

Update on Botulinum Toxin

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Botulinum toxin for facial enhancement is currently the most popular aesthetic procedure performed in the United States. New developments have occurred within the last few years. Patients prefer having multiple areas of the upper face treated which increases patient satisfaction. Treatment of the forehead is now being accomplished with fewer units of botulinum toxin. This helps preserve the natural look of some movement of the forehead. Men require more units of botulinum toxin than women. Combination therapy using botulinum toxin along with lasers or filler substances is ideal. Aesthetic medicine knowledge has progressed, contributing a greater understanding of botulinum treatment for advanced areas of the face. The orbicularis oris, mentalis, and depressor anguli oris are now routinely treated and help improve overall facial appearance. Other forms of botulinum toxins (additional type A or type B toxins) are available, each with advantages and disadvantages.

Semin Cutan Med Surg 25:115-121 © 2006 Elsevier Inc. All rights reserved.

Facial enhancement by the use of botulinum toxin has revolutionized treatment of the aging face. Wrinkle improvement by relaxation of the underlying mimetic muscles of the aging face is a remarkably elegant modality. Because of its long-standing track record, having been proven safe and efficacious for greater than 10 years and having a high degree of patient satisfaction,¹ it now has become the single most-popular cosmetic treatment modality in this country. Recent data released by the American Society of Plastic Surgery in 2005 show that more than 3.8 million botulinum toxin (Botox®; Allergan, Irvine, CA) procedures were performed in that year alone.

Botulinum toxin leads the list of minimally invasive procedures. Botox® exceeds chemical peeling (approximately 1,000,000 procedures performed per year), microdermabrasion (840,000/yr), laser hair removal (780,000/yr), and sclerotherapy (590,000/yr). Of interest is that, according to these data, patients are now choosing a more subtle approach to improvements of the aging face than traditional cutting surgery. However, it is important to note that blepharoplasty and rhytidectomy are still valuable procedures, particularly for advanced photoaging patients.

Recent reports at medical meetings and in numerous journals have confirmed the popularity of Botox® therapy.² Whereas botulinum toxin originally was recommended for

treatment of the upper third of the face, multiple areas of the face are being treated with botulinum toxin. Botox® has been approved by the Food and Drug Administration for the treatment of glabellar lines by injecting the protein into the procerus, corrugator supercili, and depressor supercili muscles. Botox® therapy has gone beyond a single treatment site. Multiple areas of the upper third of the face are treated in one session, with excellent results. Many patients have two or more areas treated routinely. Figure 1 shows injection sites marked in red, when the glabella, forehead, and crow's feet areas are treated.

Numerous articles have been published on the treatment of periorcular lines, most notably the crow's feet and the infraorbital folds.³ Regarding dosage of treatment of crow's feet, the generally accepted dose of 12 U per crow's foot was found to be the optimal dose in the study by Lowe and coworkers.⁴ Their patients received a single bilateral treatment of 18, 12, 6, or 3 U of Botox® or placebo injected in the lateral aspect of the orbicularis oculii muscle. Investigators and subjects rated the crow's feet severity at maximum smile on day 7 and at 30-day intervals. It was found that a dose-dependent treatment effect for efficacy was observed, with greater doses having a better and longer duration of effect. A clear differentiation between the 18- and 12-U doses was not apparent, and the authors felt that 12 U per side was the most appropriate dose. Figure 2 shows the remarkable improvement when 12 U is used in each lateral periorcular area.

Treatment of the infraorbital folds have been reported by Flynn et al⁵ and others. Two units of Botox® injected 3 mm below the inferior ciliary margin in the mid-pupillary line have been reported to relax wrinkles under the eye. Notably,

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Figure 1 Injection points for multiple areas of the upper third of the face. Note that the glabella, forehead, and Crow's feet are marked for injection.

widening of the eyelid apperture also was noted. This widening was noted when infraorbital fold treatment was used in combination with treatment of the crow's feet area with 12 U of Botox®. They went on to report a dose finding study⁶ and noted that 2 to 4 U injected in the infraorbital area produced significant eyelid widening most notable in patients with narrow palpebral apertures ("squinty" eyes). It was noted that Asian patients particularly enjoyed the eyelid widening obtainable with proper use of Botox® in the crow's feet and infraorbital area. However, it is important to note that an increased number of undesirable side effects such as photophobia, trouble closing the eye, lateral rounding of the lower lid, and scleral show can be present when greater than 4 U were used in the lower lid.

Treatment of forehead wrinkles has been detailed by numerous authors.⁷⁻⁹ A notable recent trend has been the use of fewer units in the frontalis in women, ie, when large number of units are used in the frontalis, there can be complete immobility of the forehead. Of note is that this immobility often is accompanied with a tight shiny forehead with an appearance that does not look natural. Because patients and expe-

rienced physicians prefer a more natural look, the frontalis is now being treated with fewer units than before. The author's current treatment average for the female forehead is 16 to 24 U. It is also very important to stay away from the lower 2 cm of the frontalis, which is the portion that controls brow position. Many female patients need a working lower frontalis to keep their brows in a correct position, and treatment of this lower area of the muscle carries a risk of lowering the female brow.

Many cosmetic dermatologists have felt that men require more Botox® than women when facial musculature is being treated. These antedotal reports, held almost universally true by the specialty, have been documented by the Carruthers in their study of glabellar lines.¹⁰ In their study, 4 doses of Botox® were used in the glabella. Eighty men received either 20, 40, 60, or 80 U of Botox®. They were evaluated at rest or maximum frown by a trained observer at 2 weeks and 4 weeks and then monthly after the injections. The results showed that men benefit from a glabellar dose of 40 U or greater. This study supports the generally held principle that men need more Botox® than women.

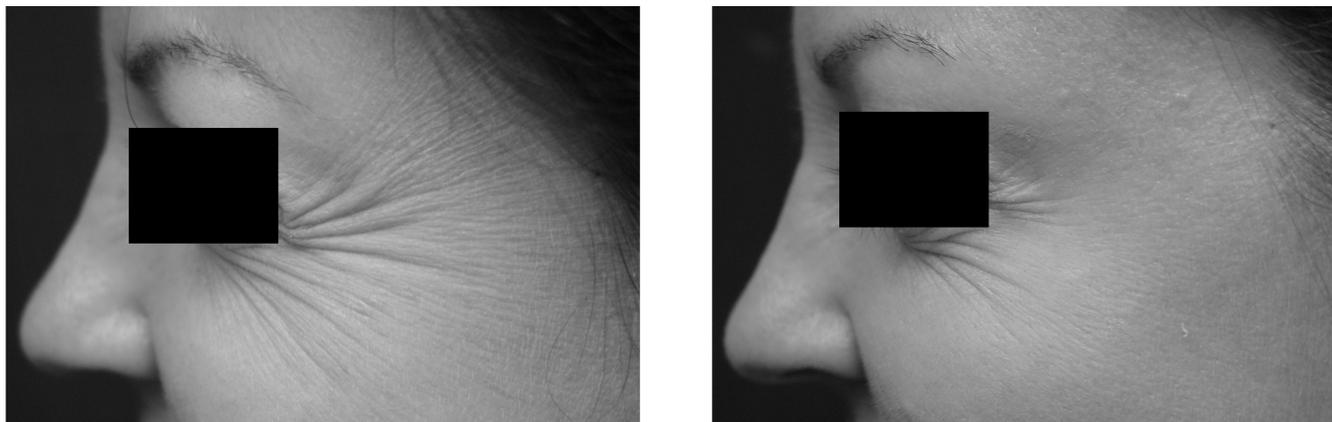


Figure 2 Treatment of Crow's feet with 12 U of Botox® in each periorbital area. Three injection points were used. The patient is shown before and 2 weeks after treatment.

Treatment of nasal wrinkles on the dorsum of the nose (“bunny lines”) can frequently be treated with botulinum toxin type A. Commonly, between 2 and 5 U of Botox® has been used; however, some clinicians have observed persistence of nasal wrinkles. The study by Tamura and coworkers.¹¹ showed that 40% of patients had satisfactory treatment of bunny lines with initial bilateral 3 U of Botox® injections. However, 60% of subjects had residual nasal wrinkles. Her article commented that injection of botulinum toxin into additional locations can show excellent resolution of the wrinkles. No complications were observed. Her article pointed out that additional injection patterns may be needed to completely eliminate bunny lines and that one will simply follow the wrinkle pattern with a few units of Botox® to improve the nasal wrinkles.

Combination therapy with botulinum toxin has expanded within the last several years.^{12,13} The most common therapy modalities used with botulinum toxin are filler substances. These include injectable collagen (both animal-based and human-based) as well as hyaluronic acid derivatives (Restylane [Medicis Aesthetics Inc., Scottsdale, AZ], Hylaform [Inamed Aesthetics], etc.). In the United States, nonanimal-synthesized hyaluronic acids in the form of Restylane have the largest market share. These substances are used to improve

wrinkles of the face by volumetric replacement under the wrinkle. An excellent study by the Carruthers¹⁴ has demonstrated that hyaluronic acid when used with botulinum toxin gives a greater degree of improvement and a more long-lasting effect than either substance used alone. Many clinicians have noticed significant improvement with combination therapy and are routinely treating their aging patients with both fillers and botulinum toxin.

This combination of fillers and botulinum toxin has led to the concept of facial sculpting.¹⁵ Many dermatologic surgeons have appreciated the fact that a very nice lateral brow lift can be created with subdermal injections of filler substances into the tail of the brow and treatment of the orbicularis with botulinum toxin. Other areas that have been treated with volumetric support in combination with botulinum toxin include the lateral lip, perioral region, nasojugal fold, and the malar and buccal fat pads. The combination of the use of filling agents with botulinum toxin can produce a very attractive natural appearance to the patient because 2 aspects of the aging face are addressed directly: hyperkinetic muscles of the face are relaxed with botulinum toxin and age associated volume loss is replaced with filling agents. The result is a soft, natural appearance with in contrast to the tight, “wind-



Figure 3 Combination treatment of the lips and perioral area. Restylane was used to fill the lips and marionette lines. 4 units of Botox® was placed in the lateral inferior aspect of the *depressor anguli oris* muscle.

blown” appearance of traditional facelift surgery, which re-drapes the aging skin by pulling it superiolaterally.

The use of Botox® in the lower face has increasingly popular, largely because the mainstay of the treatment of the lower face includes volume replacement with filler substances. However, treatment of the mentalis and the depressor anguli oris, particularly in combination with filler substances, produces a remarkable improvement in the lower aged face. The use of Botox® in the depressor anguli oris decreases the ability to frown and increases the position of the corners of the mouth at rest and at full smile. Because the depressor anguli oris is a mouth depressor, relaxation of the this muscle can raise the corner of the mouth by 1 to 2 mm at rest and give the opportunity of the patient to experience a greater, more pleasant smile. When treatment of the depressor anguli oris (DAO) is combined with volumetric filling of the “marionette lines,” a much more pleasant, more relaxed mouth can be created. Figure 3 demonstrates combination therapy of the lips on marionette lines. When additional filling is used beyond the corners of the mouth and includes radial lines around the mouth and fullness of the lip, true youthful restoration can be achieved.

Treatment of the mentalis also has improved the lower face.¹⁶ The mentalis muscle may contribute to abnormal movements of the midline of the chin where the mentalis fibers insert into the skin. This overactive mentalis can produce a “peach pit” chin. The improvement in the wrinkly chin is remarkably effective when the mentalis is treated. Many patients are not aware of this unusual nature of their chin; however, when the mentalis is relaxed, patient appreciation is high. The author has many patients who initially were treated at no cost to the patient to demonstrate the improvement of this irregular chin, and they now request treatment on a regular basis because of the significant improvement in their chin wrinkles.

Another recent trend in treatment of the perioral area has been the augmentative use of botulinum toxin for wrinkles of the lips. In the past, botulinum toxin was used as primary therapy for radial lip lines. However, it was found by many practitioners that although the numbers of wrinkles were reduced, the degree of wrinkle improvement was less than desirable. Practitioners working with volumetric filling agents in the lips noted that Botox® could be used nicely as an augmentation to improve these results. The injection of 1 to 2 U of Botox® in every quadrant of the lip can cause an increase in lip eversion and a subtle relaxation of the orbicularis oris, which is helpful in improving the lip rhytids.¹⁷ The author feels that patients need to be carefully counseled before injection particularly with changes in speech and the ability to purse the lips together.

A word of caution should be emphasized when treating the muscles below the mouth. Botox® is remarkably effective in improving mentalis-related chin irregularities and depressor anguli oris overactivity. Overtreatment of the depressor anguli oris can result in the corner of the mouth turning in producing an asymmetrical smile. Caution should be given to not completely paralyze the depressor anguli oris. In addition, treatment of the depressor anguli oris is desirable, but

relaxation of the depressor labii inferioris also may cause problems with the lower lip. The author has extensive experience with Botox® for these muscles and has experience had very few patient-related complications probably because the diffusion profile of Botox® is limited when compared with other forms of botulinum toxin. The author must emphasize caution when using other forms of botulinum toxin to treat the lower third of the face because of possible diffusion differences between the toxins.

Combination treatment with botulinum toxin also has been undertaken with lasers and light sources.^{18,19} Surface aspects of photoaged skin (dyschromia, telangiectasia, pore size, fine wrinkles) are addressed with lasers and light sources in combination with relaxation of the facial musculature. An important report²⁰ showed the improvement that could be achieved with intense pulse light in combination with botulinum toxin. The aforementioned photoaging changes can all be improved with intense pulsed light therapy. Botulinum toxin improves this result by improving larger facial wrinkles and producing an improved overall appearance in the skin. Similar synergistic improvement can be achieved with laser therapy in combination with botulinum toxin. The author feels that the best treatment for the aging face is to address all of the issues of aging in each individual patient. A 3-pronged approach is used where the musculature is relaxed with botulinum toxin; the skin is improved with lasers, light sources, and retinoids; and age-associated volume loss is addressed with deeper filling agents, such as larger size hyaluronic acids, Radiesse™ (San Mateo, CA), or autologous fat. Botulinum toxin gives improved results in periorbital resurfacing with the erbium YAG laser.²¹ Many predict an increase in this combination approach for the aging face will correlate with a decrease in cutting surgery or a delay in the timing of traditional scalpel surgery.

A study by Semchyshyn and Kilmer answers the question if lasers or light sources inactivate botulinum toxin.²² A total of 19 subjects received botulinum toxin to either the glabella or crow’s feet areas. One side of these treated areas was treated with a variety of lasers, which included vascular lasers, intense pulse light, and radio frequency within 10 minutes of the botulinum injection. Pretreatment and posttreatment photographs were compared, and no decrease in the efficacy of botulinum toxin denervation was observed when the areas were treated with lasers, light sources, or radiofrequency devices.

Important studies on other botulinum toxins have been reported. Other type A toxins are available in Europe and will soon be available in the United States. Another type A toxin (Dysport; Ipsen, Auckland, New Zealand) will have the name of Reloxin when released into the United States. Recent studies have been undertaken in the critical evaluation in the use of Dysport in treatment of glabellar folds. A dose-finding efficacy and safety study was conducted by Asher and coworkers²³ who felt that the optimal dose for the glabella was 50 U of Dysport (Reloxin) in the glabellar complex. No blepharoptosis was reported. A placebo-controlled multicenter

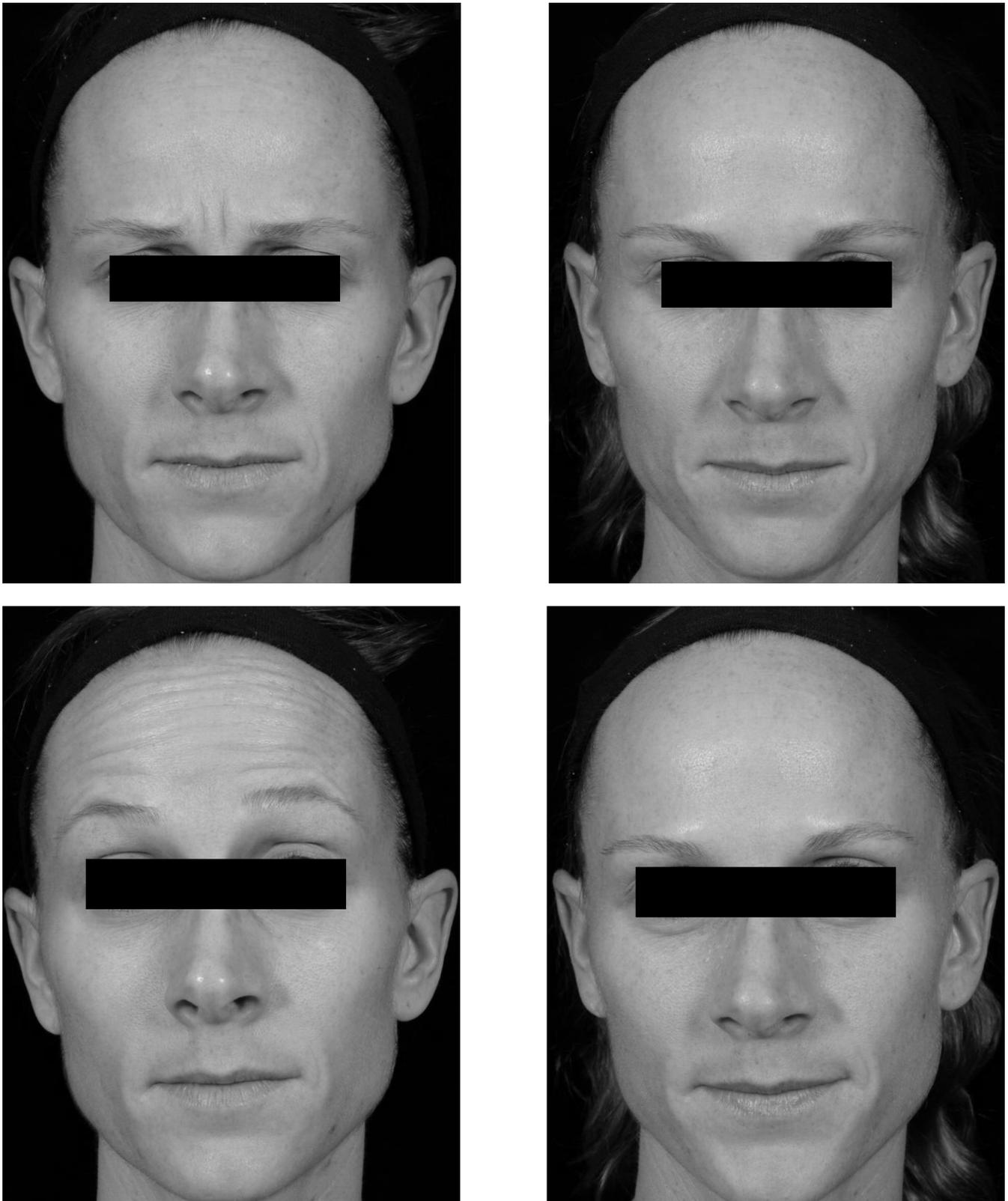


Figure 4 Treatment of the upper face. The patient was treated for both the glabella and forehead area with Botox®. Note improvement in both glabellar folds as well as horizontal lines of the forehead. The posttreatment pictures show her in a natural position even at full muscular effort.

study is now being conducted in the United States evaluating the safety and efficacy of Reloxin in treating the glabella.

A direct comparison study was conducted by Lowe and coworkers, who compared the use of Dysport and Botox® in treatment of the glabellar folds.²⁴ The doses in the glabella were 20 U of Botox® compared with 50 U of Dysport. In their study, they found that both forms of botulinum toxin type A were effective in the treatment of the glabellar folds at 4 weeks; however, there was a preferential improvement at 16 weeks with Botox® when compared with Dysport. Further studies are underway with increasing numbers of patients to more accurately estimate the duration of each particular toxin. Type B toxin is available as Myobloc® (Solstice Neuroscience, South San Francisco, CA; Neurobloc in Europe).^{25,26} This toxin has been shown to have a faster onset of action than Botox® and a longer area of diffusion.²⁷ A safety and efficacy study using Myobloc® in the glabella has been conducted²⁸ and the results are in press. The product was safe and effective up to 3000 U used in the glabella. However, the duration of effect has not been conclusively demonstrated to be as long as the type A toxins at the doses studied. It is a safe alternative to other toxins, and clinicians that are familiar with the product have noted that selective patients prefer the greatest effect of this product.

Additional new botulinum toxins are available around the world. Some additional forms include the type A toxin Xeomin, which is available from Merz in Germany, and good studies are underway on many of the newer botulinum toxins. A note of caution must be made regarding receipt of marketing materials advertising poorly studied botulinum toxin preparations with unclear preparation and purities. These products often are marketed from foreign countries. Caution must be emphasized when considering the use of these unknown products.

Several new techniques for decreasing the pain of injections have been described. An easy technique is the use of a hand-held piece of ice both preoperatively and during the botulinum toxin injections. Ice before and during injection decreases the pain of injection. Furthermore, several clinicians have noticed that precooling the skin decreases the tendency for bruising in the injection area. Smith and colleagues²⁹ reported the use of vibration to reduce discomfort. Inexpensive commercially available vibrating massagers are used to minimize pain and have been used in botulinum toxin as well as Restylane and laser treatments. They note that the use of vibratory anesthesia generally does not eliminate pain but does increase the tolerability of the injection.

Many cosmetic companies have advertised topical products that are equivalent or better than Botox®. How good are these creams? The answer was provided by Dr. Ken Beer, who reported on his study comparing Botox® with placebo and these topical products in treating glabellar lines. There were 77 patients divided into five treatment groups. Topical products included StriVectinSD, DDF Wrinkle Relax, and HydroDerm. Patients were seen at 4, 8, and 12 weeks. Botox® showed significant improvement on the facial wrinkle scale, and patients were highly satisfied. Treatment with the 3 top-

ical creams did not result in a significant difference from those treated with placebo.³⁰

The use of botulinum toxin in humans is a rapidly expanding field. Fascinating work has emerged with the use of botulinum toxin type A (Botox®) in the field of pain management. It has been noted that Botox® is effective in several forms of pain. There have been good reports of Botox® being used to improve migraine or tension-type headaches.³¹ In addition, Botox® has been reported efficacious in the treatment of post herpetic neuralgia and trigeminal neuralgia.³² This pain improvement is thought to work due to complex mechanisms still being investigated.

Two other areas of use of Botox® are of interest. Botulinum toxin injected into the gastric antrum has produced a weight loss in rats. There have been further reports of the use of botulinum toxin gastric injections in humans. A recent report³³ showed that, in 8 patients with severe obesity who had 500 U of Dysport injected into their gastric antrum had, at 1 month after injection, a significant reduction in body weight of 5 pounds. These patients had further weight loss at 4 months. Benign prostatic hyperplasia also has been improved with the use of botulinum toxin injections.^{34,35} Both Chuang and Morria have reported significant symptom relief in large and small prostates.

In summary, the use of botulinum toxin has expanded greatly in the last few years. Many patients are having multiple areas of the face treated in a single treatment session. Figure 4 shows such improvement in hyperkinetic facial lines. Combination therapy with Botox® plus fillers or lasers/light sources has provided natural "youth-like" results.

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