (*BMC Cardiovasc. Disord.* 2001;1:5). Various authors note that compression therapy is associated with poor compliance because it is uncomfortable and sometimes painful, rendering an oral (and perhaps topical) treatment such as horse chestnut preferable. The sooner such treatment is initiated, the better the chance of avoiding compression therapy.

Another study, in which 5,000 patients with CVI were treated with standardized horse chestnut extract, showed clearing or improvement of all of the symptoms—discomfort, fatigue, tension, edema in the leg, and pruritus—that were investigated (*Fortschr. Med.* 1996;114:196-200).

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New Laser System Offers Another Skin Tx Option

Fractional photothermolysis for skin rejuvenation provides results similar to those achieved with ablative laser resurfacing, but without the downtime, Tina Alster, M.D. said at the joint annual meeting of the American Society for Dermatologic Surgery and the American College of Mohs Micrographic Surgery and Cutaneous Oncology, Atlanta.

The new fiber laser technology is particularly good for treating dyspigmentation and rhytides, and can be used on areas other than the face, such as the arms, neck, chest, and hands, said Dr. Alster, Director of the Washington Institute of Dermatologic Laser Surgery.

Tina Alster, M.D.

Of about 20 lasers that she uses in her practice, the Fraxel laser (Reliant Technologies Inc., Palo Alto, Calif.) is one of those she uses most often.

According to information from Reliant, the Fraxel laser system—which is approved for the treatment of melasma but also has been used for surgical and acne scars, striae, and actinic keratoses—treats the skin fractionally, with patterns of microscopic laser spots that are 70-100 μm in diameter. Each laser spot is called a microthermal zone, or MTZ, and the laser can deliver 2,000 MTZs per cm^2 in a typical treatment session. About 200-300 μm of untreated space is left between each MTZ. However, the treating physician has the ability to vary spot pitch and fluence.

The use of the MTZs with adjacent untreated tissue allows fractional wound healing with rapid reepithelialization of the epidermis and collagen remodeling to depths of 400-700 μm. This is compared with the 200-μm depth achieved with traditional ablative laser treatments.

Histology following treatment shows that the stratum corneum remains intact and epidermal tissue is coagulated. Collagen remodeling is also demonstrated, explained Dr. Alster, who reported no financial interest in the device.

"You see reepithelialization of the whole site within 24 hours," she said.

Her treatment protocol involves skin cleansing and application of a blue tint, which is required for the laser to work. About 30-60 minutes prior to the procedure, she also applies a topical anesthetic containing 30% lidocaine.

Dr. Alster said she usually uses 8-10 MJ per cm^2, energy density of 250 MTZs per cm^2, and four to eight passes. An air cooler is used to increase patient comfort.

Patients usually require two to four treatments at 2- to 4-week intervals. Most come back monthly to complete the series of treatments, she said. The skin is erythematous immediately after each treatment and remains so for approximately 2 days. On day 2 or 3, a variable amount of peeling occurs, resulting in rough-feeling skin.

Results are incremental, with additional improvement seen after each treatment. Most patients will achieve 50% improvement when being treated for dyspigmentation and/or rhytides. Although the laser is not marketed as a skin tightening device, it does provide some skin tightening, Dr. Alster noted.

The results are better than what she has experienced with trichloroacetic acid peels, particularly for fine lines, she said, and the recovery time is much quicker than with ablative resurfacing.

David J. Goldberg, M.D., of Skin Laser & Surgery Specialists of New York/New Jersey agreed that fractional photothermolysis has several applications and a relatively good safety profile, but he cautions that adverse events are still possible. Scarring, for example, can occur when the device is held in one place for too long.

Dr. Goldberg also noted that many of the effects of this laser can be achieved with other modalities. "It clearly works," he said, but it's not the "end all and be all."

For example, acne scarring responds well to the Fraxel laser, but it can also be treated effectively with the CoolTouch or Smoothbeam lasers. Crow's-feet can be treated effectively with botulinum toxin, and lentigines can be treated effectively with the Q-switched laser and intense pulsed light, Dr. Goldberg said.

"This is not a system that you buy simply to treat lentigines; this is not a system you buy simply to treat crow's-feet ... but I think that you can't argue the fact that when you put the whole picture together, it's got tremendous diversity, and that diversity has led to its popularity," he said.

Dr. Goldberg has received a research grant from Reliant Technologies Inc. ■

By Sharon Worcester, IMNG News Service. Reprinted from Skin & Allergy News, *January 2006. Based on a presentation at the joint annual meeting of the American Society for Dermatologic Surgery and the American College of Mohs Micrographic Surgery and Cutaneous Oncology, Atlanta.*

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Horse Chestnut *Continued from page 10*

In a 12-week, randomized, partially blinded, placebo-controlled parallel study of 240 patients, significant and equivalent reduction of edema resulted from horse chestnut and compression therapy compared with placebo; both therapies were well tolerated with no adverse side effects (*Lancet.* 1996;347:292-4).

Usage and Indications

Topical and systemic HCSEs are popular in Europe for the treatment of CVI and related conditions, such as varicose veins, leg cramps, phlebitis, and hemorrhoids. Topical application of gels or creams containing 2% aescin, three or four times per day, is used in Europe for eliminating hemorrhoids, varicose veins, and skin ulcers, as well as for healing sports injuries such as bruises, acute sprains, and similar traumas. The aescin in HCSEs clearly possesses anti-inflammatory capacity and has been demonstrated to ease edema after trauma, especially following head and sports injury, and surgery (*Arzneimittelforschung.* 1994;44:25-35; *Planta Med.* 1993;59:394-7).

Standardized HCSE has been approved by Commission E (a German panel of experts that is comparable to the U.S. Food and Drug Administration) for the treatment of pathologic conditions of the leg veins, including pruritus, edema, nocturnal cramping in the calves, and the sensation of heaviness, as well as varicose and spider veins.

There are claims that horse chestnut may even be effective for treating wrinkles, hair loss, cellulite, backache, and arthritis, but there is no reliable evidence in the literature to substantiate these claims. As an ingredient in facial creams and shaving products, horse chestnut is intended for sensitive skin.

Contraindications

Horse chestnut is contraindicated in patients who have bleeding disorders or who take anticoagulant drugs, such as warfarin, because the herb reduces blood clotting. Nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, potentially interact with herbal supplements known to contain coumarin, such as horse chestnut, thus increasing the risk of bleeding (*J. Clin. Pharm. Ther.* 2002;27:391-401).

Topical horse chestnut has been associated, in a few instances, with allergic skin reactions.

At the Store

Nature's Life Horse Chestnut Herbal Balm ($20 for 2 ounces) is a topical formulation standardized to include 2% aescin, and is intended to soothe the symptoms of varicose veins. Studies have shown that the topical application of standardized HCSE balm with 2% aescin supports healthy skin, blood vessels, and muscles, particularly in the legs and hemorrhoidal plexus (*Planta Med.* 1993;59:394-7; *Clin. Ter.* 1981;98:517-24; *Clin. Ter.* 1986;118:339-42). A double-blind study assessing the effectiveness of a topical standardized HCSE balm (2% aescin) for localized swelling and hematoma showed that the product significantly reduced tenderness in the affected area, compared with placebo (*Planta Med.* 1993;59:394-7).

Beauty Naturally's Rosacea Cleansing Lotion ($18 for 4 ounces) is an anti-inflammatory, antibacterial, nondetergent cleansing lotion formulated with horse chestnut, aloe, and chamomile. It is free of alcohol and oil, and therefore appropriate for sensitive skin. The manufacturer claims it is effective in controlling rosacea flare-ups and reducing erythema.

Beauty Naturally's Rosacea Moisturizing Cream ($33 for 2 ounces) contains horse chestnut. The product is intended to arrest inflammation and reduce erythema.

Conclusion

The usefulness of horse chestnut for treating CVI and other venous disorders has been borne out by randomized, controlled clinical trials. However, much research with topical horse chestnut is needed to support some of the more recent claims regarding efficacy in treating wrinkles and hair loss. ■

DR. BAUMANN *is Director of Cosmetic Dermatology at the University of Miami. Reprinted from* SKIN & ALLERGY NEWS, *January 2006.*

Preventive Skin Care *Continued from page 5*

turers of the two devices currently on the market have initiated a lively competition for business, which should give dermatologists and other prospective buyers reason to perform a careful evaluation of the technology before making a purchasing decision.

"When all is said and done, we need to look at the images very carefully and assess which company is putting out reliable and trustworthy images that you can actually believe in," said Dr. Zachary. ■

DR. ZACHARY *has nothing to disclose.*

Maintaining Safety, Integrity of Botulinum Toxin A

Cosmetic use of botulinum toxin A has proven to be safe and effective and a valuable addition to cosmetic dermatology. However, a recent scare over clinical use of unregulated botulinum toxin has reminded the dermatology community of the need for care in the acquisition and use of the substance.

"I think all of us who use botulinum toxin need to make sure our suppliers are bona fide and that we are receiving the real stuff," said Christopher B. Zachary, F.R.C.P., Chair and Clinical Professor of Dermatology at the University of California, Irvine. "Botulinum toxin type A is here to stay, and its use is well worked out. It is extremely safe and very effective when used appropriately. People are becoming much more accomplished in using it to reduce the effects of gravity."

Botulinum toxin type A is traditionally considered to be especially useful for reducing the effects of aging on the upper portion of the face. More recently, greater expertise has been gained in its use on the lower face, around the mouth, and on the neck. The treatment has become so popular that cosmetic application of the substance has expanded outside the fields of dermatology and plastic, facial-plastic, and oculoplastic surgery.

"Therein lies a problem," said Dr. Zachary. "There is a huge difference between an experienced physician injecting botulinum toxin type A and someone who is not experienced, particularly when the treatment is done in an environment where there is no physician supervision. We have to be very careful to protect the public."

In late 2004, the medical application of botulinum toxin made headlines when several people in Florida became ill after being injected with large doses of an unapproved bulk form of botulinum toxin produced for research purposes. The case emphasized the need to acquire botulinum toxin type A only from reputable distributors and to have appropriate medical and nursing supervision whenever the substance is used, said Dr. Zachary. ■

DR. ZACHARY *has nothing to disclose.*

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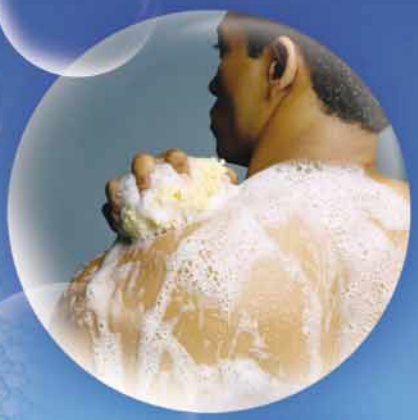

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